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ADVANCES IN THE MANAGEMENT OF PATIENTS WITH HYPONATREMIA

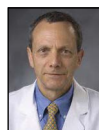
TARGET AUDIENCE

Internists, cardiologists, nephrologists, critical care physicians, emergency room physicians, hospitalists, and other clinicians who care for patients with hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH).

PROGRAM OVERVIEW

This continuing medical education activity represents a comprehensive summary of the diagnosis and treatment of all types of hyponatremia. The expert faculty present specific treatment recommendations according to the extracellular fluid volume status and the specific etiology of the hyponatremia. Rationale for effective treatment strategies are based on the in depth analysis of clinical presentation and the progress of patient data. The application of updated expert panel recommendations for goals and limits of the correction of hyponatremia are presented through case based discussions. The goal is to optimize outcomes and prevent osmotic demyelination syndrome (ODS) in patients with hyponatremia. Recently, data has become available for a new class of vasopressin receptor antagonists, also called vaptans. The expert faculty highlight recommendations for when and how to use this newer class of therapeutics.

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EDUCATIONAL OBJECTIVES

Upon completion of this activity, participants will be able to:

1. Recognize the signs and symptoms important to the early diagnosis of patients with hyponatremia.
2. Describe the pathophysiology and therapeutic targets of SIADH, including arginine vasopressin receptors.
3. Review the efficacy and safety data of pharmacotherapies for the treatment of patients with hyponatremia and SIADH.
4. Identify the role of vasopressin receptor antagonists in the management of patients with hyponatremia.

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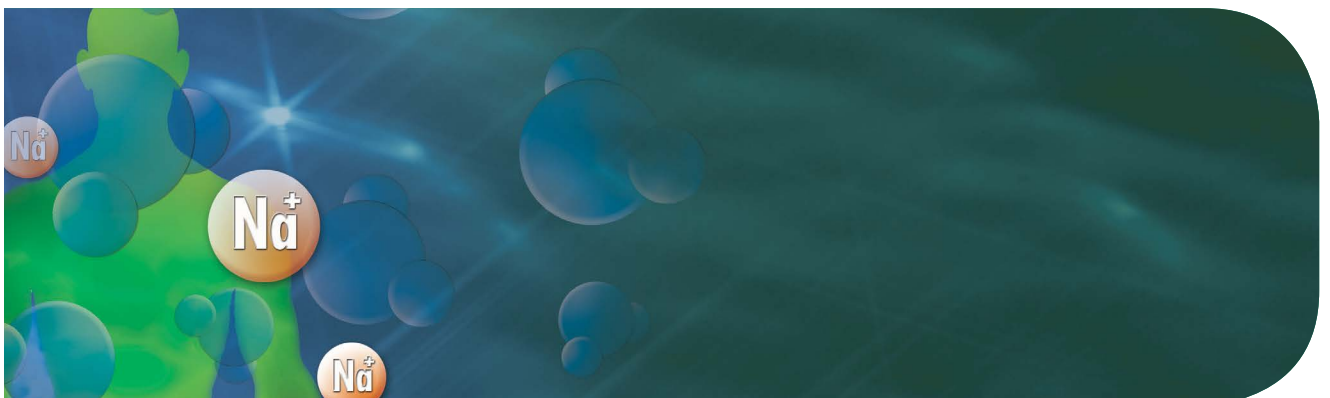
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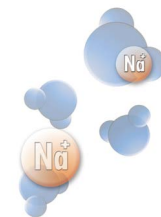
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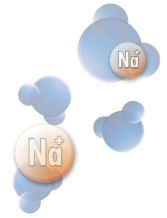
Estimated time to complete this activity: 2.0 hours

Expiration date of activity for AMA PRA credit: January 14, 2015

Pre-Activity Test Questions *Answer sheet provided on page 25*

Questions 1 and 2 should be answered on a scale of 1 to 5, with 1 meaning **NOT** confident and 5 meaning **VERY** confident.

1. Currently, how confident are you in your ability to accurately obtain an early diagnosis in patients with hyponatremia?
 2. Currently, how confident are you in your ability to describe the pathophysiology and therapeutic targets of SIADH, including arginine vasopressin receptors?
-
3. Hyponatremia is a common electrolyte imbalance in hospitalized patients that can be classified by which of the following?
 - a. Plasma tonicity
 - b. Extracellular fluid volume status
 - c. Neurological symptom severity
 - d. All of the above
 4. A hospitalized patient becomes irritable, nauseous, develops a change in mental status, and presents with an unstable gait over the last 24 to 48 hours. Lab results show serum sodium levels to range from 125 and 130 mEq/L. Based on the neurological symptoms, which severity of hyponatremia would describe this patient?
 - a. Severe
 - b. Moderate
 - c. Minimal
 - d. None of the above
 5. Which of the following statements is false in regards to acute hyponatremia followed by the volume regulation process in the brain.
 - a. During the process in response to brain edema, both electrolytes and organic osmolytes are lost from the brain
 - b. During the process in response to brain edema, excess water leaves the brain
 - c. The adaptation from volume regulation is associated with chronic hyponatremia
 - d. There is not a significant loss of excitatory neurotransmitters in the brain as a result of this process
 - e. Brain edema is no longer present as a result of this process
 6. A 54 year old post-operative male patient in the ICU diagnosed with hyponatremia also has a high urine osmolality greater than 500 mOsm/kg H₂O and a 24 hour urine volume less than 1500 mL/day. In order to correct this patient's hyponatremia, will fluid restriction alone be an effective treatment?
 - a. Yes
 - b. No
 7. According to the updated 2013 expert panel recommendations on the management of hyponatremia, patients at high risk for developing osmotic demyelination syndrome have which of the following health concerns?
 - a. Serum sodium concentration less than or equal to 105 mEq/L
 - b. Hyperkalemia
 - c. Mild obesity
 - d. Fatty liver disease
 8. Your patient with chronic hyponatremia had the benefit of a renal consultation and the decision has been made to initiate vaptan therapy. Which of the following precautions would be necessary to safely manage this patient?
 - a. Do not restrict water intake on day 1
 - b. Monitor sodium frequently
 - c. Titrate the drug dose up or down depending on response
 - d. All of the above
 9. With respect to therapeutic options for the management of patients with hyponatremia in your clinical practice, which of the following do you believe will now guide your management of hyponatremic patients? Choose all that apply.
 - a. Efficacy of therapy
 - b. Safety of therapy
 - c. Tolerability of therapy
 - d. Long-term data
 - e. Emerging data
 - f. Patient and caregiver preference
 - g. Patient insurance coverage
 - h. Other



ADVANCES IN THE MANAGEMENT OF PATIENTS WITH HYPONATREMIA

Dr. Joseph Verbalis from Georgetown University Medical Center and his colleagues, Dr. Arthur Greenberg from Duke University and Dr. Mitchell Rosner from the University of Virginia offer their expertise in considering a variety of cases illustrating the various aspects of the management of hyponatremia and how clinicians can apply their insight to everyday practice.

Classification of Hyponatremia by Plasma Sero-tonicity, Extracellular Fluid Volume Status, and the Severity of Hyponatremia

Hyponatremia can be classified in a variety of manners. The first is by plasma tonicity. Patients with hyponatremia can either be hypotonic, isotonic, or hypertonic in terms of their plasma tonicity; which depends on the relation of the plasma osmolality to the serum sodium. In the most common form, hypotonic hyponatremia, serum sodium and plasma osmolality are both low. Examples of this form of hyponatremia will be discussed later in cases involving the syndrome of inappropriate antidiuretic hormone secretion (SIADH), heart failure, and cirrhosis.

Figure 1¹

Hyponatremia: Classification by Plasma Tonicity			
	Serum Sodium	Plasma Osmolality	Typical Causes
Hypotonic	<135 mmol/L	low (<280 mOsm/kg H ₂ O)	SIADH; CHF; cirrhosis
Isotonic	<135 mmol/L	normal (280-295 mOsm/kg H ₂ O)	hyperglycemia; pseudohyponatremia (hyperlipidemia, hyperproteinemia)
Hypertonic	<135 mmol/L	high (>295 mOsm/kg H ₂ O)	severe hyperglycemia with dehydration; mannitol

- Only **hypotonic hyponatremia** causes a shift of water from the extracellular fluid into cells along osmotic gradients

CHF, congestive heart failure; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

It is important to differentiate hypotonic hyponatremia from isotonic and hypertonic hyponatremia. Isotonic hyponatremia occurs when the serum sodium is low; but, the plasma osmolality is normal. This can also be seen in conditions that we call pseudohyponatremia because of hyperlipidemia and hyperproteinemia. Hypertonic hyponatremia also has low serum sodium; but, in this case, plasma osmolality is high rather than low. This is also seen with severe hyperglycemia with dehydration, as well as during the use of some osmotic agents such as mannitol. This distinction is important

because only hypotonic hyponatremia causes a shift of water from the extracellular fluid (ECF) into cells.

