41st Critical Care Congress Review

Earn Continuing Education Credit at www.sccm.org/2012ConRev

Supported by education grants from Hospira, Inc., Otsuka America Pharmaceutical, Inc., and Optimer Pharmaceuticals, Inc.

Participants must respond to all evaluation and post-test questions to receive a statement of credit. A passing score of 70% is required to receive credit.

Learning Objectives

At the conclusion of this activity participants should be able to:

- Discuss approaches to screen for delirium and consider both pharmacologic and nonpharmacologic approaches to prevention and management.
- Discuss the importance, common causes and general approach to treatment of the critical care patient with decreased serum sodium.
- Discuss the emergence of resistant organisms in the intensive care unit, the risk factors and new treatment options to combat these pathogens.

Type of Activity

This activity was designed as an evidenced-based forum to review expert opinions of various topics in critical care. This activity will focus on increasing knowledge and its application to practice.

Competencies

SCCM supports recommendations that will promote lifelong learning through continuing education. SCCM promotes activities that encourage the highest quality in education that will enhance knowledge, competence or performance in critical care practice. This activity will meet the following:

- Patient- and Family-Centered Care
- Practice Applications
- Quality Improvement
- Multiprofessionalism

Target Audience

This continuing medical education offering is intended to meet the needs of all physicians, nurses, pharmacists, respiratory therapists and other providers who care for critically ill patients.

Physicians

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education by SCCM. SCCM is accredited by ACCME to provide continuing medical education for physicians. Earn Continuing Education Credit at www.sccm.org/2012ConRev Critical Care Congress Review

Designation Statement

The Society designates this home-study educational activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim credit commensurate with the extent of their participation in the activity.

Nurses

SCCM is approved by the California Board of Registered Nursing, Provider No. 8181 and approves this panel for 1 contact hour.

Pharmacists

The Society is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmaceutical education. This monograph will provide 1 continuing education hour. (0236-0000-12-225-H01-P). A certificate will be available for download once a passing score of 70% is obtained on the posttest.

For more information on the Congress Review, please contact SCCM at **education@sccm.org** or call **+1 847 827-6888**.

For additional information on these topics and other areas, please visit **www.learnicu.org**

CE/CME Enduring Material
Release Date: June 2012
Expiration date: June 2013

Disclosures

The content of this activity has been peer reviewed and has been approved for compliance. The faculty and contributors have indicated the following financial relationships, which have been resolved through an established conflict of interest resolution process and have stated that these reported relationships will not have any impact on their ability to provide unbiased content. The activity planner, Diane Alberson, and other employees of SCCM have no financial relationships to disclose.

Douglas B. Coursin, MD
University of Wisconsin
School of Medicine
Madison, Wisconsin, USA
No financial relationships

E. Wesley Ely, MD, FCCM
Vanderbilt University
Medical Center
Nashville, Tennessee, USA
Honoraria, Grant Support and Consulting: Hospira, Inc., Lilly, Cumberland, Masimo, Aspect

Sandra L. Kane-Gill, PharmD, MS, FCCM
University of Pittsburgh
School of Pharmacy
Pittsburgh, Pennsylvania, USA
No financial relationships

Marin H. Kollef, MD
Washington University
School of Medicine
St. Louis, Missouri, USA
Research Grants and Speakers Bureau: Merck, Cubist, Hospira, Inc.

Henry Masur, MD, FCCM
National Institutes of Health
Clinical Center
Bethesda, Maryland, USA
No financial relationships

Andrew J. Patterson, MD, PhD, FCCM
Stanford University
Stanford, California, USA
No financial relationships

Jose Javier Provencio, MD, FCCM
The Cleveland Clinic
Cleveland, Ohio, USA
No financial relationships

Denise Rhoney, PharmD, FCCM
The University of North Carolina
Eshelman School of Pharmacy
Chapel Hill, North Carolina, USA
Grant Support/Speaker Bureau: Otsuka America Pharmaceutical, Inc.

Mark E. Rowin, MD
The University of Tennessee
College of Medicine
Chattanooga, Tennessee, USA
No financial relationships

Andrew F. Shorr, MD
Washington Hospital Center
Georgetown University
Washington, DC
Consultant: Astellas

Robert D. Stevens, MD
Johns Hopkins University
School of Medicine
Baltimore, Maryland, USA
No financial relationships

Sodium Challenges in the Critically Ill Patient

Hyponatremia – a common yet underreported disorder in intensive care unit (ICU) patients – is linked to poor outcomes, including increased risk of death. Adding to its potentially deleterious effects is the fact that intensivists face challenges in recognizing and treating this electrolyte disturbance. Among the important treatment considerations are the need to determine the underlying cause, the patient's volume status, and whether the condition is acute or chronic.

