

Drug Update

Earnest Alexander, PharmD, and
Gregory M. Susla, PharmD
Department Editors

CE Syndrome of Inappropriate Antidiuretic Hormone and Cerebral Salt Wasting in Critically Ill Patients

Amanda Zomp, PharmD, BCPS
Earnest Alexander, PharmD

Serum sodium levels in critically ill patients can be altered by many factors. The human body is 60% to 70% water, with approximately 30% of that water as extracellular fluid and sodium chloride as the major electrolyte (135-145 mEq/L). Hyponatremia occurs when a person's serum sodium level is less than 135 mEq/L; it is the most common electrolyte abnormality among hospitalized patients, occurring in up to 30% of patients in the intensive care unit (ICU).¹ A sodium level less than 125 mEq/L is an independent predictor of mortality, especially among critically ill patients, and should be avoided or corrected when it occurs.²

Syndrome of inappropriate antidiuretic hormone (SIADH) and cerebral salt wasting (CSW) represent a particularly challenging subset of hyponatremias. These conditions are exceedingly common in patients with an intracranial disorder and neurosurgical patients but also may be seen in other critically ill populations. In the neurosurgical population, 62% of hyponatremias are caused by SIADH, and 4.8% to 31.5% are caused by CSW.³ These 2 conditions are very similar and may be hard to differentiate in critically ill patients. This column outlines the unique characteristics of SIADH and CSW and provides guidance about management strategies for optimal outcomes.

Pathophysiology

Hyponatremia can be associated with high, low, or normal serum osmolality. Normal serum osmolality is between 280 and 295 mOsm/L. It can be measured in the serum or calculated using the following formula: $[2 \times \text{sodium}] + [\text{blood urea nitrogen}/2.8] + [\text{glucose}/18]$. Determining osmolality is the first step in evaluating hyponatremias.

Normal and High Osmolality

Low sodium with normal osmolality is usually referred to as pseudohyponatremia or "false" hyponatremia. The causes of pseudohyponatremia include hyperlipidemia, an excess of plasma proteins, and laboratory error.^{4,5} Hyponatremia with high osmolality indicates an excess of solute other than sodium, including glucose, mannitol, and propylene glycol (an ingredient found in some intravenous [IV] medications). Excess osmolality from hyperglycemia or other substances

Amanda Zomp is Critical Care Pharmacy Resident, Tampa General Hospital, Department of Pharmacy Services, 1 Tampa General Cir, Tampa, FL 33601 (azomp@tgh.org).

Earnest Alexander is Clinical Manager, Department of Pharmacy Services, and Critical Care Pharmacy Residency Program Director, Tampa General Hospital, Tampa, Florida.

The authors declare no conflicts of interest.

DOI: 10.1097/NCI.0b013e31824ebd1b

causes water to move from the intracellular to the extracellular space, leading to a false lowering of the serum sodium value.⁶

Low Osmolality, SIADH, and CSW

Hyponatremia with low osmolality, or hypotonicity, is further divided into 3 categories, depending on the patient's volume status. The first category is hypervolemia with low osmolality, which is caused by a surplus of water. Heart failure, liver cirrhosis, and nephrotic syndrome are often associated with retention of water, leading to hypervolemia and dilutional hyponatremia. Conversely, the second category is hypotonicity with hypovolemia, which usually results from excessive water losses. Causes include vomiting, diarrhea, intense exercise/sweating, blood loss, diuretic use, and adrenal insufficiency. Cerebral salt wasting is a form of hypovolemic hypo-osmolality that is usually related to a central nervous system (CNS) disorder or neurosurgery. The exact mechanism of CSW is not fully understood, but the end result is an increase in the renal excretion of sodium, without an increase in excretion of water, which decreases the serum sodium level and increases the urine sodium level.⁷ Euvolemic hypotonicity is the third category and is caused by excessive (often psychogenic) water intake, renal insufficiency, adrenal insufficiency, hypothyroidism, and, most commonly, SIADH.⁸