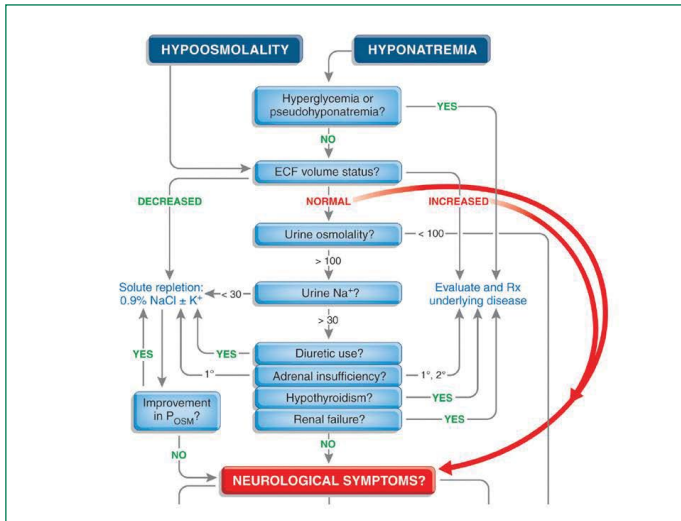
Figure 2²

Hypotonic Hyponatremia: Classification by ECF Volume Status			
ECF volume (ECFV)	Serum Sodium	Clinical Characteristics	Typical Causes
Hypovolemic: ECFV decreased	<135 mmol/L	orthostatic hypotension; dry mucus membranes; poor skin turgor; elevated BUN/creat ratio; elevated uric acid; low urine sodium	gastrointestinal, renal or skin fluid losses; diuretic therapy; cerebral salt wasting; 1° adrenal insufficiency
Euvolemic: ECFV normal	<135 mmol/L	absence of signs of ECF volume depletion or expansion; normal or low BUN/creat ratio; low uric acid; elevated urine sodium	SIADH; NSAID; 2° adrenal insufficiency; hypothyroidism; exercise-associated hyponatremia; low solute intake; polydipsia
Hypervolemic: ECFV expanded	<135 mmol/L	edema; ascites; pulmonary congestion; anasarca	heart failure; cirrhosis; kidney failure; nephrotic syndrome

BUN/Creat, blood urea nitrogen/creatinine; ECF, extracellular fluid; NSAID, nonsteroidal anti-inflammatory drug; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Once confirmed that a patient has hypotonic hyponatremia with low plasma osmolality, the next level of classification is to determine the ECF volume status of the patient. Patients with hypotonic hyponatremia can be hypovolemic with a decreased ECF volume, euvolemic with a normal clinical ECF volume, or hypervolemic with an expanded volume. Hypovolemic patients have the typical signs of volume depletion. The typical causes of this include gastrointestinal, renal, or skin fluid losses, diuretic therapy, and rarely cerebral salt wasting and primary adrenal insufficiency. In contrast, euvolemic hyponatremia has an absence of any signs of extracellular volume depletion or expansion. Typically, the blood urea nitrogen (BUN)/creatinine ratio is normal or low, the uric acid is low, and the urine sodium is elevated or reflects dietary sodium intake. This is the pattern encountered with SIADH; rare causes of which include nonsteroidal anti-inflammatory drug (NSAID) use, secondary adrenal insufficiency, sometimes hypothyroidism, exercise-associated hyponatremia, low solute intake, and polydipsia. Finally, hypervolemic hyponatremia patients are those who have edema, ascites, pulmonary congestion, or edema-forming disorders that typically include heart failure, cirrhosis, kidney failure, or the nephrotic syndrome. Classification by extracellular volume status is important because virtually all algorithms for the treatment of hyponatremia involve an initial determination of the extracellular volume status and whether the patient has a decreased, normal, or increased volume status.

Figure 3³



POSM, plasma osmolality

This dictates next steps in terms of both diagnostic and treatment decisions, and for that reason it is important to carefully assess the extracellular volume status before making treatment decisions about a hyponatremic patient.

Finally, hyponatremia is also classified by severity, which is indicated by neurological symptomatology. Severe hyponatremia generally is defined with a lower serum sodium level (less than 125 mmol/L) and with symptoms indicating significant neurological dysfunction such as vomiting, seizures, obtundation, respiratory distress, and coma. The typical duration of these cases is short and it represents a more acute form of hyponatremia. Moderate hyponatremia is also characterized by low serum sodium; however, it is generally not quite as low as in severe hyponatremia, though it can be—generally serum sodium levels are in the range of less than 130 mmol/L. The neurological symptoms of moderate hyponatremia, while still present, are not as marked as with severe hyponatremia and include nausea, confusion, disorientation, altered mental status, unstable gait, and increased falls. Typically these patients have a duration of hyponatremia that is intermediate or chronic, greater than 24 to 48 hours; but, oftentimes not weeks and/or months in duration. Finally, mild hyponatremia can have any serum sodium level, including up to 135 mmol/L and it has very mild and sometimes nonspecific neurological symptoms including headache, irritability, difficulty concentrating, altered mood, and depression. Typically



patients with this level of severity of hyponatremia have it for several days to many weeks to months; it is a manifestation of chronic hyponatremia. The severity of neurological symptoms is more dependent on the degree of brain volume regulation than on the serum sodium level itself. That is why in the serum sodium column on this table (Figure 4), there is a wide range of sodium values that may encompass the various severity levels of hyponatremia.

Figure 4

Hyponatremia: Classification by Neurological Symptoms

	Serum Sodium	Neurological Symptoms	Typical Duration of Hyponatremia
severe	<125 mmol/L	vomiting; seizures; obtundation; respiratory distress; coma	acute (<24-48 hrs)
moderate	<130 mmol/L	nausea; confusion; disorientation; altered mental status; unstable gait/falls	intermediate or chronic (>24-48 hrs)
mild	<135 mmol/L	headache; irritability; difficulty concentrating; altered mood; depression	chronic (several days to many weeks/months)

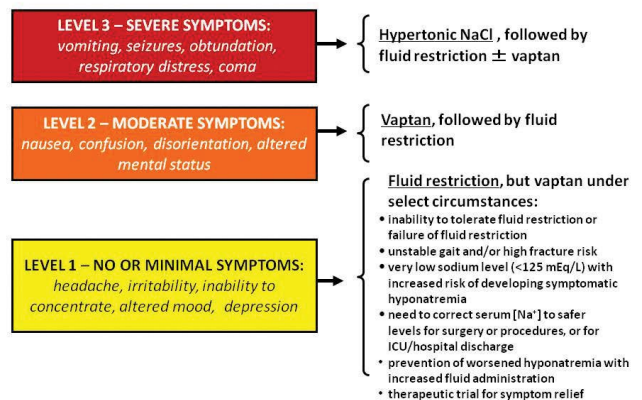
- The severity of neurological symptoms is more dependent on the degree of brain volume regulation than on the serum [Na⁺] level

It is important to assess the severity of the hyponatremia because many treatment algorithms use the severity, and the presence of neurological symptoms as some of the factors that influence the chosen therapy. One of these algorithms is shown here; but, many different algorithms and recommendations focus on both acuteness and severity of the hyponatremia to gauge recommended therapy.

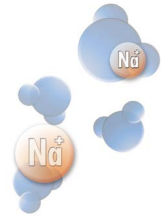
Figure 5

Hyponatremia Treatment Algorithm

Euvolemic Hyponatremia (SIADH)

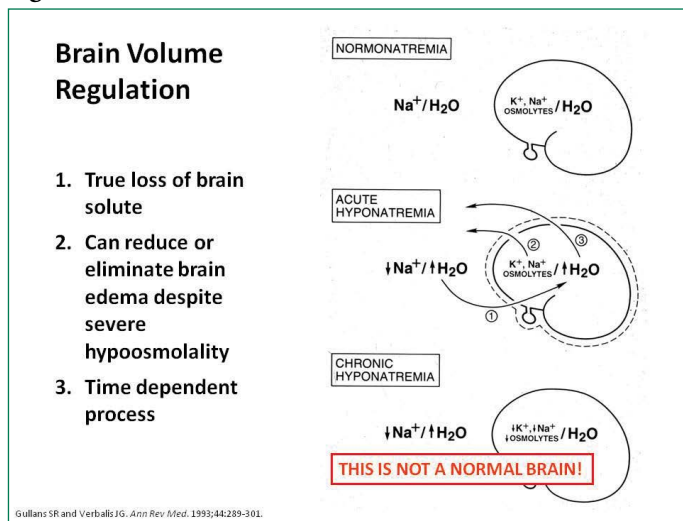


Under normal conditions, there is an osmotic equilibrium between the sodium concentration and osmolality outside of the brain and the osmolality inside the brain. With an acute fall in the



osmolality and sodium concentration outside the brain, due to a decrease in body sodium or an increase in body water, there is an osmotic gradient established between the ECF in the brain and water flows across osmotic gradients into the more concentrated brain cells. This causes brain swelling or edema. Brain edema is responsible for most of the severe symptoms of acute hyponatremia; however, in response to the cell and brain swelling, the brain undergoes a process called volume regulation, in which both electrolytes and organic osmolytes are lost from the brain, allowing the excess water to also leave the brain. This results in adaptation associated with chronic hyponatremia in which there is now an osmotic equilibrium between the ECF and the brain, but now the brain edema is not present. As a result, patients with chronic hyponatremia have significantly less symptomatology because the brain edema is, for the most part, gone. However, this is not a normal brain in chronic hyponatremia because the process needed to get from acute hyponatremia to chronic hyponatremia is a significant loss of solute from the brain, including many osmolytes that in fact are important excitatory neurotransmitters in the brain. This adaptation is one of the causes of the symptomatology, which may persist, despite the fact that a brain edema is no longer present.

Figure 6³



Role of Arginine Vasopressin in the Generation of Hyponatremia

Water is the largest component of the human body and the major determinant of the level of body water is arginine vasopressin (AVP)-regulated water excretion by the kidneys. This is a very powerful regulatory mechanism; and therefore, plasma osmolality only varies within ±2% tolerances under normal physiological conditions.

AVP regulation is controlled via a variety of positive and negative modulatory signals that affect the neurons in the brain that both manufacture and secrete AVP on the pituitary. Once secreted into the blood, AVP acts on its receptors, including the V1a receptors on the vascular smooth muscle that cause vasoconstriction in response

to AVP. AVP also acts on the V2 receptors located in the kidney, which are responsible for renal water reabsorption, which will be covered later.

AVP is also commonly referred to as antidiuretic hormone (ADH). There is no difference between ADH and AVP. They describe the same molecule that has the same actions, simply two different terms for the same hormone.

This is how AVP acts in the kidney collecting duct.