The Epidemiology and Burden of Sodium Issues in ICU Patients

Presented by Andrew F. Shorr, MD, MPH, FCCP, FACP, a pulmonary and critical care physician at Washington Hospital Center and associate professor at Georgetown University in Washington, DC.

Supported by a medical education grant from Otsuka America Pharmaceutical, Inc.

Although more research is needed to clarify the role of hyponatremia treatment on outcomes, evidence shows that low sodium is common among critically ill patients and is associated with higher mortality rates, morbidity and costs. "The negative impact of hyponatremia is seen in multiple ICU settings and other areas of the hospital, and it persists after adjustment for multiple potential confounders," said Andrew Shorr, MD, MPH, FCCP, FACP.

In discussing epidemiologic findings regarding hyponatremia in ICU patients, Shorr began with a word of caution. "The literature shows patterns and trends, but does not necessarily demonstrate that the association is responsible for the measured outcome," he said. "Therefore, the fact that hyponatremia is linked to poor outcomes does not necessarily mean that correcting the sodium problem will always fix the outcome."

The incidence of hyponatremia among hospitalized patients was investigated in a multicenter retrospective study of nearly 200,000 hospitalizations (Zilberberg MD, et al. *Curr Med Res Opin*. 2008:24:1601). Results showed that 5.5% of all patients had hyponatremia, defined as a serum sodium concentration under 135 mEq/L. Hyponatremia was more common in older patients and those with comorbidities. ICU admission, need for mechanical ventilation and hospital mortality rates were significantly higher among patients who had hyponatremia on hospital admission versus those who did not.

"The analysis also showed that having hyponatremia is independently associated with one extra day in the hospital," said Shorr. Moreover, adjustment for confounders (e.g., disease severity, underlying comorbidities, age) revealed an independent relationship between hyponatremia and ICU admission, need for mechanical ventilation or hospital mortality.

Another study employed a different approach, using a higher defining threshold of less than 138 mEq/L serum sodium (Wald R, et al. *Arch Intern Med*. 2010;170:294). The investigators analyzed data on 53,000 patients admitted to one hospital system over a seven-year period, looking at three hyponatremia subtypes: community-acquired (present on admission), hospital-aggravated (present on admission, then fell lower within the first 48 hours of admission), and hospital-acquired (evolved 48 hours post-admission). About 38% of the patients had community-associated hyponatremia, 6% had hospital-aggravated hyponatremia and 38% had hospital-acquired hyponatremia.

"These findings tell me we need to pay attention to this, because we currently approach this disease state very differently in our minds," said Shorr. "When hyponatremia is present on admission, we tend to be very aggressive about considering it. But, when it appears around day three, four, or five, and we're worried about other issues, we often miss it. Therefore, I think it's important to readjust our mindset."

Other data from the study – obtained after analyzing various sodium levels in terms of hospital mortality, discharge location, and hospital length of stay and adjusting for confounders – demonstrated a strong correlation between lower sodium levels and poor outcomes. "This supports the biologic hypothesis that sodium is, in fact, causally linked to poor outcomes," noted Shorr.

Investigators have also looked at a particular disease state to determine whether a pattern exists among a more homogeneous population, thereby substantiating biological reasons for focusing on sodium issues. Shorr described an analysis of about 8,000 patients admitted to the hospital with hyponatremia, defined as sodium levels below 135 mEq/L (Zilberberg MD, et al. *BMC Pulm Dis*. 2008;8:16). "We found that patients who had pneumonia and low sodium on hospital admission were nearly two times more likely to be admitted to the ICU or end up on mechanical ventilation," he reported. This was true after adjusting for age, gender, race, region, teaching hospital, admission source, payer, and comorbidities.

"We also looked at independent resource utilization, and found that length of ICU stay increased about eight-tenths of a day and hospital stay increased about one-third of a day among this patient population," Shorr added. "This resulted in increased hospital costs of $1,324 per patient."

