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Vol. 25, Issue 8, November 2017
AHCMedia.com

# Critical Care [ALERT]

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SPECIAL FEATURE

# Hyponatremia in the Critically Ill

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**Drs. Lopez Ruiz and Niven report no financial relationships relevant to this field of study.**

Hyponatremia (serum sodium [Na] < 135 mmol/L) is the most common electrolyte disorder encountered in hospitalized patients (30-40%) and is present in 17.7% of patients admitted to the ICU.[1,2] A recent registry demonstrated significant practice variation regarding this common disorder, underlining the frequent diagnostic and therapeutic challenges clinicians face in this area.[3]

## ETIOLOGY AND CLINICAL SIGNIFICANCE

Mortality increases in critically ill patients with hyponatremia, with adjusted odds ratios of 1.89 (95% confidence interval [CI], 1.71-2.09) and 1.81 (95% CI, 1.56-2.10) in the presence of mild (125-129 mmol/L) or severe (< 125 mmol/L) cases.[3] The heterogeneous disease states that lead to hyponatremia underline the fact that this syndrome is a secondary pathophysiologic process due to a disturbance in water homeostasis rather than a distinct disease entity. Careful assessment and classification is important to direct diagnosis and treatment, reduce the risk of substantial morbidity and mortality in acute severe cases, and avoid the neurological complications associated with overly rapid correction.[4] In the ICU, hyponatremia is associated most frequently with chronic conditions such as congestive heart failure, advanced renal disease, and cirrhosis. Acute symptomatic hyponatremia (coma, seizures) or subacute cases (mild to moderate altered mental status) commonly are due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH), central nervous system disorders, and drugs such as narcotics, haloperidol, cyclophosphamide, thiazides, 3,4-methylenedioxymethamphetamine (ecstasy), or desmopressin.[5]

## PATHOPHYSIOLOGY AND CLINICAL FEATURES

Decreased extracellular compartment osmolarity in hyponatremic patients creates an osmotic gradient relative to the intracellular space causing water influx into cells and resulting expansion. In the brain, a compensatory process occurs, first through decreases in intracellular electrolytes ($K^+$ and $Cl^-$) and then extrusion of organic solutes (including inositol, taurine, creatine, and glutamine) over the course of the next 24-72 hours to decrease brain water content. Brain edema occurs when

**Financial Disclosure:** *Critical Care Alert*'s Physician Editor Betty Tran, MD, MSc, Nurse Planner Jane Guttendorf, DNP, RN, CRNP, ACNP-BC, CCRN, Peer Reviewer William Thompson, MD, Executive Editor Leslie Coplin, Editor Jonathan Springston, and AHC Media Editorial Group Manager Terrey L. Hatcher report no financial relationships relevant to this field of study.

Critical Care [ALERT]
Authoritative, evidence-based summaries for the critical care clinician

*Critical Care Alert,* (ISSN 1067-9502) is published monthly by AHC Media, a Relias Learning company, 111 Corning Road, Suite 250, Cary, NC 27518

Periodicals Postage Paid at Atlanta, GA, and at additional mailing offices.

GST Registration Number: R128870672.
**POSTMASTER: Send address changes to *AHC Media, LLC, P.O. Box 74008694, Chicago, IL 60674-8694***



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the inflow of water exceeds the compensatory mechanism.[6] Reversal of the brain's adaptive process is slower and less efficient (three to seven days). During hyponatremia correction, extracellular compartment osmolarity increases, resulting in movement of water from the intracellular space. Rapid correction of hyponatremia can lead to effective dehydration of brain cells and demyelination.[7]

Patients with chronic hyponatremia frequently are asymptomatic, although data suggest that mild neurologic deficits, such as increased falls, may be common. Mild symptoms of hyponatremia include headache, difficulty concentrating, impaired memory, muscle cramps, weakness, and dysgeusia.[8] Severe hyponatremia exhibits serious sequelae, especially when the condition develops rapidly (within 48 hours). Symptoms include confusion, hallucinations, seizures, coma, decerebrate posturing, and respiratory arrest, leading to death.[9]

### DIAGNOSTIC APPROACH AND CLASSIFICATION

The diagnostic approach to hyponatremia is summarized in Figure 1. Initial evaluation should include a careful history and physical exam to determine the potential etiology and time course of illness. Pseudohyponatremia (falsely low sodium with normal plasma osmolality) is a laboratory artifact that may occur with high triglycerides (> 1,000 mg/dL) or hyperproteinemia (> 10 g/dL). Electrolytes are measured routinely by indirect potentiometry, a dilution method that assumes water constitutes 93% of the sample plasma volume. To avoid this artifact, sodium should be measured by ion-selective electrode using direct potentiometry.[10]

Hyperglycemia usually causes nonhypotonic hyponatremia. Depending on its severity and the degree of osmotic diuresis, patients may develop isotonic (glucose 300-700 mg/dL) or hypertonic (glucose > 800 mg/dL) hyponatremia.[11] Hypertonic hyponatremia also has been described with mannitol, intravenous immunoglobulin (IVIG), or hypertonic radiocontrast. In these settings, management usually is conservative.