Figure 7

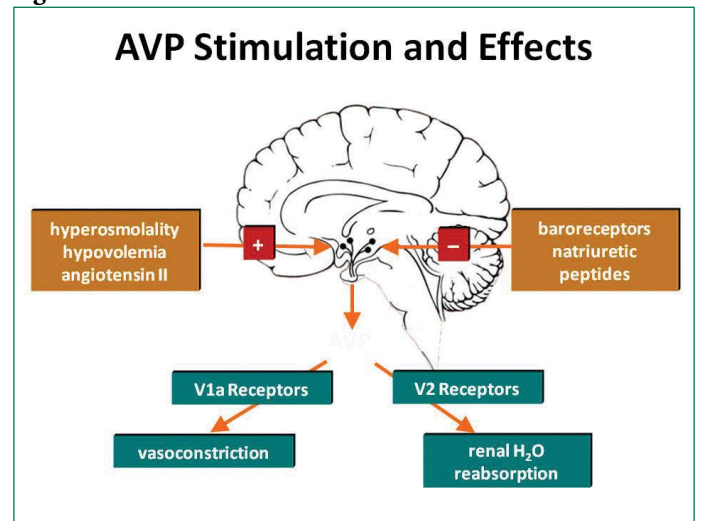
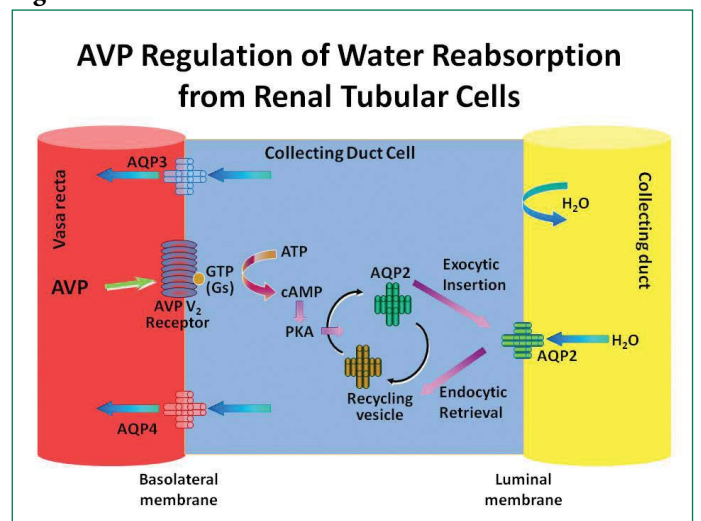


Figure 8⁴



The principle cells of the collecting duct are shown above by the green squares. The AVP V2 receptors are located on the basolateral membrane between the blood in the vasa recta and the collecting duct itself. Under normal conditions, when there is no AVP binding to the V2 receptor, the luminal membrane in between the collecting

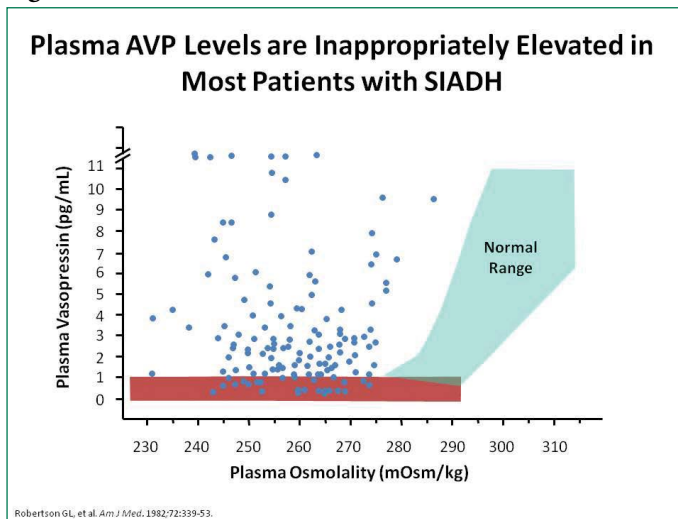
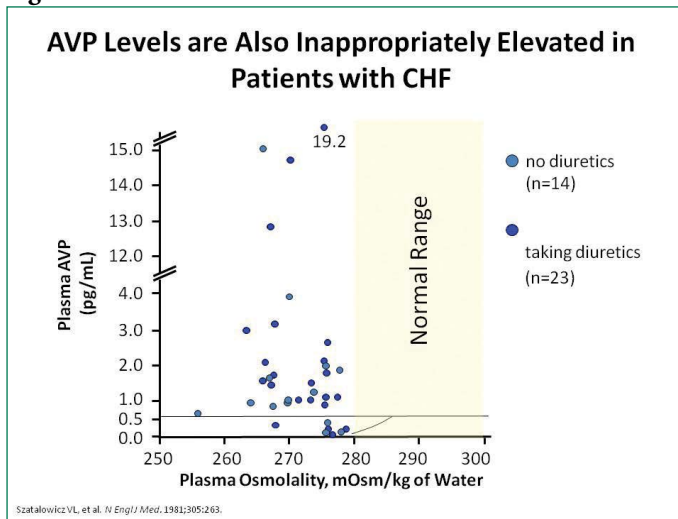
duct and the collecting duct cell is relatively impermeable to water. Therefore, water that is in the collecting duct after passing through the more proximal parts of the nephron travels through the collecting duct and out the ureter to the bladder. This is aquaresis because there is no water reabsorption back into the blood. When AVP is secreted and levels in the blood rise, regardless of the reasons for the AVP secretion, this activates the V2 receptor, which results in the signal transduction cascade of the generation of cyclic adenosine monophosphate (cAMP) and the phosphorylation of protein kinase A (PKA) that ultimately results in the insertion of water channels called aquaporin 2 (AQP2) into the collecting duct luminal membrane. Once AQP2 is inserted in the membrane it allows transfer of water across the osmotic gradient from the collecting duct back into the collecting duct cell, then back into the blood via other constitutively expressed aquaporins. This is antidiuresis, which causes free water retention and water reabsorption. When a patient is dehydrated, it is a beneficial process to prevent further dehydration from occurring. However, when AVP is elevated for inappropriate reasons, or for reasons not related to osmotic homeostasis, it results in free water retention, when in fact, osmolality is not threatened and normal. This can then lead to hyponatremia.

AVP is in fact the major cause of hyponatremia in the majority of patients who have hypotonic hyponatremia, certainly in cases of SIADH.

In Figure 9, individual patients with SIADH are shown by the blue dots and have inappropriately elevated plasma AVP levels when levels should be suppressed into the zone indicated by the red bar. Note that these are not necessarily very high AVP levels, although some at the upper end of the graph are, but these are simply levels that are inappropriate because they should be suppressed when plasma osmolality is low and they are not. Therefore, they are causing water retention via the mechanism shown in Figure 8—there should be free water excretion rather than water retention.

This occurs not only in congestive heart failure, but also in edema forming disorders such as heart failure and cirrhosis.

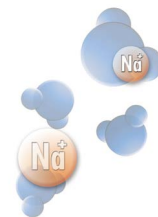
Figure 10 shows a series of patients with heart failure showing the same phenomenon, that the majority of patients who are hypoosmotic; and therefore, hyponatremic, have inappropriately elevated levels of AVP that should be suppressed to less than 0.5 pg/mL, which is the threshold for being able to measure plasma AVP levels.

Figure 9⁵Figure 10⁶

Recommendations for the Treatment of Hyponatremia by the Recently Published Expert Panel in *The American Journal of Medicine* in 2013.⁷

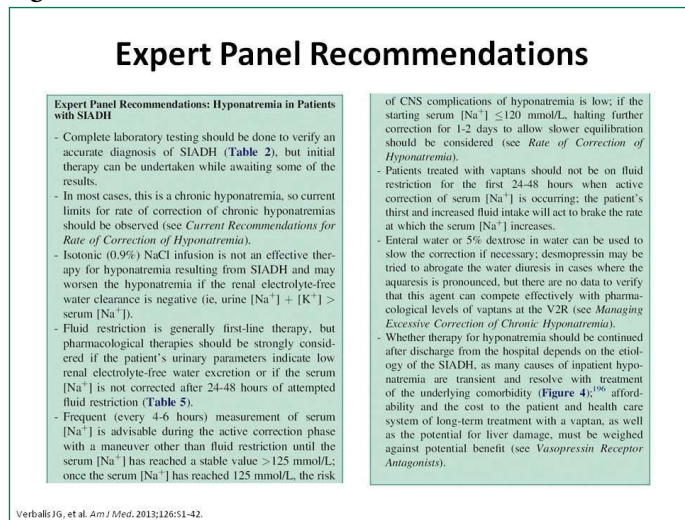
Recommendations for the Treatment of Hyponatremia were first published in 2007 in *The American Journal of Medicine* and in 2012, the same panel along with a few additional experts held a meeting to discuss and revise the recommendations.

This publication represents a comprehensive summary of the diagnosis and treatment of all types of hyponatremia. It provides specific treatment recommendations according to the ECF volume status and the specific etiology of the hyponatremia. There is a focus on making the best choice of initial therapy based on the clinical presentation of the patients. There are updated recommendations for goals and limits of correction of hyponatremia to prevent osmotic demyelination syndrome (ODS). And finally, there are specific recommendations for when and how to use the new class of vasopressin receptor antagonists, also called vaptans.



This is an example of the expert panel recommendations for treatment of hyponatremia in patients with SIADH (Figure 11). This is a very comprehensive and complete; but concise, discussion of what should be done to verify the diagnosis of SIADH, to choose treatment for patients with SIADH, and to guard against consequences of inappropriate or inadequate treatment of SIADH. For each of the etiologies of hyponatremia that are covered, recommendations exist, offering physicians detailed recommendations for how to treat hyponatremia of various etiologies.