Epidemiologic research has also analyzed hyponatremia prevalence in different types of ICUs (medical, surgical and neuro/trauma). In a study that defined hyponatremia as sodium levels below 133 mEq/L and hypernatremia as over 145 mEq/L, results showed a lower incidence of hyponatremia than hypernatremia in various ICUs (Stelfox HT, et al. *Crit Care*. 2008;12:R162). Hypernatremia occurred in 3% of all ICU admissions, fluctuating substantially over the ICU stay. "Several variables were associated with ICU-acquired hyponatremia, many of them related to neurologic status and disease severity," said Shorr.

European data from medical, surgical and mixed ICUs over 10 years indicate that nearly 15% of about 150,000 patients had mild to moderate hypernatremia (Funk GC, et al. *Intensive Care Med*. 2010;36:304). "About 8% of patients had sodium levels that would scare all of us, so this is more serious and prevalent a disease than we typically assess," emphasized Shorr. As with other studies, this investigation found that mortality rates increased as sodium levels decreased. "The risk of hyponatremia nearly doubled the risk of hospital mortality."

A retrospective Canadian study examining acquired sodium disorders among patients in the cardiac surgery ICU found a higher incidence of hyponatremia than hypernatremia (Stelfox HT, et al. *Can J Anaesth*. 2010;57:650). The incidence peaked early and then declined. "Sodium issues, either high or low, occurred in about 11% of the more than 8,000 patients, many of whom were undergoing a bypass without necessarily a valve replacement," said Shorr.

The study also showed that hyponatremia is associated with poor outcomes in ICU/ hospital length of stay and renal replacement therapy. Both hypo- and hypernatremia were linked to higher mortality rates.

In reviewing the implications of epidemiologic evidence, Shorr concluded: "Although the observational nature of these data does not provide a causal link, clinicians need to consider the findings overall." He also noted that research is needed to shed light on how treatment of hyponatremia in the ICU might alter outcomes.

Hyponatremia: What Causes It, How Do We Treat It?

Presented by Denise H. Rhoney, PharmD, FCCP, FCCM, associate professor and chair in the Division of Pharmacy Practice and Experimental Education at The University of North Carolina Eshelman School of Pharmacy in Chapel Hill, North Carolina, USA.

The consequences of hyponatremia in hospitalized patients are numerous, ranging from longer hospital stays and increased ICU admissions to medical concerns relating to neurologic dysfunction, gait disturbances, osteoporosis, cerebral edema, seizures, coma, and increased risk of mortality. "It's not surprising, then, that the direct costs of hyponatremia are substantial, estimated to be $1.6 to $3.6 billion annually," said Denise H. Rhoney, PharmD, FCCP, FCCM.

Multiple medical conditions, many present in critically ill patients, increase the risk of developing hyponatremia. Among these are congestive heart failure, cirrhosis, syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH), very young or very old age, adrenal insufficiency, hypothyroidism, renal dysfunction, central nervous system (CNS) impairment, surgery, and injury. In addition, many medications can induce hyponatremia.

"Despite its common occurrence in the hospital and ICU, hyponatremia appears to be underreported and improperly coded," noted Rhoney. In one study, two thirds of more than 2,600 cases of hyponatremia did not have an appropriate International Classification of Diseases (ICD-9) code (Movig KL, et al. *J Clin Epidemiol*. 2003;56:530).

One reason for this underreporting may be that hyponatremia often has an asymptomatic presentation. "The symptoms of hyponatremia can be viewed in terms of severity (see Table 1) and in terms of acute versus chronic," said Rhoney. The majority of patients with hyponatremia have a mild decline in serum sodium (130 to 135 mEq/L), which is either asymptomatic or manifested by subtle, nonspecific symptoms common to many hospitalized patients. "In the ICU, mild hyponatremia is difficult to recognize because many of its symptoms might be masked," stated Rhoney.

In moderate hyponatremia (serum sodium 120 to 130 mEq/L), the clinical presentation includes additional nonspecific symptoms (e.g., malaise, unsteadiness). With even further acute declines (serum sodium <120 mEq/L), nonspecific symptoms may persist while overt symptoms become more apparent. Rapid sodium declines can provoke restlessness and lethargy that may progress to seizures, coma, brainstem herniation, respiratory arrest, and death.