Physical exam findings (presence of edema, ascites) of hypervolemic hyponatremia usually are obvious, but differentiation of hypovolemic and euvolemic hyponatremia based on clinical assessment is notoriously difficult (sensitivity 50-80%, specificity 30-50%).[12-14] Recent recommendations support an algorithm that prioritizes urine osmolality ($U_{Osm}$) and urine sodium concentration ($U_{Na}$) over volume status assessment.[15] $U_{Osm}$ accurately reflects arginine vasopressin (AVP) hormone activity, offering better diagnostic performance and outcomes.[16] A rise in serum sodium after isotonic saline volume challenge also supports the diagnosis of hypovolemic hyponatremia, although this also can occur in SIADH patients if the stimulus for vasopressin release was transient (nausea, pain, or hypoxia) or $U_{Osm}$ < 500 mOsm/kg.[17]

Hypotonic hyponatremia with maximally dilute urine ($U_{OSM}$ < 100 mOsm/kg) suggests that AVP is not a contributing factor. Common causes in this setting include excessive fluid intake and/or low solute intake (psychogenic polydipsia, beer potomania). It is worth noting that normal saline resuscitation in patients with hypovolemic hyponatremia may suppress AVP, resulting in excretion of excess free water and a low urine osmolality.

Other causes of hypotonic hyponatremia remain traditionally classified into hypovolemic, euvolemic, and hypervolemic categories. In hypovolemic hyponatremia, the patient has a deficit in total body water with disproportionate sodium loss commonly due to renal ($U_{Na}$ > 30 mmol/L) or extrarenal ($U_{Na}$ < 30 mmol/L) losses from vomiting, diarrhea, pancreatitis, or burn injury.[18] Cerebral salt wasting (CSW) is a rare (< 6.5 %) cause of hypovolemic hyponatremia (central venous pressure < 5 cm $H_2O$, hypotension) with $U_{Na}$ > 40 mmol/L in the setting of intracranial disease.[19,20] Careful attention to the onset of hyponatremia, including the urine sodium excretion and volume status, is important in distinguishing CSW from SIADH.[19]

The most common cause of euvolemic hyponatremia in hospitalized patients is SIADH, a condition characterized by increased release of AVP or potentiation of its effects on renal vasopressin ($V_2$) receptors independent of plasma osmolality.[20] (*See Table 1.*) Patients classically present with low $S_{Osm}$, $U_{Na}$ > 30 mmol/L, and abnormally high (higher than serum) $U_{Osm}$ (> 100 mOsm/kg). Serum uric acid level < 4 mg/dL, fractional excretion of uric acid ($FE_{UA}$) >12% (independent of the use of diuretics), and fractional excretion of urea ($FE_{Urea}$) > 55% all have excellent positive predictive value for a diagnosis of SIADH.[20,21]

Patients with hypervolemic hyponatremia suffer from systemic arterial underfilling, resulting in increased beta-adrenergic activity, non-osmotic AVP release, activation of the renin-angiotensin-aldosterone system, and increases in sodium and water reabsorption. Because the renal response to low effective arterial blood volume is sodium retention, $U_{Na}$ < 30 mmol/L is common in this setting.[22]

## TREATMENT

Because of brain compensatory mechanisms, 48 hours is used commonly to differentiate acute from chronic hyponatremia. In daily practice, this distinction is difficult because the time of hyponatremia onset usually is unknown. Symptom presence and severity commonly drive treatment selection. Current guidelines recommend hypertonic saline (typically 3% saline) for acute or symptomatic hyponatremia.[4,16] Hypertonic saline will reverse cerebral edema rapidly, and may be combined with loop diuretics in patients with hypervolemic hyponatremia.[16] The Adrogué-Madias formula[9,10] can estimate the volume required to reach a predefined increase in serum sodium, but current recommendations favor the use of fixed boluses for rapid, partial, and lifesaving correction (3-4 mmol/L) of sodium for acute, life-threatening symptoms to reduce the risk of overcorrection.[4,9,16] In patients with life-threatening symptoms, 100 mL bolus of 3% saline (513 mmol/L) over 10 minutes predictably will increase serum sodium by 1-2 mmol/L, and can be repeated up to three times or until symptoms resolve.[23,24] An initial 4-6 mmol/L increase in sodium concentration can reduce intracranial pressure by 50% and frequently resolve neurologic symptoms.[25] Previous reports in adults with severe traumatic brain injury or post-traumatic hypotension have shown that 3% saline administered via peripheral access is safe.[26,27] When symptoms are less severe, 3% saline infusion at a rate of 1-2 mL/kg per hour can be used to increase the serum sodium by 1-2 mmol/L per hour.[20] Potassium replacement will cause an increase in sodium, and should be considered when calculating the projected rate of correction.[10] Serum sodium should be checked every two hours and the rate of the infusion adjusted accordingly based on the rate of change.