Serum osmolality is primarily regulated in the body via antidiuretic hormone (ADH), or arginine vasopressin, and the kidneys. Antidiuretic hormone is released from the pituitary gland when the body senses an elevation in serum osmolality. It can also be released in response to reduced intravascular volume, although high serum osmolality is the primary trigger.⁹ The ADH then binds to vasopressin receptors in the kidneys and causes them to reabsorb water, without reabsorbing sodium. Release of ADH in the presence of normal or low serum osmolality is considered "inappropriate," as water continues to be reabsorbed by the kidneys, decreasing the serum sodium level and increasing the urine sodium level. The kidneys are still able to excrete sodium normally, because sodium excretion is regulated by aldosterone and atrial natriuretic peptide. This process results in concentrated urine, with a high urine sodium level and high urine osmolality. The urine osmolality remains constant in SIADH because changes in water intake/osmolality do not affect ADH secretion, and thus the amount of water excreted

in the urine in SIADH does not change.^{7,10} The causes of SIADH include CNS disorders, pulmonary disorders, malignancy, surgery, and medications (Table 1).⁷

Symptoms

Symptoms of hyponatremia typically depend on the acuity and severity of the decrease in sodium. A slower or mild decrease in the serum sodium level can be associated with anorexia, headache, irritability, and muscle weakness. A significant subset of patients is asymptomatic. More severe symptoms following a rapid decrease in sodium or a serum sodium level less than 120 mEq/L include cerebral edema, nausea, vomiting, delirium, hallucinations, lethargy, seizures, respiratory arrest, and potentially death.¹¹ Volume status also affects other symptoms that the patient experiences. Assessment of volume status is important to help determine the cause of hyponatremia and optimal treatment.⁷

Diagnosis

Differentiating between SIADH and CSW may be difficult but is an important factor in determining the appropriate treatment strategy. Both conditions are encountered in the ICU.^{7,8} In both conditions, patients experience hypotonic hyponatremia with serum osmolality less than 280 mOsm/L and serum sodium levels less than 135 mEq/L. The urine sodium level (normal 20-40 mEq/L) is also elevated in both conditions, with a level often greater than 50 mEq/L. The primary difference between SIADH and CSW is the volume status. Patients with SIADH are euvolemic or slightly hypervolemic, whereas patients with CSW are hypovolemic. Signs of volume depletion, including orthostatic hypotension, decrease in central venous pressure or pulmonary capillary wedge pressure, increase in hematocrit, and physical signs of dehydration, provide clues that the patient is experiencing CSW instead of SIADH.⁷

Rate of Correction

Hyponatremia must be corrected slowly during treatment, at a rate of about 8 to 12 mEq/L in 24 hours or 0.5 mEq/L per hour. Rapid correction of the sodium level in hyponatremia has been associated with central pontine myelinolysis, an irreversible disorder affecting the pontine white matter of the brain. Central pontine myelinolysis can cause altered mental status, flaccid quadriplegia, cranial nerve abnormalities,

Table 1: Causes of Hyponatremia

Hyponatremia Conditions by Osmolality Status	Serum Sodium Level (Normal 135-145 mEq/L)	Serum Osmolality (Normal 280-295 mOsm/L)	Urine Sodium Level (Normal 20-40 mEq/L)	Potential Causes
Hypertonic				
Hyperosmolar hyponatremia	↓	↑	↓	Excess of solute other than sodium, including glucose, mannitol, and propylene glycol
Normal osmolality				
Pseudohyponatremia	↓	Normal	Normal	Hyperlipidemia, an excess of plasma proteins, and laboratory error
Hypotonic				
Hypervolemic hyponatremia	↓	↓	↓	Heart failure, cirrhosis, and nephrotic syndrome
Hypovolemic hyponatremia	↓	↓	↓	Vomiting, diarrhea, intense exercise/sweating, blood loss, cerebral salt wasting, diuretic use, and adrenal insufficiency
Euvolemic hyponatremia	↓	↓	↓	Excessive water intake, renal insufficiency, adrenal insufficiency, hypothyroidism, and syndrome of inappropriate antidiuretic hormone

and coma.¹² Patients who develop hyponatremia more quickly are at higher risk of morbidity and mortality from the condition. Patients with acute hyponatremia seem to be able to tolerate a quicker correction of their sodium values than those with chronic hyponatremia without as much risk for central pontine myelinolysis.¹³ Serum sodium values should be monitored frequently (eg, every 6-12 hours) during correction. The goal serum sodium level during treatment of hyponatremia is 130 to 135 mEq/L, with 135 mEq/L being the lower limit of the normal range. This targeted strategy level

usually allows for the reversal of symptoms and avoids overcorrection of sodium levels.