Symptoms differ in acute and chronic hyponatremia. With the onset of hyponatremia and development of hyposmolarity, cerebral swelling occurs. In an acute onset, water moves across osmotic gradients, causing more symptomatic cerebral edema. Cerebral swelling exceeding about 8% of skull capacity leads to herniation and death.

In chronic hyponatremia, little cerebral edema occurs due to compensatory volume regulation mechanisms. "However, patients with chronic hyponatremia are at increased risk of overcorrection because these volume-regulating mechanisms can dehydrate the brain with the development of osmotic demyelination," Rhoney said. "They also have a greater risk of falls due to gait disturbances and attention impairment."

The classification of hyponatremia is based on serum sodium concentration, serum osmolality and body volume status. Serum osmolality indicates whether the patient has hyperosmolar, normal osmolar or hypoosmolar (the most common) hyponatremia. Volume status determines whether the patient has hypervolemia, euvolemia or hypovolemia. Euvolemia is the most common type of hyposmolar hyponatremia, occurring primarily in SIADH. It is typically associated with increased total body water, essentially unchanged total body sodium and no edema.

Hyponatremia can be attributed to various etiologies. The antidiuretic hormone arginine vasopressin (AVP), which regulates body water balance, plays a central role in the pathogenesis of hyponatremia (see Figure 1). Excessively high levels of AVP override the osmotic regulation of AVP and can cause hyponatremia. AVP is present at high levels in SIADH.

Common causes of SIADH include a multitude of CNS disorders, pulmonary diseases, tumors, and drugs. "Drugs are indeed a common cause of hyponatremia, yet few cases are recognized as drug-related," noted Rhoney. Some commonly implicated agents are diuretics, nonsteroidal anti-inflammatory agents (NSAIDs), opioid derivatives, tricyclic antidepressants, selective serotonin reuptake inhibitors, antipsychotics, and antiepileptics. Antihypertensive agents and proton pump inhibitors are less commonly involved.

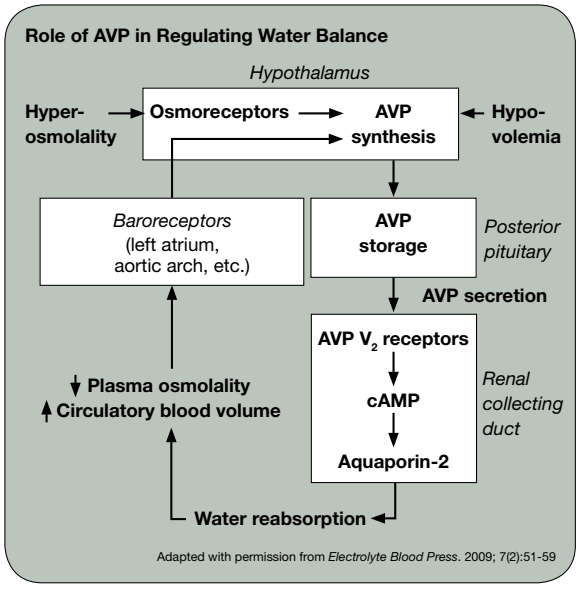
"Drug-induced hyponatremia can result from one of three major

Table 1.

Common Symptoms Associated With Hyponatremia

Serum [Na^+] 130–135 mEq/L	Serum [Na^+] 120–130 mEq/L	Serum [Na^+] <120 mEq/L
• Asymptomatic • Headache • Nausea • Vomiting • Fatigue • Anorexia • Muscle cramps • Depressed reflexes	• Malaise • Unsteadiness • Headache • Nausea • Vomiting • Fatigue • Confusion • Anorexia • Muscle cramps	• Headache • Restlessness • Lethargy • Seizures • Brainstem herniation • Respiratory arrest • Death

Data were derived from Bagshaw SM et al. *Can J Anesth*. 2009; 56:151-167 and adapted with permission from S. Karger AG. Basel. Ghali JK. *Cardiology*. 2008; 111:147-157



Adapted with permission from *Electrolyte Blood Press*. 2009; 7(2):51-59

Figure 1.

mechanisms," Rhoney explained. "The first is increased hypothalamic production of AVP, as seen with antidepressants, antipsychotics, antiepileptics, and opiates. The second involves altered homeostasis in the kidney, which primarily occurs with diuretics. The third involves an increased vasopressin effect in the renal tubule, and this is associated with some common antidiabetic agents, antiepileptics and NSAIDs."