Less symptomatic patients with hyponatremia should be managed based on their underlying condition. The minimum goal of correction of chronic hyponatremia is 4-8 mmol/L per day, with a maximum of 10-12 mmol/L in the first 24 hours and 18 mmol/L over the first 48 hours.[4,16] A lower limit of 6-8 mmol/L per day has been proposed in patients at high risk for osmotic demyelination syndrome (ODS), such as those with chronic serum sodium < 120 mmol/L, alcoholism, hepatic failure, orthotopic liver transplantation, potassium depletion, and malnutrition regardless of symptom duration.[10]

Patients with hypovolemic hyponatremia can be treated with normal saline and hypervolemic hyponatremia with diuretics with serial serum sodium every four to six hours. The treatment of other causes of chronic hyponatremia relies on reducing free water intake and/or increasing renal free water excretion. Free water restriction (< 1 L/d) is effective in 59% of SIADH patients.[20,28] The urine to serum electrolyte ratio ($[U_{Na} + U_K]/S_{Na}$) indicates if the patient is in an antidiuretic or aquaretic phase and can help estimate the degree of fluid restriction required to increase $S_{Na}$.[31]

A $U_{Na} \geq 130$ mmol/L and $U_{Osm} \geq 500$ mOsm/kg predict a poor response to this therapy.[28] These patients require pharmacologic therapy to increase renal free water excretion, using loop diuretics, vasopressin receptor antagonists, urea, and demeclocycline. Vasopressin receptor antagonists block AVP type 2 receptors in the collecting system, inducing aquaresis and increasing $S_{Na}$ in patients with SIADH, heart failure, or cirrhosis. Their role in the treatment of hyponatremic critically ill patients remains unclear.[30] Current recommendations do not support their use in acute, severe ($S_{Na}$ < 125 mmol/L), or severely symptomatic hyponatremic patients at risk for ODS, as these drugs cause a slow, unpredictable increase in $S_{Na}$.[4,16] In certain cases of euvolemic or hypervolemic hyponatremia with concern for rapid correction or volume overload with saline, oral tolvaptan can increase $S_{Na}$ 5-6 mmol/L after 30 days of therapy[29] and IV conivaptan 6-9 mmol/L within four days.[32] Conivaptan exhibits a higher rate of overcorrection and ODS.[32] Urea is a new therapeutic tool that induces an osmotic diuresis and renal free water excretion. Interestingly, vaptans and urea demonstrate a similar efficacy and side-effect profile. Although urea does not prevent overcorrection, it may reduce the risk of associated brain injury.[30] Demeclocycline decreases $U_{Osm}$ by downregulating the activity of aquaporin.[2] Nephrotoxicity is common, particularly in cirrhotics.[4,20]

Hypotonic fluids (10 mL/kg) or desmopressin (2-4 µg IV) are recommended when sodium correction limits are exceeded (> 6-8 mmol/L/day), especially when initial $S_{Na}$ is < 120 mmol/L. A combination of hypotonic fluids and desmopressin may be required in hypovolemic hyponatremia because a persistent water diuresis may

ensue after hyponatremia correction. Experimental data indicate reversal of ODS symptoms and improved outcomes with reinduction of hyponatremia after rapid overcorrection.[33,35]

## OSMOTIC DEMYELINATION SYNDROME

ODS is a serious demyelinating disorder typically involving the central pons (central pontine myelinolysis) but often extending into extrapontine structures (extrapontine myelinolysis). The clinical manifestations include hyperreflexia, pseudobulbar palsy, quadriparesis, parkinsonism, locked-in syndrome, and even death, and can arise one to seven days after overcorrection of hyponatremia. Two or more weeks from the initial neurologic manifestations might elapse before diagnostic findings on brain MRI and CT become evident. Fear of inducing osmotic demyelination from overcorrection of hyponatremia caused by excessive aquaresis has prompted the recommendation of treating severe hyponatremia with the combination of hypertonic saline boluses and IV desmopressin (2-4 µg) every six to eight hours to prevent a rapid increase in sodium.[33] An infusion of D5W can be administered to lower the serum sodium if an overcorrection has occurred. A potential complication of this combined strategy is an aggravation of hyponatremia from retention of prescribed (e.g., medication diluents or tube feedings) or unprescribed hypotonic fluids. Moreover, the sodium and water retention resulting from this strategy can cause pulmonary edema and hypoxemia, especially in elderly patients. A retrospective observational study of 36 ICU patients diagnosed with ODS showed that 11 patients died but 14 patients exhibited good functional recovery at one year.[34] Table 2 summarizes the treatment of hyponatremia as well as management of overcorrection. ■

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ABSTRACT & COMMENTARY

# Is There Still a Role for High-frequency Oscillatory Ventilation in ARDS?

*By Trushil Shah, MD*

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**Dr. Shah reports he serves on the speakers bureau for Gilead Sciences.**

SYNOPSIS: In this patient-level meta-analysis of four well-known randomized, controlled trials of high-frequency oscillatory ventilation (HFOV) in acute respiratory distress syndrome (ARDS), the authors found that HFOV increases mortality for most patients with ARDS but may improve survival among patients specifically with severe ARDS.