Treatment Options

The first step in the treatment of SIADH or CSW is to identify the cause and then reverse or treat it. The most common reversible causes of SIADH include medications, such as carbamazepine, oxcarbazepine, cyclophosphamide, and selective serotonin reuptake inhibitors, and pulmonary disease, such as pneumonia. Medication-induced SIADH can be reversed by discontinuing the medication, and SIADH caused

by pneumonia can be reversed by treating the pneumonia. Unfortunately, many common causes of SIADH and CSW, such as subarachnoid hemorrhage and malignancy, are irreversible, at least in the short term. The next step is initiation of hyponatremia treatment. Treatment options are outlined in Table 2, along with dosing and monitoring considerations. The use of all agents reviewed for the treatment of SIADH and CSW is considered off label, with the exception of the vasopressin antagonists.

Fluid Restriction

Fluid restriction is an option for patients with SIADH. This strategy is not an option for patients with CSW because they are already in a hypovolemic state, which further stresses the importance of differentiating between the 2 conditions. Fluid restriction is especially dangerous in patients with subarachnoid hemorrhage, because further intravascular volume depletion could increase the risk for vasospasm.⁷ In SIADH, the total amount of fluid intake

Table 2: Treatment Options for SIADH and CSW

Treatment	Use	Dose	Monitoring ^a
Fluid restriction	SIADH	800-1200 mL/d	Volume status, intake, output, and dehydration (eg, heart rate, blood gas pressure)
Isotonic saline	CSW	100-200 mL/h IV (correction rate of 0.5 mEq/L)	Volume status, intake, and output
Salt tablets	CSW	Up to 12 g/d orally in divided doses	Volume status, intake, and output
Hypertonic saline	SIADH CSW (with caution)	0.5 mL/kg/h IV	Volume status, intake, output, and central catheter status
Furosemide	SIADH	20-120 mg IV/orally	Volume status, urine output, salt intake, and renally excreted electrolytes (ie, potassium, chloride, and magnesium)
Demeclocycline	SIADH	600-1200 mg/d orally in divided doses	BUN, SCr, and urine output
Lithium	SIADH	900 mg/d orally	Mental status, tremor, electrolytes, BUN, SCr, urine output, thyroid function, CBC, weight, vomiting, and diarrhea
Urea	SIADH	30 g/d orally	Nausea, vomiting, mental status, and BUN
Fludrocortisone	CSW	200 mcg twice daily orally	Respiratory function, potassium, and glucose
Conivaptan	SIADH	20 mg IV over 30 min, then 20-40 mg/d continuous infusion over 96 h	Constipation, urine output, and thirst
Tolvaptan	SIADH	15, 30, or 60 mg/d orally	Edema, potassium, urine output, and thirst

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood cell; CSW, cerebral salt wasting; IV, intravenous; SCr, serum creatinine; SIADH, syndrome of inappropriate antidiuretic hormone.

^aIn addition to serum sodium level monitoring.

should be less than the patient's total output (urine and insensible losses). Fluid restriction of 800 to 1200 mL/d is effective in both acute and chronic SIADH. However, patients with SIADH have normal thirst, so fluid restriction can discomfort the patient and may be difficult to maintain.^{14,15} Fluid restriction may be especially difficult to maintain in the ICU because of continuous infusions, IV antibiotics, and other medications as obligate intake for the patient.

Isotonic Saline

The primary treatment of CSW is fluid replacement with isotonic (0.9%) sodium chloride, or normal saline. The first step in treatment of CSW is to replace the intravascular volume and maintain a neutral fluid balance.¹³ The total fluid requirement for volume replacement can be calculated by starting with the sodium deficit, which is determined by subtracting the patient's sodium level from a normal sodium level (ie, 140 mEq/L) and then dividing by 2 (ie, [(140 – sodium) ÷ 2]). The next step is to calculate the total body sodium deficit on the basis of the size of the patient using the following formula: (sodium deficit × [0.6 × weight in kg]). The rate of sodium replacement should be about 0.5 mEq/h to avoid rapid correction; the sodium deficit (in mEq) ÷ 0.5 (target rate of sodium replacement in mEq/h) equals the number of hours over which the sodium should be replaced. Finally, the infusion rate of sodium chloride (in mL/h) is determined using the following formula: ([total body sodium deficit ÷ 0.154 mEq/mL] ÷ total hours). An example calculation is shown in Table 3. Once the patient is rehydrated, the euvoletic state can be maintained by matching fluid intake to the urine output. Although sodium chloride is the first-line treatment in CSW, it often does not fully correct the serum sodium level.