Treatment of hyponatremia depends on several factors, including the underlying pathophysiology, the patient's volume status, presence of symptoms, and severity and duration of symptoms. "It's important to consider the severity of the neurologic symptoms, and whether the hyponatremia is acute or chronic, because this will direct how fast you treat the patient," said Rhoney. "Certainly, you also need to monitor sodium frequently, address the underlying disease and remove any offending medication."

Appropriate hyponatremia treatment requires recognition that both overly rapid correction and no correction can be harmful. "Treatment considerations include a risk-benefit assessment," Rhoney said. "The risk of insufficient correction is worsening of cerebral edema and worsening of the symptoms. On the other hand, too aggressive of a correction can result in osmotic demyelination syndrome."

The literature contains upper-limit recommendations for treatment of chronic hyponatremia (Sterns RH, et al. *Semin Nephrol*. 2009;29:282). In general, correction should not exceed 10 mEq/L in the first 24 hours, 18 mEq/L in 48 hours, or 20 mEq/L in 72 hours; these are limits, not therapeutic goals. To maximize patient safety, the goals of therapy should be more modest: 6 to 8 mEq/L per 24 hours, 12 to 14 mEq/L per 48 hours, and 14 to mEq/L 16 per 72 hours.

"We know that hyponatremia is mismanaged, and many cases are never identified," stated Rhoney. The various management errors reported for hyponatremia include illogical treatment, such as fluid restriction and intravenous saline given together (Huda MS, et al. *Postgrad Med J.* 2006;82:216).

The therapies traditionally available in hyponatremia include saline, fluid restriction, demeclocycline, loop diuretics, lithium, urea, and AVP receptor antagonists. Lithium is not used, primarily because of toxicities. Demeclocycline is not approved by the U.S. Food and Drug Administration (FDA) for hyponatremia, although it can be used in chronic asymptomatic hyponatremia when loop diuretics and fluid restriction have failed. Urea is rarely used in the United States due to its poor palatability. "That leaves us with saline, fluid restriction and AVP receptor antagonists – the most common approaches used today," said Rhoney.

Hypertonic saline is appropriate in symptomatic patients with concentrated urine. Its onset is rapid and it is recommended for severely symptomatic patients, such as those seizing or in a coma. Saline can be combined with a loop diuretic. Disadvantages include the need for monitoring to prevent drug errors and for performing complex calculations due to a high risk of overcorrection.

Fluid restriction is inexpensive and effective, but is slow to produce a response. "In an ICU population, where fluid restriction could do more harm, this would not be an ideal approach," said Rhoney.

AVP receptor antagonists (also called vaptans) represent a new therapeutic option for hyponatremia. These agents directly target the underlying pathophysiology (i.e., elevation of plasma AVP), competitively binding to the V2 receptor in the renal-collecting duct and preventing activation. Intravenous conivaptan and oral tolvaptan are the only AVP antagonists approved for euvolemic and hypervolemic hyponatremia in the United States. A newer agent, lixivaptan, is not yet FDA-approved. Because all three agents are metabolized using the cytochrome P450 3A4 isoenzyme, significant drug-drug interactions occur.

In summing up treatment considerations, Rhoney emphasized: "No one treatment fits all. Each patient must be evaluated independently, and it's important to determine the underlying cause of the hyponatremia." Treatment will largely depend on the etiology, symptom severity and duration of the hyponatremia.

Managing SIADH and the Neurocritical Care Patient

Presented by Jose Javier Provencio, MD, FCCM, director of the Neurocritical Care Fellowship Program at The Cleveland Clinic in Cleveland, Ohio, USA, and chair of the Neuroscience Section for the Society of Critical Care Medicine.

"For the neurocritical care patient, evaluating hyponatremia can be a conundrum, because a number of entities in the neuro ICU can affect sodium levels," said Jose Javier Provencio, MD, FCCM. In addition, patients with brain injuries are particularly at risk for complications due to hyponatremia. The major risks associated with hyponatremia in neurocritical care patients are cerebral edema and seizures. "People with previously known seizure disorders are far more likely to have seizures if their sodium falls. This is often made more challenging because many anticonvulsant agents are strong precipitators of SIADH," he noted.