Figure 11⁷



The recommendations focus significantly on the choice of appropriate initial therapy. One of the most commonly employed therapies for hyponatremia is fluid restriction. The guidelines provide general recommendations for fluid restriction, including the predictors of the likely failure of fluid restrictions. These predictors of failure include patients with very high urine osmolality, generally over 500 mOsm/kg H₂O. It has also been shown that the ratio of the urine electrolytes to the serum electrolytes is a predictor of failure to fluid restriction. In this case, if the sum of the urine sodium and potassium concentrations is greater than the serum concentration, then it is predicted that fluid restriction will not be successful in that patient. If the 24-hour urine volume is less than 1500 mL per day then that patient will likely fail fluid restriction because the recommendations aim for fluid restriction that is 500 mL per day below the 24-hour urine volume. Therefore, if the 24-hour urine volume is 1500 mL and you want to be 500 mL below that which results in a fluid restriction of 1000 mL per day. This is difficult to maintain long-term due to other fluids that patients receive in the hospital, as well as decreased compliance by the patient outside of the hospital. And finally, if fluid restriction is tried but results in increased serum sodium less than 2 mmol/L per day in the first 24 to 48 hours of fluid restriction equal to or less than 1 L per day, again, the patient is likely to fail fluid restriction on a long-term basis. By more carefully evaluating the patient before choosing an initial therapy, one can make a more intelligent choice of therapy and not choose fluid restriction simply because it is the easiest thing to do, particularly if there are clear predictors

that the patient is likely not to respond adequately to fluid restriction.

Another point emphasized in the 2013 recommendations is a set of new goals and limits for correction of hyponatremia. Overly rapid correction of hyponatremia may cause ODS. Therefore, recommendations were made for limits of how far one should correct within a 24 to 48 hour period of treatment of hyponatremia. However, it is not just one set of limits and goals, it depends on the patient and the patient's presentation. Figure 13 shows three different scenarios that are commonly encountered in clinical practice.

Figure 12⁷

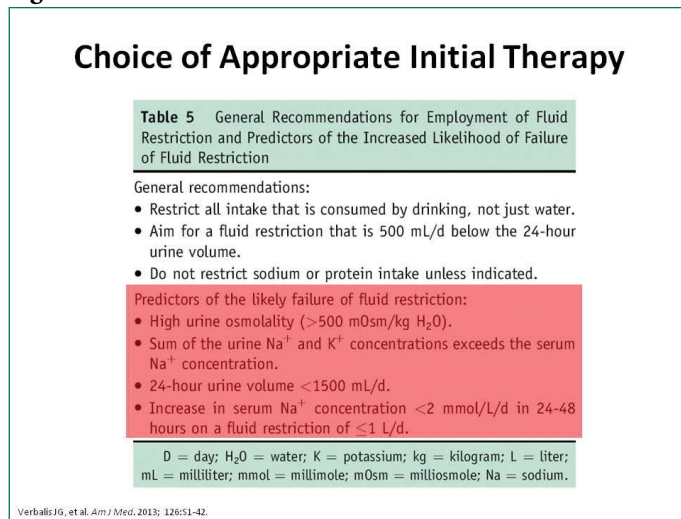
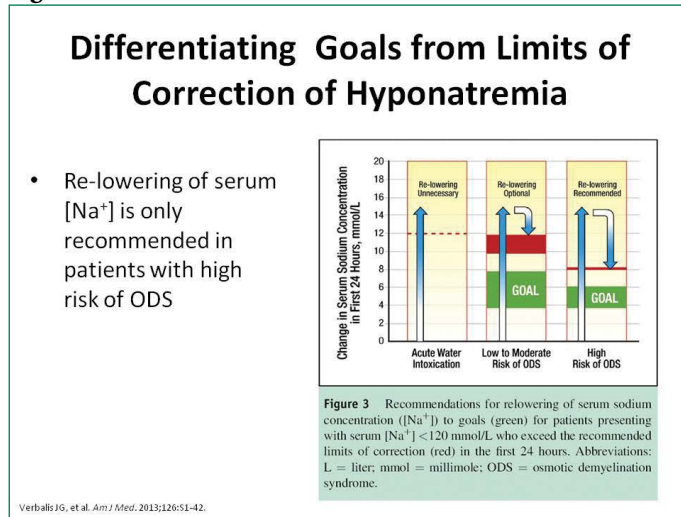


Figure 13⁷



With acute water intoxication, such as that which occurs in psychogenic water drinking or in patients with exercise-induced hyponatremia, which can occur during marathon or ultra-marathon endurance exercise events, very often the patient autocorrects the hyponatremia via an aquaresis or free water excretion without

any intervening therapy. This correction seems to be within what is generally considered to be the limit of safe correction of 12 mmol/L per day; however, in this situation it is not recommended that the correction be stopped or that the sodium be lowered because this is a very acute hyponatremia, one in which the risk of osmotic demyelination syndrome is very low.

In Figure 13, the middle column shows patients that are typically seen with low to moderate risk of ODS, these are patients with more chronic hyponatremia than in the left column. In these patients, the goal now should be a 4 to 8 mmol/L reduction in serum sodium in the first 24 hours. That is what one should attempt to correct by, the limit is more than that, in the range of 10 to 12 mmol/L per day, depending on how cautious one wants to be, and it is important to distinguish your goal from your limit. The goal should be what one aims to achieve, if one overshoots the goal, that is okay, but in no cases should the limit be exceeded. If the limit is exceeded, as shown with the blue arrow, there is an option to use free water to re-lower the serum sodium back to the limit, it has not been definitively proven in this classification that it is necessary; but, it is an option that many clinicians employ. Finally, in the right column are patients with a high risk of ODS, in those patients, we know that both the goal and the limit of correction should be lower than in the typical patient. The goal should be a reduction of no more than 4 to 6 mmol/L per day, with a limit of 8 mmol/L per day in any 24 hour period. If that limit is exceeded, re-lowering the serum sodium to the limit is recommended, as opposed to having that be an option. The 2013 expert panel recommendations specifically discuss these three scenarios and why these recommendations are being made.

Factors that place patients at high risk of ODS are shown in Figure 14. Patients with very severe hyponatremia by serum sodium concentration, can also have hypokalemia, alcoholism, malnutrition, or advanced liver disease. Even though there are no rigorous criteria for what defines those comorbidities, nonetheless the presence of any of them in patients with hyponatremia dictates lower goals and lower limits of correction.

The indication for long-term treatment depends on the relative risk of chronic SIADH and the likely duration of the SIADH, which is directly related to the etiology. Patients with tumors producing vasopressin that cannot be resected or treated will have indefinite hyponatremia; and therefore, are candidates for long-term therapy. Patients with transient causes of hyponatremia such as post-operative state, nausea, pain, or pneumonia

generally have a short-term duration of hyponatremia and SIADH, and generally will not need long-term therapy.

Figure 14⁷

Patients at High Risk of ODS

Table 3 Factors That Place Patients at High Risk of Developing the Osmotic Demyelination Syndrome with Correction of Chronic Hyponatremia

High Risk of Osmotic Demyelination Syndrome

- Serum sodium concentration ≤ 105 mmol/L
- Hypokalemia*
- Alcoholism*
- Malnutrition*
- Advanced liver disease*

L = liter; mmol = millimole.

*Unlike the rate of increase in serum sodium concentration, neither the precise level of the serum potassium concentration nor the degree of alcoholism, malnutrition, or liver disease that alters the brain's tolerance to an acute osmotic stress have been rigorously defined.

Verbalis JG, et al. *Am J Med*. 2013;126:51-62.

If long-term therapy is necessary, newly available options include the vasopressin receptor antagonists. Figure 16 summarizes the SALT studies—the pivotal trials of the vasopressin receptor antagonist—tolvaptan. The drug is effective in raising serum sodium levels over 30 days when compared with placebo. The left panel shows correction of hyponatremia to serum sodium levels of greater than 135 mmol/L. This is relative to the placebo arm (open circles) where patients remain hyponatremic. After the drug is stopped at 30 days, the serum sodium levels return to pretreatment levels, indicating bioactivity of the vaptan for the 30-day period of time. The open label extension trial of tolvaptan (Figure 16, right panel) shows the same pattern—normalization of the serum sodium for as long as 4 years; but, then a drop to hyponatremic levels as soon as the drug is stopped. There is no question that we now have therapies that can effectively treat hyponatremia for long periods of time, but the question remains as to when the therapy should be employed and what the benefit is. One of the ongoing unanswered questions in the field is the association between hyponatremia and long-term morbidity and mortality.

The study by Wald (Figure 17) shows the relationship between in-patient mortality and serum sodium levels in which a large number of patients were treated in an academic healthcare setting.⁸ Notably, mild levels of hyponatremia (less than 137 mmol/L) are associated with a significant increase in predicted probability of inpatient mortality, which then continues to increase as the serum sodium level drops. Some of the questions that will be addressed in the cases to follow include: what are the indications for treatment of hyponatremia, what should be the duration of treatment, and what are the potential benefits of that treatment?