Salt Tablets

Oral salt tablets have been used in CSW to replace the sodium lost by the kidneys. The goal of treatment in CSW is to create a positive sodium balance in the patient. Sodium chloride tablets, up to 12 g/d in divided doses, have been used orally in CSW to correct the serum sodium level.¹⁶ The addition of salt tablets usually occurs if the serum sodium level is still low despite adequate volume repletion.

Hypertonic Saline

Renal sodium excretion remains intact in SIADH, so the sodium administered via IV fluid

Table 3: Example Calculation of Sodium Chloride Replacement in Cerebral Salt Wasting

Patient data for calculation

Serum sodium level = 124 mEq/L

Weight = 68 kg

Sodium deficit

$(140 - 124 \text{ mEq/L}) / 2 = 8 \text{ mEq/L}$

Total body sodium deficit

$8 \text{ mEq/L} \times (0.6 \text{ L/kg} \times 68 \text{ kg}) = 326.4 \text{ mEq}$

Total hours for correction

$8 \text{ mEq/L} \div 0.5 \text{ mEq/h} = 16 \text{ h}$

Infusion rate of sodium chloride

$(326.4 \text{ mEq} \div 0.154 \text{ mEq/mL}) \div 16 \text{ h} = 132.5 \text{ mL/h}$

will be excreted in the urine. This concept is different from fluid replacement in hypovolemia, where both the sodium and water are retained in the intravascular volume. For this reason, hypertonic saline is usually preferred to sodium chloride for SIADH. The osmolality of 3% sodium chloride, which is the most commonly used concentration of hypertonic saline, is 1027 mOsm/L, and the osmolality of sodium chloride is 308 mOsm/L. When sodium chloride is administered to a patient with SIADH, it can actually worsen the hyponatremia because the osmolality of sodium chloride is less than the osmolality of the patient's urine.

Hypertonic saline at a concentration of 3% or higher must be administered through a central catheter. A continuous infusion of 3% sodium can be administered at a rate of 0.5 mL/kg per hour to increase the serum sodium level approximately 0.5 mEq/L per hour. Serum sodium levels must be monitored very carefully during treatment with hypertonic saline, as the rate of sodium correction is sometimes variable and difficult to control. Hypertonic saline can also be used in CSW, with extra caution to prevent volume depletion. A concentration of 1.5% sodium chloride may be safer to use in patients with CSW, especially when the condition is caused by subarachnoid hemorrhage, to decrease the risk of volume depletion. However, hypertonic saline is rarely administered in patients with CSW.

Furosemide

Furosemide (Lasix), a loop diuretic, has been used for SIADH to promote excretion of excess water. It blocks the absorption of sodium and chloride in the kidney, causing excretion of sodium, chloride, and water. Furosemide, in combination with electrolyte replacement, has been shown to increase serum sodium values rapidly in patients with SIADH. This rapid correction is especially useful in those patients with acute hyponatremia.¹⁷ The use of furosemide for SIADH must be monitored carefully, and a balance must be achieved between the furosemide and salt intake. If the balance is shifted too far in either direction, the patient can be at risk of dehydration or fluid overload.

Demeclocycline

Demeclocycline can be used as a treatment for SIADH and has been used in chronic SIADH in an attempt to maintain normal serum sodium levels over the long term. Demeclocycline is a tetracycline antibiotic that works for SIADH by inducing nephrogenic diabetes insipidus (DI) in about 60% of patients. Diabetes insipidus is a condition characterized by decreased responsiveness to ADH, water excretion, and inability of the kidneys to concentrate urine. Demeclocycline causes DI by blocking the vasopressin (ADH) receptors in the kidney. Demeclocycline is available orally and is given at a dose of 600 to 1200 mg in divided doses for SIADH. The effect of demeclocycline is relatively unpredictable, working in less than two-thirds of patients, usually starting at days 2 to 5 of therapy.⁷ Demeclocycline can lead to azotemia and nephrotoxicity, especially in patients with hepatic failure and cirrhosis, and significant photosensitivity.