In the evaluation of a neurologic ICU patient for suspected hyponatremia, the differential diagnosis includes SIADH, cerebral salt-wasting, naturesis associated with renal disease, and medications. A number of conditions in the neurologic ICU can lead to development of SIADH. These include brain injuries (e.g., brain tumors, meningitis, brain trauma, and subarachnoid hemorrhage/intracerebral hemorrhage), peripheral nerve injuries (e.g., Guillain-Barré syndrome), and medications (e.g., antiepileptics, opiates). "Whereas, in non-neurologic ICUs, physicians may be more apt to attribute most hyponatremia to SIADH, in the neuro ICU, low sodium levels can often reflect other water regulation problems including – most commonly – a condition known as cerebral salt-wasting," noted Provencio.

Cerebral salt-wasting was discovered in 1950 by Peters et al (Peters JP, et al. *Trans Assoc Am Physicians*. 1950;63:57), who described a syndrome in which three patients with neurologic injury had profound loss of sodium and volume depletion early in their course. Seven years later, Schwartz et al wrote the original description of SIADH, first observed in pulmonary conditions and later in several neurologic conditions (Schwartz WB, et al. *Am J Med*. 1957;23:529). At that point, cerebral salt-wasting was discounted and SIADH was believed to be the exclusive cause of ICU hyponatremia.

"In the 1970s and 1980s, however, cerebral salt-wasting captured renewed interest, largely precipitated by the way subarachnoid hemorrhage was treated at that time," explained Provencio. Patients with subarachnoid hemorrhage were routinely deprived fluids in an attempt to control cerebral edema (a strategy that we now know to be incorrect). An important study by Wijdicks et al showed that patients with subarachnoid hemorrhage and hyponatremia treated with volume restriction had a much greater chance of stroke and death. Pivotal research later revealed different patterns of urine output for patients with subarachnoid hemorrhage and those with brain tumors (Berendes H, et al. *Lancet*. 1997;349:245). This study showed that no appreciable changes in urine output occurred in the brain tumor group (likely with SIADH) despite declining sodium levels, whereas increased diuresis concomitant with declining sodium (naturesis) occurred in the subarachnoid hemorrhage group (likely representing cerebral salt-wasting).

"The results seen with subarachnoid hemorrhage were not what one would expect in SIADH," said Provencio. In these patients, *urine* sodium concentrations rose rapidly, peaked around day four, and then began to decline. "The problem," he noted, "is that by the time patients become severely hyponatremic, their urine sodium concentration has usually returned to normal levels, making cerebral salt wasting difficult to diagnose."

Cerebral salt-wasting – defined as acute, intermittent, excessive dieresis of salt and water – appears within the first week of CNS injury and may persist for two to four weeks. Serum sodium concentrations can be less than 130 mEq/L, and urine sodium concentrations are typically high (>80 mEq/L) early. The urine/plasma osmolality ratio is greater than 1, and often greater than 2, distinguishing it from SIADH. A negative water and salt balance is typical in cerebral salt wasting.

"Serum sodium concentration is one of the major differences between cerebral salt-wasting and SIADH, which has a 'basement effect,'" said Provencio. "If SIADH progresses to its nadir without intervention, typically the patient's serum sodium will bottom out at approximately 130 mEq/L, or perhaps a little less. This differs from cerebral salt-wasting, where serum sodium continues to fall unless it is corrected. In our institution, we have seen levels as low as 103 mEq/L. For patients who are at risk of brain ischemia, hypovolemia due to cerebral salt-wasting is an important concern. If cerebral salt-wasting is not treated in a timely manner, the results can be very serious."

The favored hypothesis regarding etiology of cerebral salt-wasting implicates natriuretic peptides in the pathogenesis of cerebral salt-wasting (Diringer MN, et al. *Stroke*. 1991;22:577; Tomida M, et al. *Stroke*. 1998;29:1584). Investigators theorize that an increased release of brain natriuretic peptide (BNP) produces isotonic volume loss, which causes volume depletion. Volume depletion may trigger vasopressin release, causing free water retention despite hypotonicity.

"A common misconception in the neuro ICU is that all patients with neurologic disease develop cerebral salt-wasting," said Provencio. "Another misconception is that SIADH does not exist in our patient population. These misconceptions end up being very problematic." Despite scarce data to support his views, Provencio offered his own impressions, noting that cerebral salt-wasting is a disease of acute, severe neurologic injury that affects the hypothalamus. "Cerebral salt wasting is typically not seen in stroke or mild trauma. Rather, we see it in patients with subarachnoid hemorrhage, massive head trauma, or temporal lobe epilepsy. It is likely that the irritation or disruption of the hypothalamic pathways leads to the cerebral salt wasting."