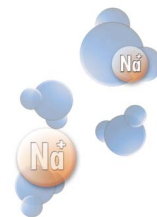


Figure 15⁷

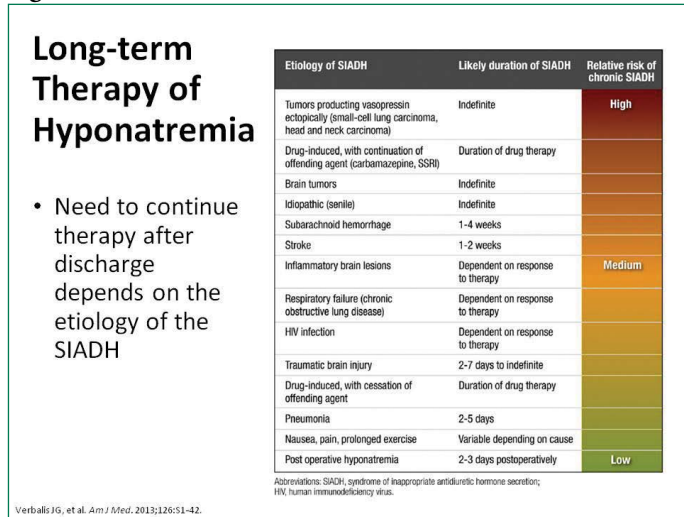


Figure 16⁸

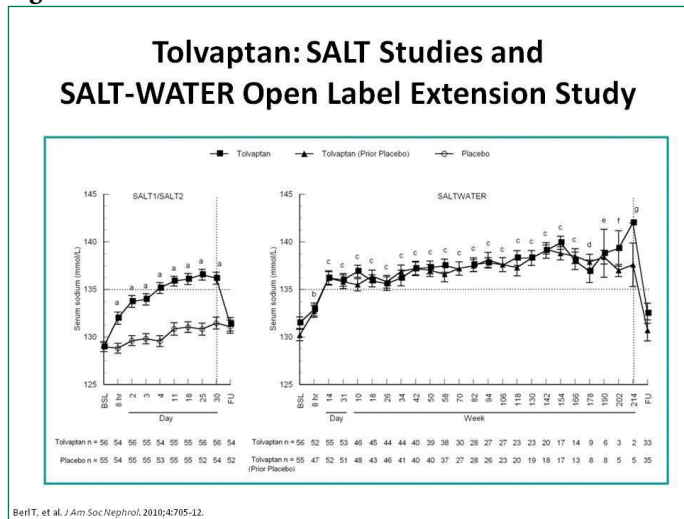
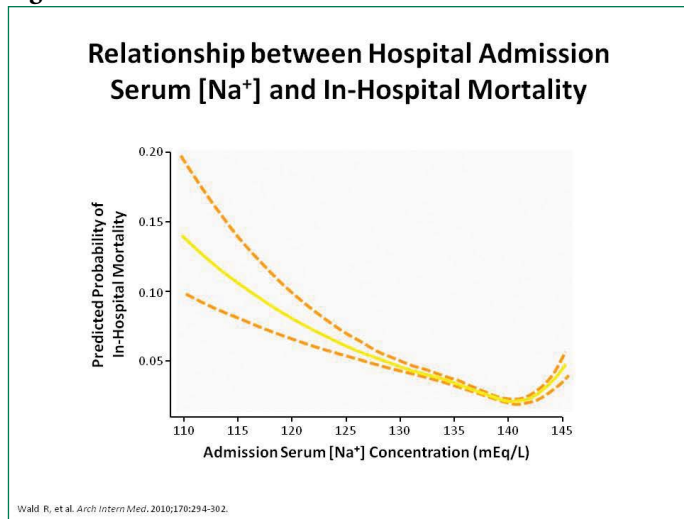


Figure 17⁹



DISCUSSION 1

I would like to turn to the panel now and ask if there are any comments or any observations about what I presented.

Dr. Rosner: You mentioned that the chronic hyponatremic brain is not a normal brain. Can you elaborate on how we clinically see that manifested?

Dr. Verbalis: First, studies have shown that chronic hyponatremia is associated with gait instability and an inability to maintain a tandem heel-to-toe walking with eyes open. This is also associated with an increased frequency of falls in hyponatremic patients compared with normal natremic patients. One possibility is that the osmolyte depletion, which occurs in order to regulate the brain, may cause this disruption of fine motor regulation. The major reason is that one of the major osmolytes, which is lost from the brain during adaption to hyponatremias, is glutamate. Glutamate levels can fall as much as 25% to 35% in the hyponatremic brain, which is important because glutamate is the major excitatory neurotransmitter in the brain. All motor movements of any muscle in our body are controlled by glutamate activity inside the brain. Therefore, depleted levels of glutamate in the brain may result in slow nerve conduction inside the brain, which would result in impaired fine motor activity that is required to maintain balance and maintain stability of gait. The importance of the gait instability and increased number of falls in hyponatremic patients is also illustrated by the fact that four independent international studies have shown increased frequencies of bone fractures in patients that are hyponatremic. Therefore, the logical scenario is one in which hyponatremia causes impaired fine motor control that leads to gait instability and increased falls. Since hyponatremia typically affects older individuals, the increased falls are more likely to result in increased fractures.

Dr. Greenberg: Is the increased fall risk the only reason why patients with hyponatremia seem to have a high fracture rate?

Dr. Verbalis: No, we don't think so. Studies from my laboratory have documented that in experimental animals, hyponatremia causes increased loss of bone mass to levels that cause osteoporosis. And in preliminary epidemiological population studies of human databases, there is an increased odds ratio for osteoporosis in patients who are hyponatremic. Therefore, we think that the hyponatremia has a dual effect that results in increased fractures. Not just increased falls, but weaker bones because of increased rates of osteoporosis in hyponatremic patients.

Dr. Greenberg: Sounds like a perfect storm for fracture—altered mental status, impaired gait and balance, and weak bones.

Dr. Verbalis: Yes, you're exactly right. Perfect storm—all those things are coming together to result in increased morbidity in terms of fractures, but also mortality, given that we know the high rate of mortality in elderly people that suffer hip fractures.

Thank you. We will now move to the case presentations. Three cases are presented that span multiple types of hyponatremia. I think it will become clear that understanding the commonalities

and the differences in these very three different types of patients will provide a good platform for discussion of how hyponatremia should optimally be managed depending upon how it presents and in who it presents.

Clinical Case Presentation

A 68-year-old female is brought to the emergency department with symptoms of drowsiness and confusion. Two weeks prior, she was started on a thiazide diuretic, hydrochlorothiazide, and a low salt diet for hypertension. Her family noted that over the past three days she has been lethargic, more confused, and had some diarrhea, as well as poor appetite. At baseline, she performed all of her activities of daily living and she worked part-time as an accountant. Her physical examination was notable in that she was only oriented to self, but was able to follow commands. Her blood pressure was 98/50 mmHg, she had a pulse of 98 beats/min, and the rest of her examination was only notable for dry mucous membranes. Her other medications include omeprazole, aspirin, and simvastatin. Of note, her initial lab showed a serum sodium level of 106 mEq/L, potassium of 2.2 mEq/L, a BUN of 46 mg/dL, a creatinine of 2.0 mg/dL, a urine osmolality of 650 mOsm/kg, and a low serum osmolality of 232 mOsm/kg.

The key initial question should be what is the best initial therapy for this patient's hyponatremia? The options here include hypertonic saline, normal saline, normal saline with potassium supplementation, or hypertonic saline with potassium supplementation. Let us go through this case and discuss some of the treatment options, as well as what actually happened in the course of her care.

The diagnosis here is hypotonic hyponatremia due to the thiazide diuretic, as well as her associated gastrointestinal losses, and poor per os appetite. Her associated potassium depletion also worsens the hyponatremia. Her volume status—based on her physical examination including hypotension, mild tachycardia, and dry mucus membranes—is consistent with volume depletion. Therefore, the initial treatment, and really the focus of therapy, should be volume repletion with normal saline along with treatment of her significant potassium depletion. And the goal here is to restore euolemia as well as hemodynamic stability. Given the fact that she did not have any significant neurological findings, although she was somewhat confused, there was no actual indication for hypotonic saline, certainly no emergent indication in this case.

Thiazide-induced hyponatremia is one of the most common etiologies of hyponatremia that the clinician is likely to encounter. The mechanisms include thiazide inhibition of sodium chloride reabsorption in the distal part of the nephron that leads to direct inhibition of urinary dilution capacity. This is in contrast to loop diuretics, which do not interfere with the urinary concentration ability. Due to their direct diuretic action, thiazide diuretics lead to an associated increase in vasopressin secretion (induced by volume depletion) and an associated sodium loss from their diuretic effect that may be relatively higher than water loss that is impeded by the vasopressin action. There is also some data that thiazides may up-regulate the AQP2 channels. Furthermore, potassium depletion will exacerbate the hyponatremia. Typically, after the initiation of a thiazide a new equilibrium in sodium and water balance is reached, usually within a period of two weeks and hyponatremia is most likely to occur in that early two week period after initiation. However, hyponatremia can occur at other times if there are other physiological or environmental changes. Interestingly, women have about a threefold increased risk of hospitalization due to diuretic-induced hyponatremia. In addition, older age and lower body mass index are consistent risk factors for the development of thiazide-induced hyponatremia.

Figure 18^{10,11}

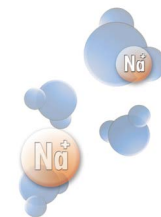
Thiazide Induced Hyponatremia

- Mechanisms:
 - Thiazides inhibit sodium chloride reabsorption in the distal convoluted tubule, which leads to direct inhibition of urinary dilution capacity.
 - As opposed to loop diuretics, they do not interfere with urinary concentration
 - Furthermore, due to direct diuretic action and an increase in vasopressin secretion, sodium loss (diuretic) may be relatively higher than water loss (impeded by vasopressin action)
 - May upregulate aquaporin-2 channels
 - Potassium depletion exacerbates the hyponatremia
- After the initiation of thiazide therapy, a new equilibrium in sodium-water balance is reached, usually within a period of 2 weeks and hyponatremia is most likely to occur in this period
- However, hyponatremia can occur at any time due to physiologic or environmental changes
- Women have a 3x ↑ risk of hospitalization due to diuretic-induced hyponatremia
- Older age and lower body mass index are risk factors for hyponatremia

Rodenburg EM, et al. *Am J Kidney Dis.* 2013;62:67-72.
Sonnenblick M, et al. *Chest.* 1993;103:601-6.

In terms of thinking about her care, one of the useful things is to think about is the anticipated change in serum sodium when we initiate fluid therapy. There are several formulas available to determine this change and the Adrogue-Madias equation is one of the more common ones that allow us to determine the amount of sodium needed to raise the serum sodium by a given amount.

The equation shown in Figure 19 states that the change in serum sodium is equal to the infused sodium in the IV fluid minus the serum sodium, divided by the total body water plus 1. The 1 here represents giving a liter of a solution with the infused sodium concentration shown. Now importantly for this case, if a significant amount of potassium is given in the infusion that also must be added to the infused amount of sodium to calculate the



change in serum sodium. If we give her a liter of fluid, such as normal saline with 30 mEq/L of potassium, we have 154 (mEq of sodium) plus 30 (mEq of potassium) minus her initial sodium of 106 mEq/L divided by her total body water of 27 plus 1 (for one liter of the infused fluid). That would anticipate that our serum sodium would rise by about 2.8 mEq/L for administration of a liter of this fluid.