Lithium

Lithium has been used historically for SIADH. It works in the same manner as demeclocycline by causing nephrogenic DI, but it is even less predictable than demeclocycline, working in only about 30% of patients.¹³ Lithium is given orally, at a dose of 900 mg daily. Lithium was compared with demeclocycline for chronic SIADH in a small study of 10 patients for whom water restriction failed to correct the condition. Demeclocycline was shown to be superior to lithium in both efficacy and safety.¹⁸ Adverse effects of lithium are a significant limitation for its use, and patients must be monitored for symptoms. Lithium can cause CNS disturbance, including

loss of memory, extrapyramidal symptoms, and myasthenia gravis. It can also cause tremor, cardiac effects, electrolyte disturbances, nephrotoxicity, hypothyroidism, leukocytosis, weight gain, vomiting, diarrhea, and many other adverse effects.

Urea

Urea is an osmotic diuretic that has been used in SIADH because of its ability to increase water excretion by the kidneys. Urea has also been shown to decrease sodium excretion and help correct the hypotonic state associated with SIADH. Urea powder is administered orally at a dose of 30 g daily for SIADH and should be dissolved in water or a strongly flavored beverage (eg, orange juice) to help with the unpleasant taste.¹⁹ In some patients, urea is not completely effective in maintaining a normal sodium and water balance, but those patients are able to maintain an acceptable sodium level with more liberal fluid restriction.²⁰ Adverse effects of urea include nausea, vomiting, headache, disorientation, and azotemia.

Fludrocortisone

Fludrocortisone (Florinef) is a steroid that causes increased absorption of sodium by the kidneys and has been studied in hyponatremia. In a study of patients with subarachnoid hemorrhage, fludrocortisone was used to prevent sodium depletion and maintain a euvolemic state. Subjects were randomized to receive either fludrocortisone 200 mcg twice daily orally or intravenously or placebo. Fludrocortisone was significantly more effective than placebo in maintaining a negative sodium balance for the first 6 days and the full 12 days of treatment. Adverse effects included pulmonary edema, hypokalemia, and hyperglycemia.²¹ Fludrocortisone is available only in the oral formulation in the United States. It may be effective for CSW, but its use is limited by adverse effects.

Vasopressin Antagonists

The vasopressin V2 receptor antagonists are novel medications that are very effective for the treatment of hyponatremia. The 2 medications that are currently available in the United States are conivaptan (Vaprisol) and tolvaptan (Samsca). These medications work by binding to the V2 receptor in the kidney and blocking ADH (arginine vasopressin) from binding. This process causes excretion of free water; thus, these medications are referred to as aquaretics.

Both agents have been studied in SIADH,^{22–25} with the main difference being that tolvaptan is available for oral use, and conivaptan is available for IV use. Another difference is that conivaptan also blocks the V1a receptor, located in the vasculature, and can cause hypotension, although the clinical significance of this effect remains undetermined.

Both tolvaptan and conivaptan are effective in increasing the sodium level in patients with SIADH.^{22–25} Tolvaptan is given orally at a dose of 15, 30, or 60 mg daily, depending on the sodium levels. Adverse effects of tolvaptan include constipation, dry mouth, thirst, and increased urination.²² Conivaptan is given as a 20-mg IV bolus over 30 minutes, followed by a continuous infusion of 20 to 40 mg/d for up to 96 hours. The primary adverse effects of conivaptan are infusion-site reactions, edema, hypokalemia, increased urine output, and increased thirst.²³ Vasopressin antagonists should not be used in patients for whom CSW is suspected.

Conclusion

Hyponatremia is a common electrolyte abnormality seen in the ICU and can be a significant cause of morbidity and mortality. The management of SIADH and CSW in the ICU can be difficult, from the differentiation of the 2 disease states to the treatment, with minimal evidence to guide optimal treatment strategies. The primary treatment strategy for CSW remains isotonic fluid and sodium replacement. Current evidence suggests that hypertonic saline and vasopressin antagonists may be the most effective treatment strategies for SIADH in the ICU. Additional studies are needed to further determine optimal treatment of hyponatremia in critically ill patients.