SOURCE: Meade MO, et al. Severity of hypoxemia and effect of high-frequency oscillatory ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017;196:727-733.

Theoretically, high-frequency oscillator ventilation (HFOV) is beneficial for lung protection. Meta-analyses of four early randomized, controlled trials (RCTs) comparing HFOV to conventional ventilation showed a survival benefit favoring HFOV.[1] However, two large RCTs (OSCAR and OSCILLATE) did not show clear benefit of HFOV over conventional ventilation.[2,3] A more recent study-level meta-analysis of 10 RCTs comparing HFOV to conventional ventilation did not show any statistical difference in mortality.[4] Moreover, the OSCILLATE trial ended early because of potential harm from HFOV.[3] As such, current guidelines recommend against the use of HFOV in the management of ARDS.[5] However, this study suggests that HFOV may produce a different effect in a subpopulation of acute respiratory distress syndrome (ARDS) patients.

Meade et al performed an individual patient data meta-analysis to identify subgroups of ARDS patients who are likely to benefit or be harmed from the use of HFOV. They included 1,552 patients from four RCTs (MOAT, EMOAT, OSCAR, and OSCILLATE). Effects of $PaO_2/FiO_2$, respiratory system compliance, and body mass index (BMI) were studied in the association of HFOV and 30-day mortality. Out of 1,552 patients, complete data were available for 1,327 patients. The two groups (HFOV vs. conventional ventilation) demonstrated similar baseline characteristics. Lung injury was relatively severe, with a mean $PaO_2/FiO_2$ of 114 ± 39 mmHg and an average positive end-expiratory pressure (PEEP) of 12 ± 3 cm $H_2O$. Thirty-day mortality was 40.9% for HFOV vs. 37.6% for conventional ventilation ($P = 0.16$).

The authors found a statistically significant interaction between baseline $PaO_2/FiO_2$ and the effect of HFOV ($P = 0.0003$), with increasing harm from HFOV at higher values of $PaO_2/FiO_2$ and suggestion of possible benefit at lower $PaO_2/FiO_2$ levels. The line of best fit crossed an odds ratio (OR) of 1.0 at a $PaO_2/FiO_2$ value close to 100 mmHg (95% confidence interval [CI], 64-117), suggesting a benefit of HFOV over conventional ventilation below $PaO_2/FiO_2$ of 64 and harm above $PaO_2/FiO_2$ of 117. Interaction between respiratory system compliance and BMI and the effect of HFOV on 30-day mortality was not statistically significant. There was weak interaction between the treatment effect and degree of low tidal volume ventilation. For the lowest quartile of tidal volume (< 6.29 mL/kg predicted body weight), the OR for HFOV vs. conventional ventilation was 1.92 (95% CI, 1.18-3.13; $P = 0.01$), consistent with harm with HFOV over low tidal volume ventilation. The overall rate of barotrauma was 98 in 1,458 patients, and the odds of barotrauma was higher with HFOV (adjusted OR, 1.87; 95% CI, 1.06-3.28; $P = 0.03$). Contrary to conventional wisdom, survival was better among earlier quartiles of HFOV patients enrolled in each hospital when compared with later patients ($P < 0.02$), with a clear dose-response relationship. This association was consistent in the three largest trials and was preserved after adjusting for the total number of patients at each hospital and when the analysis was restricted to hospitals enrolling more than 10 patients.

## ■ COMMENTARY

Conventional study-level meta-analyses so far have suggested no net benefit and perhaps even harm from HFOV. This meta-analysis suggests that adults with ARDS may be harmed or helped with HFOV, depending on the severity of lung injury as measured by $PaO_2/FiO_2$. It shows definite harm of HFOV over conventional mechanical ventilation, especially when low tidal volume ventilation is adhered to in patients with moderate ARDS ($PaO_2/FiO_2 > 117$).

This review suggests barotrauma from HFOV as one of the potential reasons for increased harm. Interestingly, this analysis also found increasing harm associated with HFOV as more patients were enrolled in any given hospital. Although it is difficult to draw conclusions, it does refute the role of lack of experience as a cause of

increased mortality in HFOV. The meta-analysis shows a possible benefit of HFOV in patients with very severe ARDS ($PaO_2/FiO_2$ < 64). However, unmeasured confounding factors could alter this threshold. Notably, the study was underpowered to detect a benefit in severe ARDS, as only 140 patients registered a $PaO_2/FiO_2$ < 64 (i.e., adjusted OR was 0.68; 95% CI, 0.3-1.50; $P$ = 0.34). Further studies are needed to confirm the benefit of HFOV over conventional low tidal volume ventilation in severe ARDS patients. HFOV should not be used in patients with mild-moderate ARDS. These patients should be managed with strict low tidal volume ventilation. The role of HFOV in severe ARDS remains debatable.