Figure 19

Anticipating the Change in Serum Sodium

- To determine the amount of sodium needed to raise the serum sodium by any amount (Adrogue-Madias equation):
 - Change in serum Na = $\frac{\text{infusate Na} - \text{serum Na}}{\text{Total body water} + 1}$
 - Note: if significant amounts of K+ are given in the infusion this amount MUST be added to the infusate Na to calculate the change in serum Na
 - From the formula, retention of 1 liter of this fluid will increase the serum sodium 2.8 mEq/L:

$$\{(154 + 30) - 106 / 27 + 1\} = 2.8$$

Now, we have to use a lot of caution when we use these formulas. First of all, no calculation has been determined to be the gold standard. And this is really a rough estimation of the sodium requirement. Some of this caution was really highlighted in a single center, retrospective study where patients were treated with 3% hypertonic sodium chloride and they compared the predicted sodium using this formula to the actually-achieved serum sodium. In this study, 11% of the patients exceeded safe correction rates, more than 12 mmol/L in 24 hours, and 10% of the patients exceeded 18 mmol/L in 48 hours. In particular, patients that present with a serum sodium less than 120 mmol/L seem to have a more rapid rise in serum sodium than would be predicted by this formula. So while these formulas can be useful to give us initial estimates, they still require careful monitoring of serum sodium with laboratory tests. At least in patients with severe hyponatremia, serum sodium should be monitored every two to three hours for the first 12 to 24 hours to avoid over correction.

Because sodium shifts out of cells in exchange for potassium, it is important that the supplementation with potassium is included as deficits in potassium are corrected. Potassium dosage should be taken into account in the hyponatremia treatment plan.

Now let's go back to the case. The patient received 2 L of the intravenous fluid—normal saline with potassium. Her blood pressure improved dramatically and her mental status was improved. However, her serum sodium went up approximately 6 mEq/L to 112 mEq/L and her potassium became 3.0 mEq/L. At this point, what would be your next step? Would you continue the current hydration with normal saline? Would you change the

fluid to now half normal saline with 30 mEq/L of potassium? Would you begin fluid restriction? Or would you begin tolvaptan, 30 mg daily?

Figure 20¹²

Calculation Caution

- No calculation is the “Gold Standard”
- Rough estimation of sodium requirement
- A single-center retrospective study of 62 patients treated with 3% sodium chloride compared predicted serum sodium (using Adrogue-Madias equation with actual achieved serum sodium)
 - 11% exceeded 12 mmol/L in 24 hr
 - 10% exceeded 18 mmol/L in 48 hr
 - 74% with serum sodium <120 mEq/L exceeded sodium calculation estimate (Adrogue-Madias equation)
- Monitor serum sodium every 2-3 hours for first 12-24 hours to avoid overcorrection

Mohmand HK, et al. Clin J Am Soc Nephrol. 2007;2:1110-7.

Figure 21¹³

Role of Potassium in Rate of Correction

- Sodium shifts out of cells in exchange for potassium as deficits of the potassium are corrected after supplementation
- Thus, administering potassium will raise the [Na] to an equivalent degree as administering sodium
- Therefore, potassium dosing should be taken into account in the hyponatremia treatment plan.

Berl T and Rastegar A. Am J Kidney Dis. 2010;55:742.

This is an important point, especially in patients that present with hypovolemic hyponatremia, where you need to begin anticipating what will happen to vasopressin levels during your treatment plan. It is important to anticipate that as the fluid status improves, the initial stimulus for vasopressin secretion will rapidly disappear and free water excretion will increase as the vasopressin levels return to low levels. This change in vasopressin level and the associated increase in kidney free-water excretion risks over rapid correction of the serum sodium. Thus, a reasonable option here would be to change her IV fluid to half normal saline and continue her potassium supplementation. Again, if you use the formula and plug in those values, 77 for the half normal saline plus 30 for the potassium minus her current serum sodium of 112 mEq/L divided by her total body water of 27 plus 1, you essentially get an equal balance of -0.2 mEq/L. Again, I want to point out caution that this estimating

formula does not account for continued urine losses of water and solute. Therefore, the anticipated production of urine with a lower sodium and potassium than the infused sodium will probably continue to promote correction of the serum sodium. And in fact, the next morning her serum sodium had increased slightly to 114 mEq/L with this hypotonic fluid regimen.

Now, you heard a little about this earlier. It is important to think about those patients that risk rapid correction of their serum sodium. Certain subgroups may have hyponatremia that, in essence, corrects unexpectedly during the course of treatment. Extreme caution and close monitoring is required for these patients. They include patients with volume depletion, cortisol deficiency when you are replacing the cortisol, desmopressin-induced hyponatremia, and as in this case, thiazide-induced hyponatremia. Without a nonosmotic stimulus for AVP secretion, hyponatremic patients can begin to excrete a maximally dilute urine that can actually increase the serum sodium by more than 2 mmol/L per hour and thus risk rapid correction.

This leads into a discussion of some of the complications that we see during the treatment of hyponatremia. And certainly the most feared complication is central pontine myelinolysis, or perhaps more properly termed, osmotic demyelination syndrome recognizing that demyelinating lesions can occur throughout the brain. This is associated with rapid correction of serum sodium and includes risk factors such as female sex, alcoholism, malnutrition, prolonged diuretic use, psychogenic polydipsia, post-liver transplantation, and a serum sodium at presentation that is less than 105 mmol/L.

We heard a little bit earlier of the brain adaptation to hyponatremia, so that in chronic hyponatremic states the intracellular osmolyte concentration is lower as an adaptation to maintain cellular volume. So that, in chronic hyponatremia, the brain cells extrude organic solutes from their cytoplasm and that allows intracellular osmolality to equal plasma osmolality without a large increase in cell water and volume. However, when we rapidly correct hyponatremia and increase the extracellular serum sodium, water movement moves the other way and the cells begin to decrease their cell volume, leading to shear stress and other injury to neuronal tissues.

That can manifest itself on magnetic resonance imaging (MRI), shown here, as osmotic demyelination. Figure 25 shows an example MRI of osmotic demyelination. A severe demyelinating lesion is shown highlighted in the white area and the blue arrow in the pons.



Figure 22

Risk of Rapid Correction of Serum Sodium

- Certain subgroups of patients may have hyponatremia that “auto-corrects” unexpectedly during the course of treatment
- Extreme caution and close monitoring is required for these patients
 - Volume depletion – Desmopressin-induced
 - Cortisol deficiency – Thiazide-induced
- Without a non-osmotic stimulus for AVP secretion, hyponatremic patients can begin to excrete a maximally dilute urine which can increase the serum sodium by more than 2 mmol/L/hour

Figure 23¹⁴

Complications of Hyponatremia

- Most feared complication is central pontine myelinolysis or osmotic demyelination syndrome associated with rapid correction of serum sodium
- Risk factors include: female sex, alcoholism, malnutrition, prolonged diuretic use, psychogenic polydipsia, post-liver transplantation, serum sodium < 105 mmol/L

Kling JD and Rosner MH. Am J Med Sci. 2010;339:561-7.

Figure 24¹⁵

Pathogenesis of CNS Symptoms Brain Adaptation to Hyponatremia

A Normonatremia Acute hyponatremia Chronic hyponatremia

- In chronic hyponatremia, brain cells extrude organic solutes from their cytoplasm, allowing intracellular osmolality to equal plasma osmolality without a large increase in cell water

http://www.kidneyatlas.org/book1/ADK1_01.pdf

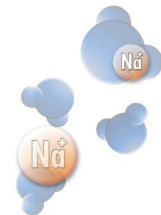
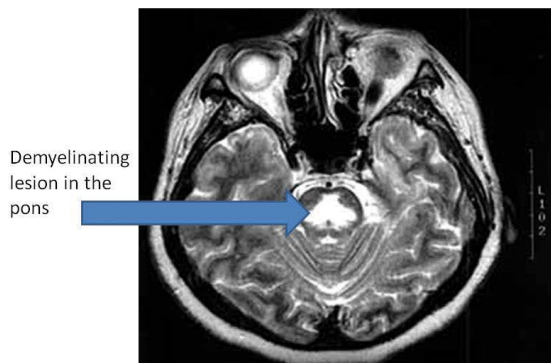


Figure 25

MRI Findings- Osmotic Demyelination



Some key points about the osmotic demyelination syndrome. It has a stereotypical biphasic pattern; patients may initially improve neurologically when they have correction of their hyponatremia. However, one to several days later, they develop new, progressive, and sometimes permanent neurological deficits. The diagnosis of ODS should be considered in patients who have failed to recover as expected from their hyponatremia and also considered in patients manifesting unusual psychiatric, or neurological symptoms after treatment of hyponatremia. Recent data has shown that prognosis is not uniformly bad, but many patients are left with debilitating neurological syndromes. The MRI changes may be delayed, but diffusion MRI imaging is much more sensitive and often shows the lesions early. The clinical picture can still evolve over days and interestingly enough patients with uremia seem to have some protection from developing the syndrome.

Figure 26¹⁶

Osmotic Demyelination Syndromes: Key Points

- Stereotypical biphasic pattern
 - Patients improve neurologically with correction of hyponatremia
 - One to several days later, develop new, progressive and sometimes permanent neurological deficits
- Should be considered in patients who have failed to recover as expected from hyponatremia
- Consider in a patient manifesting psychiatric symptoms after treatment of hyponatremia
- Prognosis is not uniformly bad
- MRI changes may delayed up to 14 days (diffusion weighed imaging may be most sensitive) and MRI severity is not prognostic
- The clinical picture can evolve over days
- Uremia seems to be protective

Sterns RH, et al. J Am Soc Nephrol. 1994;4:1522-30.
King JD and Rosner MH. Am J Med Sci. 2010;339:561-7.

Now, referring to the recent expert consensus panel, I think it is important to bring up the rate of correction for chronic hyponatremia.

And a quote from the article says that, “Because a 6 mmol/L increase appears to be sufficient for patients with the most severe manifestations of hyponatremia, we believe that the goal of therapy, i.e., the desired increase in serum, in chronic hyponatremia should be 4 to 8 mmol/L/d for those at low risk of osmotic demyelination, with an even lower goal of 4 to 6 mmol/L/d if the risk of ODS is high.”