REFERENCES

- DeVita MV, Gardenzswartz MH, Konecky A, Zabetakis PM. Incidence and etiology of hyponatremia in an intensive care unit. *Clin Nephrol*. 1990;34:163–166.
- Bennani SL, Abougal R, Zeggwagh AA, et al. Incidence, causes and prognostic factors of hyponatremia in intensive care [abstract only]. *Rev Med Interne*. 2003;24:224–229.
- Sherlock M, O'Sullivan E, Agha A, et al. Incidence and pathophysiology of severe hyponatremia in neurosurgical patients. *Postgrad Med J*. 2009;85:171–175.
- Oster JR, Singer I. Hyponatremia, hyposmolality, and hypotonicity: tables and fables. *Arch Intern Med*. 1999;159:335.
- Weisberg LS. Pseudohyponatremia: a reappraisal [review]. *Am J Med*. 1989;86:315–318.
- Aabakken L, Johansen KS, Rydningen EB, et al. Osmolal and anion gaps in patients admitted to an emergency medical department. *Hum Exp Toxicol*. 1994;13:131–134.
- Greenberg MS. *Handbook of Neurosurgery*. 6th ed. New York, NY: Thieme Medical Publishers; 2006:12–15.
- Ferri FF. *Practical Guide to the Care of the Medical Patient*. 8th ed. Philadelphia, PA: Mosby Inc, an affiliate of Elsevier Inc; 2011:529–530.
- Bourque CW, Oliet SH, Richard D. Osmoreceptors, osmoreception, and osmoregulation. *Front Neuroendocrinol*. 1994;15:231–274.
- Lehrich RW, Greenberg A. Hyponatremia and the use of vasopressin receptor antagonists in critically ill patients [published online ahead of print May 13, 2011]. *J Intensive Care Med*. doi: 10.1177/0885066610397016
- Arief Al, LLach F, Massry SG. Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. *Medicine*. 1976;55:121–129.
- Sterns RH, Riggs JE, Schochet SS Jr. Osmotic demyelination syndrome following correction of hyponatremia. *N Engl J Med*. 1986;314:1535–1542.
- Verbalis JG, Goldsmith SR, Greenberg A, et al. Hyponatremia treatment guidelines 2007: expert panel recommendations. *Am J Med*. 2007;120:S1–S21.
- Troyer AD, Demanet JC. Correction of antiuretic by demeclocycline. *N Engl J Med*. 1975;293:915–918.
- Smith D, Moore K, Tormey W, et al. Downward resetting of the osmotic threshold for thirst in patients with SIADH. *Am J Physiol Endocrinol Metab*. 2004;287:E1019–E1023.
- Betjes MG. Hyponatremia in acute brain disease: the cerebral salt wasting syndrome. *Eur J Intern Med*. 2002;13:9–14.
- Hantman D, Rossier B, Zohlman R, Schrier R. Rapid correction of hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone. An alternative treatment to hypertonic saline. *Ann Intern Med*. 1973;78:870–875.
- Forrest JN, Cox M, Hong C, et al. Superiority of demeclocycline over lithium in the treatment of chronic syndrome of inappropriate secretion of antidiuretic hormone. *N Engl J Med*. 1978;298:173–177.
- Decaux G, Brimiouille S, Genette F, et al. Treatment of the syndrome of inappropriate secretion of antidiuretic hormone by urea. *Am J Med*. 1980;69:99–106.
- Decaux G, Genette F. Urea for long-term treatment of syndrome of inappropriate secretion of antidiuretic hormone. *Br Med J*. 1981;283:1081–1083.
- Hasan D, Lindsay KW, Wijidicks EFM, et al. Effect of fludrocortisone acetate in patients with subarachnoid hemorrhage. *Stroke*. 1989;20:1156–1161.
- Schrier RW, Gross P, Gheorghiane M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med*. 2006;355:2099–2112.
- Zeltser D, Rosansky S, van Rensburg H, et al. Assessment of the efficacy and safety of intravenous conivaptan in euvoletic and hypervolemic hyponatremia. *Am J Nephrol*. 2007;27:447–457.
- Potts MB, DeGiacomo AF, Deragopian L, Blevins LS. Use of intravenous conivaptan in neurosurgical patients with hyponatremia from syndrome of inappropriate antidiuretic hormone secretion. *Neurosurgery*. 2011;69:268–273.
- Wright WL, Abury WH, Gilmore JL, Samuels OB. Conivaptan for hyponatremia in the neurocritical care unit. *Neurocrit Care*. 2009;11:6–13.