This analysis suggests further research should be conducted in this subpopulation of patients with very severe ARDS using HFOV as rescue therapy. ■


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## ABSTRACT & COMMENTARY

# In-hospital vs. Telephone Availability of an Intensivist at Night


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**Dr. Radigan reports no financial relationships relevant to this field of study.**



SYNOPSIS: When overnight shifts were staffed by nighttime intensivists rather than residents with attending intensivists on call remotely, most nurses perceived improvements in clinical care, procedures, efficiency, communication, and job place comfort.


SOURCE: Stanton ES, et al. Nurses' perceptions of in-hospital versus telephone availability of an intensivist at night in an intensive care unit. *Am J Crit Care* 2017;26:203-209.

Studies have shown that in-hospital management of critically ill patients does not change patient mortality rates in high-intensity ICUs. There is concern that outcomes such as mortality may be flawed and incomplete. To better understand the areas affected by nighttime intensivist staffing that have not been addressed, Stanton et al conducted a randomized clinical trial in a U.S. academic center. The trial included semi-structured interviews of 13 night-shift bedside nurses in the medical ICU toward the end of a previously published randomized trial of nighttime intensivist staffing that included randomization of attending presence in one-week blocks from 7 p.m. to 7 a.m.

Participation was voluntary, and nursing participants were compensated $50 for a 30-45 minute phone or in-person interview that included a script designed to elicit participants' perceptions of employing an intensivist in the hospital at night. One trained investigator moderated interviews, and three investigators independently reviewed interview transcripts to identify key domains. A qualitative analysis was completed by using a grounded theory approach. Investigators found that in addition to the five themes that were purposefully discussed during the interview (efficiency, communication, job place comfort, quality of care, and procedures), participants also identified three additional themes, including supervision of trainees, experience, and system issues. Examples of system issues included making an additional physician available when resources are limited and timely transfer of patients in and out of the ICU. Most of the nurses who were interviewed thought that nighttime intensivists improved clinical care, procedures, efficiency, communication, and comfort in the job place. All nurses believed that system issues improved. Twelve out of the 13 nurses believed supervision of trainees improved.

Nurses, who are constantly present at the bedside and carry a more detailed perspective on patient care issues, perceived improvements in communication, efficiency, supervision, system issues, and experience with night-

time intensivist staffing. Since this study cannot provide concrete associations or quantifiable outcomes, further studies are needed to assess whether these improvements may lead to a change in patient outcomes and if there are other areas affected by nighttime staffing, including burnout rates, educational outcomes of residents, and family satisfaction.

## ■ COMMENTARY

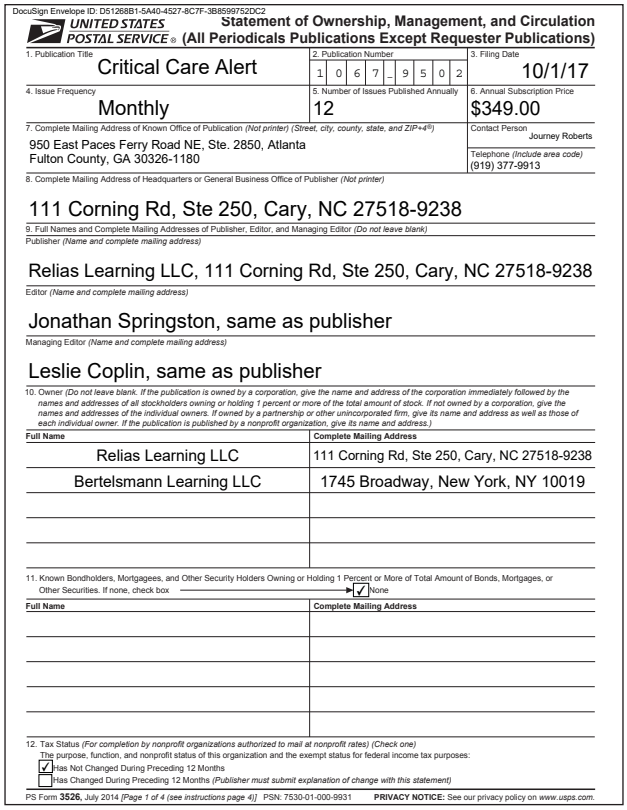
Supporters of 24-hour intensivist staffing suggest that intensivist staffing at night may result in prompt establishment of treatment plans, rapid resuscitation of patients without delay, and adjustment of complex therapies more efficiently. Others have questioned the benefits of nighttime intensivists without data to support their presence, especially when factoring in cost.

In 2012, researchers showed that critically ill patients who were not cared for routinely by intensivists during the day experienced lower risk-adjusted mortality with the presence of in-hospital nighttime intensivists.[1] This study sparked interest in whether there was a dose-adjusted response to the presence of nighttime intensivists in the setting of an ICU with established daytime intensivist staffing.