Figure 27¹⁷

Rate of Correction for Chronic (>48h) Hyponatremia

- Recent Expert Consensus Panel:
 - “Because a 6-mmol/L increase appears to be sufficient for patients with the most severe manifestations of hyponatremia, we believe that the goal of therapy (i.e., the desired increase in serum [Na]) in chronic hyponatremia should be 4-8 mmol/L/d for those at low risk of ODS, with an even lower goal of 4-6 mmol/L/d if the risk of ODS is high”

Verbalis JG, et al. Am J Med. 2013;126:51-42.

The limits not to exceed for patients with a high risk of osmotic demyelination is 8 mmol/L in any 24 hour period and for those at normal risk, 10 to 12 mmol/L in any 24-hour period, and 18 mmol/L in any 48-hour period.

Figure 28⁷

Limits Not to Exceed

- For high risk of ODS: 8 mmol/L in any 24-hour period
- For normal risk of ODS: 10-12 mmol/L in any 24-hour period; 18 mmol/L in any 48-hour period

Verbalis JG, et al. Am J Med. 2013;126:51-42.

Figure 29⁷

Case 1: Laboratory Evaluation

- $[\text{Na}^+]$ 125, $[\text{K}^+]$ 4.0, BUN 4 mg/dL, creatinine 0.6 mg/dL
- Uric acid 4.1 mg/dL
- Osmolality 265 mOsm/kg
- Urine Osmolality 555 mOsm/kg
- Urine Sodium 85 mmol/L

To summarize some key points about thiazide-induced hyponatremia: think about diuretic induced hyponatremia as a chronic form of hyponatremia. Hyponatremia is reversed by withholding the diuretic and by correcting sodium and potassium deficits. You have to worry that the serum sodium may correct rapidly and have a risk for developing osmotic demyelination syndrome. It is critically important to serially follow changes in urine osmolality, together with the urine volume, to detect the development of an aquaresis (excretion of a very dilute urine) and the heightened risk of overly rapid correction. The focus of therapy for patients with a serum sodium of less than 120 mmol/L is typically not on

achieving adequate correction; but, it may often be on restraining the rate at which the sodium increases. This may require use of hypotonic fluids. You want to frequently measure the serum sodium during the active correction phase until the serum sodium has reached a stable level of at least 125 mmol/L. It is critically important to include potassium dosing in the hyponatremia treatment plan.

DISCUSSION 2

Dr. Verbalis: So, Mitch, this patient has a serum sodium of 106 mmol/L and the criteria for an increased risk of osmotic demyelination says patients with a serum sodium of 105 mmol/L or less, so how would you classify this patient? High risk or low risk?

Dr. Rosner: I would think she would be high risk for several reasons. One, she was also hypokalemic, she was elderly, and she had a low body mass index. So, I think for many reasons,

I would certainly consider her high risk and therefore be very cautious in the terms of the rate of correction for her hyponatremia.

Dr. Verbalis: Right, you make a good point that any one of those criteria put a patient at high risk, even if the others are borderline in their manifestation.

Dr. Rosner: I think it is always safer to think of patients as high risk if you are at all concerned.

Dr. Greenberg: Mitch, is every patient with serum sodium of this level at the same risk for ODS? Do you want to comment about chronicity of hyponatremia? Would you treat a patient with an endurance exercise-induced hyponatremia or someone who developed hyponatremia to this degree after ecstasy use in the same fashion, with the same cautions about rate correction?

Dr. Rosner: Sure, I think that one of the difficult things that clinicians face is determining the chronicity. I think one of the points with diuretic-induced hyponatremia is that the default diagnosis should be chronic hyponatremia. The other conditions that you mentioned, exercise-associated hyponatremia and hyponatremia associated with ecstasy clearly are acute hyponatremic with often more acute severe central nervous system symptoms. In those patients, rapid correction of serum sodium is certainly safe and warranted and even the use of hypertonic saline is much safer in those patients.

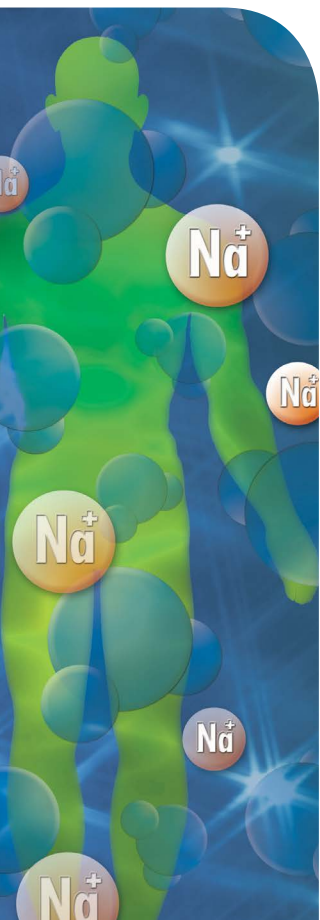
Dr. Verbalis: In this patient, you were able, after the initial correction, to maintain a slow rate of correction with half the normal saline infusion that you chose. But as you indicated, sometimes the free diuresis or aquaresis that occurs can be voluminous and result in an excessively rapid correction. So, what do you recommend in terms of both volume, the urine parameters in the patient, and what steps would you take if you found that despite your half normal saline, the sodium was going up more rapidly than you wanted?

Dr. Rosner: I think you have two options if the serum sodium is still going up. One, is to change the infusion to have no sodium and you can go to something like dextrose 5% in water, which will hopefully match the aquaresis that is occurring. You can measure the urine osmolality to get a sense of how much of the urine is free water versus how much has got some solute in it and replace the water component back with the IV fluid to limit the rise in serum sodium levels. Or, you can give desmopressin to put a clamp on the urine osmolality and not let a rapid aquaresis develop so that the serum sodium is going to rise so quickly.

Dr. Verbalis: Let's now turn to Dr. Greenberg for presentation of a patient with euvoletic hypotonic hyponatremia.

Clinical Case Presentation

Dr. Greenberg: The case that I would like to present is one that we had seen on our cardiothoracic service not long ago. It is a 67-year-old man with chronic obstructive pulmonary disease (COPD) that had experienced a 5 kg weight loss over three months. He had a nonproductive cough at the time that he presented. He was confused, had an unsteady gait, and his family noted that he





had been forgetful. He had the additional symptoms of being dyspneic on climbing a single flight of stairs. He was on relatively few medications, which included amlodipine, clonidine, and an albuterol inhaler. A notable social history showed he was a 40-pack/year smoker and he drank about a glass wine per night.

This chest X-ray was obtained and there was little mystery in what might be the candidate for the weight loss, but the need to obtain a precise diagnosis was present.

The patient underwent bronchoscopy and mediastinoscopy, but they were inconclusive. He was admitted to the cardiothoracic surgery service in advance of a planned biopsy.

The routine laboratory studies showed that he was hyponatremic with a serum sodium 125 mEq/L, his potassium was 4.0 mEq/L, he had a BUN that was relatively low at 4 mg/dL, and a creatinine that was also fairly low at 0.6 mg/dL. His uric acid was low at 4.1 mg/dL and the serum osmolality was 265 mOsm/kg, which confirmed that he had hypotonic hyponatremia, and the urine was quite concentrated with a urine osmolality of 555 mOsm/kg. There was plenty of urine sodium at 85 mmol/L indicating that he was not volume depleted. Low urine sodium would have raised question of whether or not the patient was volume depleted.

Dr. Verbalis showed you one scheme for a diagnostic approach for hyponatremia, and this is another. What we want to do, of course, is decide if the patient is genuinely hyponatremic and whether he is hypotonic. Having excluded those relatively uncommon entities, we want to decide whether the patient has a diluting effect because treatment varies a great deal between patients that already have a maximally dilute urine and patients who have something interfering with the ability of the kidney to excrete a water load, namely in patients that have significant vasopressin levels present. Once it is established that the patient has a diluting defect (i.e., excreting a concentrated urine despite a low serum sodium value), which this patient certainly had with a urine osmolality of 555 mOsm/kg, then we proceed to assess extracellular volume status. Patients will either have a low, normal, or high extracellular volume and determining this aids therapy. For patients who are hypovolemic, we would correct the volume depletion, and in patients who are volume expanded and have an excess of sodium as well as an excess of water, we would try to improve the underlying pathophysiological state and certainly try to reduce the water content of the patient without adding sodium as treatment is undertaken.

The diagnosis of this patient was SIADH. The cardinal features of SIADH are true low plasma osmolality, urine that is not maximally dilute; this patient's urine was not nearly maximally diluted as it was quite concentrated. The patient should be euvolemic by clinical criteria. Urine sodium should be high enough, typically 30 mmol/L, but it should be high enough to indicate that the patient is not in a sodium retentive state as might be seen in a patient with subtle volume depletion or in a patient with hyponatremia related to a condition characterized by ineffective arterial volume, like heart failure or cirrhosis. By convention, we do not diagnose SIADH in patients who have adrenal or thyroid dysfunction and thyroid dysfunction would have to be quite severe. Therefore, you want to have evidence that the patient's kidney function, adrenal function, and thyroid function are all normal. Additional features that can

be helpful in the diagnosis are a low BUN, which can be an indicator of volume expansion rather than volume contraction, a low uric acid, and a nonsuppressed vasopressin level that could be established by measuring vasopressin levels. However, vasopressin levels are seldom assessed because of the expense, difficulty, and because of the delay in getting vasopressin levels back—we need to make a diagnosis well before we have a vasopressin level on hand.