Because cerebral salt-wasting typically occurs during the first week of injury, "it is an ICU problem," stated Provencio. "It's not something you see in the subarachnoid hemorrhage patient who suddenly becomes hyponatremic two weeks into hospitalization."

The diagnosis of cerebral salt-wasting can be very difficult, as mentioned. In distinguishing cerebral salt-wasting from SIADH, the ultimate difference is seen in plasma volume: it is low in cerebral salt wasting, and either normal or elevated in SIADH. Unfortunately, clinical signs of volume depletion including serum sodium concentration and urine sodium concentration are similar in both conditions, whereas net sodium loss is high in cerebral salt-wasting and low in SIADH. Only continuous monitoring of urine sodium levels is sensitive enough to find this difference in sodium loss between the two entities. "Interestingly, serum uric acid can be normal in cerebral salt-wasting and low in SIADH, but nephrologists believe uric acid levels can be normal in SIADH," said Provencio. Other laboratory parameters may not always be definitive, according to Provencio. "The tests typically done for outpatients to enable clinicians to say, 'this person is dry, this person is not dry,' do not work for ICU patients with subarachnoid hemorrhage," he said. "We often are unable to determine whether a patient is euvolemic or hypovolemic, and without that information we can't make the diagnosis."

Treatment of cerebral salt wasting requires replacement of both sodium and water. This can be done orally, although it is less effective than 2% or 3% intravenous hypertonic saline. The role of AVP receptor antagonists in cerebral salt-wasting is unclear. For patients with subarachnoid hemorrhage in the periods of vasospasm, for whom it is difficult to distinguish cerebral salt wasting from SIADH, 3% hypertonic saline will correct the sodium level.

Provencio discussed common mistakes he sees in his practice, including what he calls the syndrome of generalities. "I think it's unfortunate to treat all neuro ICU patients who have low serum sodium levels with concentrated salts," he said. "You have to know when you can and when you can't make the definitive diagnosis of the cause of hyponatremia. It is difficult to do early in the course of subarachnoid hemorrhage, but with other diseases – such as brain tumors – and later in subarachnoid hemorrhage, you can. That's when appropriate treatment is indicated." On a separate but related note, once the diagnosis of SIADH or cerebral salt-wasting is made, determining how quickly to correct low sodium concentrations ultimately is a neurologic issue because the major complication is in the brain. Osmolar demyelination syndrome (ODS), a potentially life-threatening event, is not common in the ICU, even with overcorrection of low sodium levels. ODS occurs in chronic, but not acute, hyposmolality (most cases in the ICU are acute).

Acute hyposmolality, defined as developing over hours, produces an electrolyte osmolar gradient across the membranes, driving extracellular water intracellularly. In the first seven or so hours, when hyponatremia is developing, water rushes into the brain to equalize the tonicity. In response, the brain moves electrolytes like sodium out of cells to the blood to help return brain homeostasis. If this system is overwhelmed, cerebral edema results. While other organs can swell with minimal functional consequences, the brain has limited tolerance for increased volume before intracranial pressure rises.

Over the ensuing one to three days, if the gradient continues to exist and the brain has moved all of the electrolytes it can, the brain begins to expel organic osmolytes, which serves to equalize the brain water content. "The problem is that if hyponatremia persists, the cells are solute-depleted (particularly for these large organic osmolytes)," said Provencio. Organic osmolytes, unlike electrolytes, cannot freely enter the protected space inside the blood brain barrier. "When the sodium level is corrected quickly, the reversed sodium gradient results and water rushes out. The cells contract quickly because they cannot pull in enough of the organic osmolytes. The rapid cell contracture causes destruction of the myelinating cells as well as neurons and other glia. This is the osmolar demyelination syndrome."

Continuing Education Self-Assessment

Sodium Challenges in the Critically Ill Patient

3. Which of the following treatments for hyponatremia is recommended for patients who are severely symptomatic?
   a. AVP receptor antagonist plus demeclocycline
   b. AVP receptor antagonist plus loop diuretic
   c. Hypertonic saline
   d. Lithium

4. Cerebral salt-wasting is atypical in which of the following conditions?
   a. Massive head trauma
   b. Stroke
   c. Subarachnoid hemorrhage
   d. Temporal lobe epilepsy