In 2013, Kerlin et al conducted a one-year randomized trial in an academic medical ICU examining the effects of nighttime staffing with in-hospital intensivists as compared with nighttime coverage by daytime intensivists who were available for consultation by telephone.[2] There was no evidence that nighttime staffing had a significant effect on length of stay in the ICU or hospital, ICU or in-hospital mortality, readmission to the ICU, or the probability of discharge to home. These findings were consistent whether the patient was admitted at night regardless of the severity of illness or experience of the resident.

Although it is well described that in-person management by nighttime intensivists does not change patients' mortality rates in the ICU, there are concerns that these traditional ICU outcomes are flawed. To elicit insights from the nursing perspective of nighttime staffing with attending intensivists vs. residents with attending intensivists on call, Stanton et al further investigated and revealed that all nurses appreciate improvements in communication, efficiency, supervision, system issues, and experience with nighttime intensivist staffing.

This study supports the theory that staffing by an intensivist at night produces benefits that are not captured by previous studies. It has been hypothesized that endpoints such as mortality are not as valuable when attempting to capture benefit in this scenario. For instance, the presence of an attending at night may lead to more prompt end-of-life discussions by a physician who inevitably has



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|---|---|---|
| Critical Care Alert | 1 0 6 7 _ 9 5 0 2 | 10/1/17 |
| **4. Issue Frequency** | **5. Number of Issues Published Annually** | **6. Annual Subscription Price** |
| Monthly | 12 | $349.00 |

7. Complete Mailing Address of Known Office of Publication *(Not printer) (Street, city, county, state, and ZIP+4®)*: 950 East Paces Ferry Road NE, Ste. 2850, Atlanta Fulton County, GA 30326-1180 — Contact Person: Journey Roberts; Telephone *(Include area code)*: (919) 377-9913

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not printer)*: 111 Corning Rd, Ste 250, Cary, NC 27518-9238

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do not leave blank)*

Publisher *(Name and complete mailing address)*: Relias Learning LLC, 111 Corning Rd, Ste 250, Cary, NC 27518-9238

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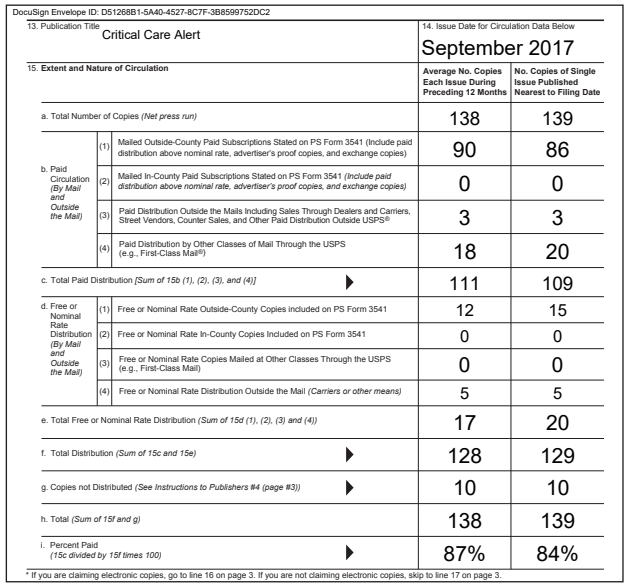

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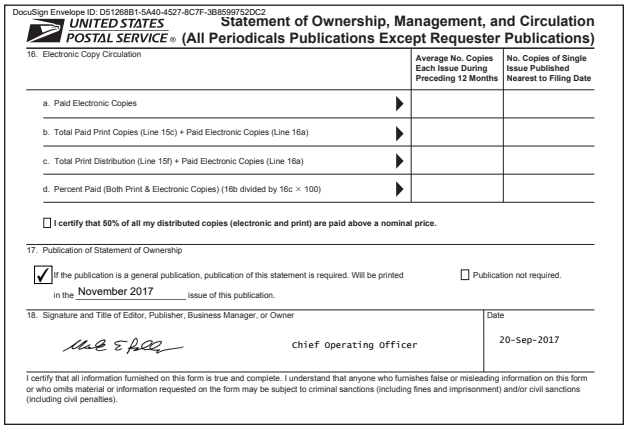

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more expertise than a resident physician. Of course, addressing code status and altering goals of care would represent deaths that do not reflect poor delivery of care as a traditional mortality analysis would assume.

Other areas that may be affected by nighttime intensivist staffing include burnout rates of attending physicians, nurses, and trainees, along with educational outcomes of residents and family satisfaction. It also remains unclear how the intensity of the attending presence may affect patient outcomes.

It is clear that overnight attending physicians may vary drastically in their practice, with some involved with every patient plan of care while others may adhere to a philosophy of "call me if you have any trouble." These different philosophies also may alter outcomes significantly. Although this study was not designed to provide concrete associations between nighttime intensivist staffing and quantifiable outcomes, nurses perceived improvements in communication, efficiency, supervision, system issues, and experience with nighttime intensivist staffing. More studies are necessary to assess whether these improvements lead to a change in patient outcome and if other areas, including burnout rates, educational outcomes of residents, and family satisfaction, are affected. ■

## REFERENCES

1. Wallace DJ, et al. Nighttime intensivist staffing and mortality among critically ill patients. *N Engl J Med* 2012;366:2093-2101.
2. Kerlin MP, et al. A randomized trial of nighttime physician staffing in an intensive care unit. *N Engl J Med* 2013;368:2201-2209.

## CME/CE QUESTIONS

1. **A 60-year-old man with heart failure with reduced ejection fraction is admitted to the ICU for pulmonary edema and generalized volume overload. He is alert, oriented, and requires continuous positive airway pressure. Blood pressure is 170/90 mmHg. Initial laboratory results reveal a serum sodium of 125 mEq/L. Which of the following therapies is recommended to improve serum sodium within 24 hours of admission?**
   a. Hypertonic saline
   b. Urea
   c. Furosemide
   d. Desmopressin

2. **A 71-year-old woman was admitted to the neurosciences ICU four days ago for management of a traumatic subdural hematoma secondary to a fall. She reports mild dizziness and a bad taste in her mouth. On exam, she is euvolemic, breathing room air, and registers a blood pressure of 130/80 mmHg. Laboratory results show a sodium of 126 mEq/L. Which of the following will support the diagnosis of syndrome of inappropriate antidiuretic hormone secretion?**
   a. Undiagnosed thyroid dysfunction
   b. Urine sodium > 40 mmol/L
   c. Urine osmolality > 200 mOsm/L
   d. Serum uric acid > 4 mg/dL

3. **In the article by Meade et al., high-frequency oscillatory ventilation was associated with improved survival among which group of patients?**
   a. Very severe acute respiratory distress syndrome (ARDS)
   b. Moderate ARDS
   c. ARDS with cardiac comorbidity
   d. ARDS with no history of lung disease

4. **Nurses perceived improvement in what area(s) with nighttime intensivist staffing?**
   a. Communication
   b. Efficiency
   c. Supervision
   d. All of the above

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# Critical Care [ALERT]

Vol. 25, Issue 8, November 2017
*Special Supplement*
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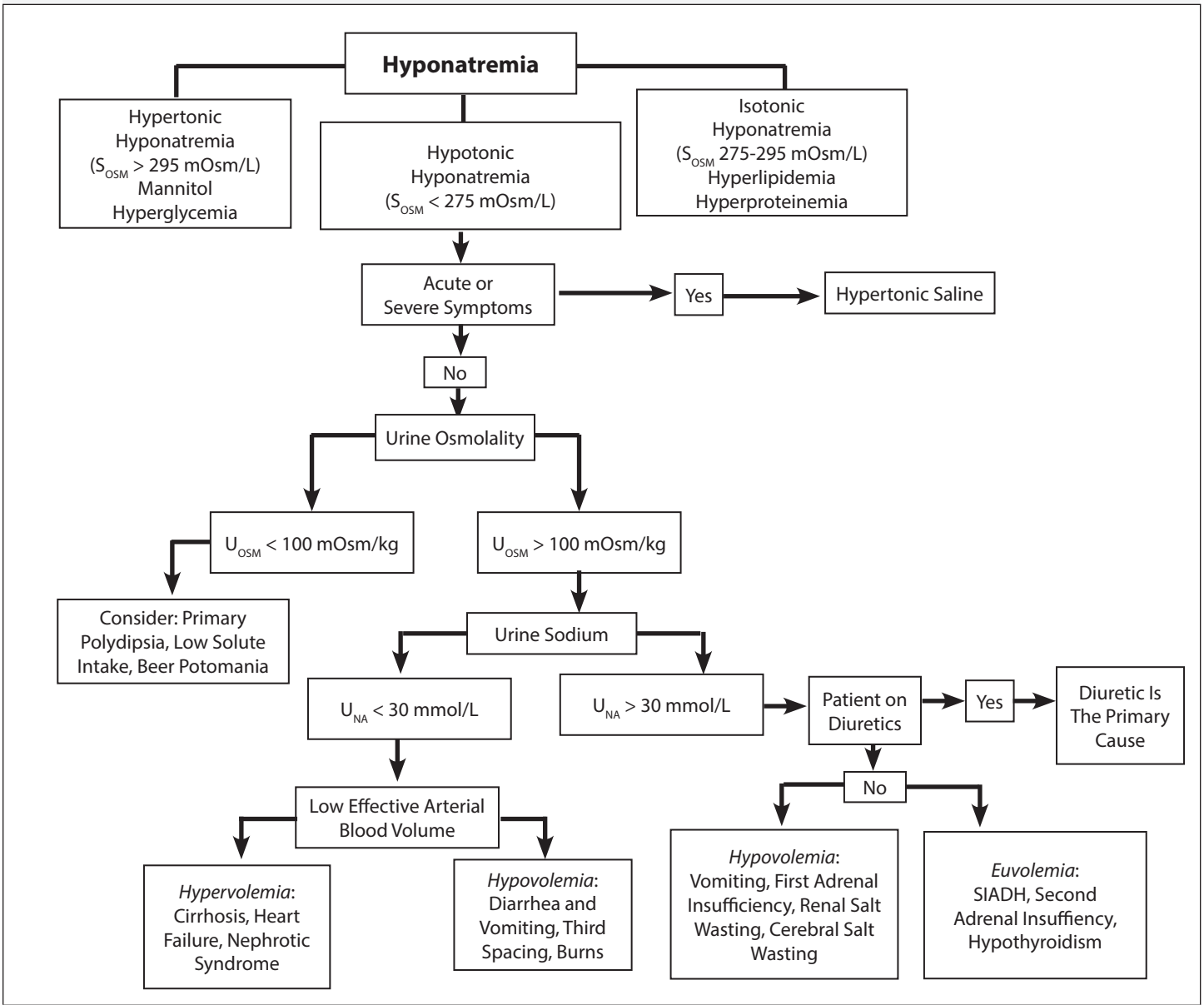
## Figure 1. Diagnostic Algorithm for Hyponatremia




Adapted from: Hoorn EJ, Zietse R. Diagnosis and treatment of hyponatremia: Compilation of the guidelines. *JASN* 2017;28:1340-1349.

## Table 1. Causes of the Syndrome of Inappropriate Antidiuretic Hormone Secretion

**Malignant Diseases**
Carcinoma
- Lung
  - Small cell
  - Mesothelioma
- Oropharynx
- Gastrointestinal tract
  - Stomach
  - Duodenem
  - Pancreas
- Genitourinary tract
  - Bladder
  - Prostate
- Lymphomas

**Other Causes**
Hereditary (gain of function mutation in $V_2$ receptor)
Idiopathic
Transient
- General anesthesia
- Pain, nausea, stress
- Endurance exercise

**Pulmonary Diseases**
Infections
- Bacterial pneumonia
- Viral pneumonia
- Lung abcess
- Aspergillosis

Asthma
Cystic Fibrosis
Respiratory failure associated with positive pressure breathing

**Disorders of CNS**
Infections
- Encephalitis and meningitis
- Brain abscess
- AIDS
- Rocky Mountain spotted fever

Bleeding and masses
- Subdural hematoma
- Subarachnoid hemorrhage
- Cerebrovascular accident
- Brain tumors
- Head trauma
- Hydrocephalus
- Cavernous sinus thrombosis

Other
- Multiple sclerosis
- Guillain-Barré syndrome
- Delirium tremens
- Shy-Drager syndrome

**Drugs**
Stimulates arginine vasopressin (AVP) release
- Chlorpropamide, clofibrate
- Carbamazepine, valproate
- Vincristina, cisplatin
- Selective serotonin reuptake inhibitors (fluoxetine, sertraline)
- Tricyclics (amitriptyline)
- Ifosfamide, melphalan
- Antipsychotics (Haloperidol)
- Narcotics (codeine, fentanyl, tramadol)

Potentiate action of AVP
- Chlorpropamide
- Oxcarbamazepine
- Cyclophosphamide
- Nonsteroidal anti-inflammatory drugs
- Imatinib
- Methotrexate
- Ciprofloxacin

AVP analogues
- Desmopressin
- Oxytocin
- Vasopressin

Adapted from: Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007;356:2064-2072.

## Table 2. Treatment of Hyponatremia Summary

| Condition | Therapy |
|---|---|
| Acute or symptomatic hyponatremia | • Severe symptoms: Bolus 3% saline 100 mL x 3 as needed<br>• Moderate symptoms: Continuous infusion 3% saline 0.5-2 mL/kg/hour |
| Chronic hyponatremia<br>Syndrome of inappropriate antidiuretic hormone secretion | • Fluid restriction (first-line)<br>• Loops, diuretics, urea, vaptans, salt tablets, demeclocycline (second-line) |
| Hypovolemic hyponatremia | • Isotronic saline or balanced crystalloids solutions |
| Hypervolemic hyponatremia | • Fluid restrictions, loop diuretics |
| Sodium correction rates | • Minimum: 4-8 mmol/L/day, 4-6 mmol/L/day if high risk for osmotic demyelination syndrome (ODS)<br>• Limits: 10-12 mmol/L/day, 8 mmol/L/day if high risk for ODS |
| Management of overcorrection | • Baseline $S_{NA}$ > 120 mmol/L: Start once limit of Na correction is exceeded<br>• Baseline $S_{NA}$ < 120 mmol/L: Start relowering with electrolyte-free water (10 mL/kg) with or without desmopressin 2µg IV after correction exceeds 6-8 mmol/L/day |

Adapted from: Hoorn EJ, Zietse R. Diagnosis and treatment of hyponatremia: Compilation of the guidelines. *JASN* 2017;28:1340-1349.