Figure 30

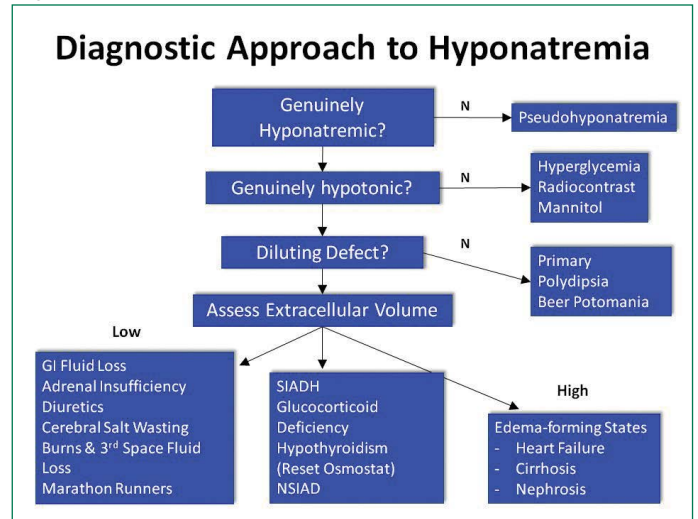
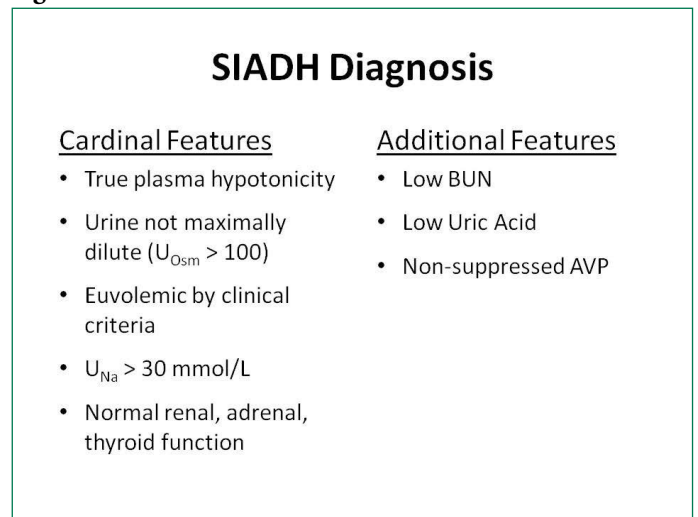


Figure 31



So, to review this patient's course, he was admitted to the cardiothoracic service in advance of the biopsy. He was treated by the surgeon with fluid restriction with salt tablets; he was given about 6 g of salt per day, which is about 100 mmol of sodium chloride for two days and at the end of that, the sodium did not improve as it was at 124 mmol/L. That was followed by infusion of normal saline for a day and after that the sodium was actually a bit lower and at that point, advice from nephrology service was solicited.

So, to summarize the treatment so far, you can see that initial treatment with 1 L of fluid restriction and supplemental salt given as salt tablets and as normal saline did not result in an improvement.


But we can ask, what should we do now? The choices are: to fluid restrict to 500 mL/d, to begin hypertonic saline with furosemide, to begin demeclocycline, or to begin tolvaptan.

Now, first a bit about fluid restriction. Figure 32 shows the derivation of the free water clearance.

Figure 32

Free Water Clearance and Electrolyte-Free Water Excretion

$$\begin{aligned}
 V &= C_{\text{Osm}} + C_{\text{H}_2\text{O}} \\
 C_{\text{H}_2\text{O}} &= V - C_{\text{Osm}} \\
 C_{\text{H}_2\text{O}} &= V - \frac{U_{\text{Osm}} \times V}{P_{\text{Osm}}} \\
 C_{\text{H}_2\text{O}} &= V \times \left(1 - \frac{U_{\text{Osm}}}{P_{\text{Osm}}}\right) \\
 C_{\text{EFH}_2\text{O}} &= V \times \left(1 - \frac{U_{\text{Na+K}}}{P_{\text{Na+K}}}\right)
 \end{aligned}$$



Free-water clearance is an expression of how much water is being excreted by the kidneys, which is water that would have the effect of allowing the serum sodium to rise. It is derived by looking at urine content, or urine flow rate (V), as being the sum of osmolar clearance, the virtual volume from which osmoles are cleared plus the free-water clearance. One can rearrange that expression and substitute a standard clearance expression for osmolar clearance, and then factor that expression and one is left with free water clearance being equal to the urine flow rate (V) times 1 minus the urine osmolality divided by the plasma osmolality. It is apparent that if urine osmolality is greater than the plasma osmolality, then the free-water clearance is going to be negative and the urine is not going to make a great contribution of getting rid of water. One can also consider the electrolyte free water clearance and that is shown in the final line of this slide. In this case, one considers the urine electrolyte content, which is really the heart of the matter, since this does not include any osmoles contributed by urea. The

results are going to be quite similar whether one looks at osmolality or electrolyte free-water clearance.

To recap, in this patient, the urine osmolality was 555 mmol/L and the plasma osmolality was 265 mmol/L. The free water clearance would be quite negative.

Figure 33

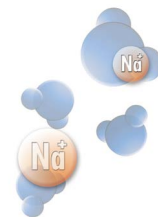
Free Water Clearance and Electrolyte-Free Water Excretion

$$\begin{aligned}
 V &= C_{\text{Osm}} + C_{\text{H}_2\text{O}} \\
 C_{\text{H}_2\text{O}} &= V - C_{\text{Osm}} \\
 C_{\text{H}_2\text{O}} &= V - \frac{U_{\text{Osm}} \times V}{P_{\text{Osm}}} \quad \text{555} \\
 C_{\text{H}_2\text{O}} &= V \times \left(1 - \frac{U_{\text{Osm}}}{P_{\text{Osm}}}\right) \quad \text{265} \\
 C_{\text{EFH}_2\text{O}} &= V \times \left(1 - \frac{U_{\text{Na+K}}}{P_{\text{Na+K}}}\right)
 \end{aligned}$$

Therefore, fluid restriction is not going to help us and 500 mL/day of fluid restriction is not by any means practical. Well, I think the correct thing to do in this instance would be to give tolvaptan. Hypertonic saline with furosemide would not be a good choice in this patient because it is a bit tricky to manage those two together and that combination is generally used in patients in whom hypertonic saline may not be tolerated because of the volume load and one would give furosemide to encourage loss of the administered sodium. But this patient's mild confusion and chronicity of the hyponatremia does not make him a candidate for such aggressive treatment. One could consider giving demeclocycline; however, it is not FDA approved for the treatment of hyponatremia and it is quite slow acting with the potential for nephrotoxicity.

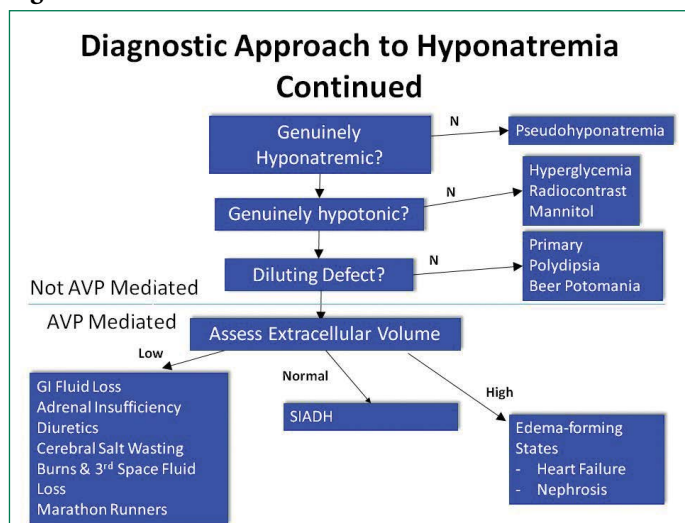
Which patients are candidates for receiving a vaptan? In order to determine whether to use a vaptan, one must first establish that the hyponatremia is vasopressin-mediated. So, only the patients shown below the horizontal line in Figure 34 would be considered.

One should really focus attention on considering vaptans in patients who have normal or increased extracellular volume. Patients with low extracellular volume, like the one we just heard about, respond to simple volume expansion. There is no reason to consider a vaptan in those patients. We generally only consider a vaptan for a patient with normal extracellular volume or an increased extracellular volume. Now, not every one of those patients will be a candidate. If the patient has a glucocorticoid deficiency, then replacement of cortisol deficiency will rapidly result in a correction of the hyponatremia and there would be no reason to consider addition of a vaptan. Similarly, correction of edema will lead to correction of hyponatremia. In patients with increased extracellular volume, the drug has the potential to be



effective in all three of the cardinal disorders, heart failure, cirrhosis, and nephrosis. But the package labeling tells us not to use tolvaptan in patients with cirrhosis. When tolvaptan was used in another setting for treatment of polycystic kidney disease, transaminase elevations were observed and that has led to the need for caution in considering their use in patients with cirrhosis.

Figure 34



So to get back to the patient, with the failure of initial therapy, the nephrology consultation was obtained and 15 mg of tolvaptan was initiated.

With the initiation of tolvaptan, there was a nice response and the sodium came up at an acceptable rate, reaching a value of 137 mmol/L and the patient was able to go into the operating room for lung biopsy.

In the operating room, the right upper lobe and the superior segment of the right middle lobe were resected and the pathologic finding was that of large cell lung cancer with neuroendocrine elements; squamous cell elements were absent. Curiously, this was not small cell lung cancer that would be more typically responsible for SIADH. Subsequent to the biopsy, the patient’s sodium drifted downward, fluid restriction and salt tablets were begun and the patient was discharged to home. Not long thereafter, the patient became short of breath, was readmitted and was found to have a postoperative empyema.

Here is the course of this admission. He underwent the resection sometime before Day 15 and sodium was in the 125 to 130 mmol/L range during that time to about 126 or 127 mmol/L at the time of discharge. The patient was readmitted for the empyema and fluid restriction was the principle treatment and that did not result in any change in serum sodium.

Urine osmolality was measured at that point and it was still quite high at 551 mOsm/kg and tolvaptan was initiated. With that, serum sodium again rose and there was an associated reduction in the urine osmolality to 179 Osm/kg and water diuresis that accounted for the rise in serum sodium.

While the patient was in the hospital, he did well initially; but, then experienced respiratory deterioration. He developed pneumonia becoming dyspneic requiring BiPAP. He experienced reduced level of consciousness.

This brings us to a point where we can consider what precautions should be used when treating a patient with a vaptan. Here are some precautions to consider: do not restrict water intake on Day 1, monitor sodium frequently with therapy initiation, titrate the drug dose up or down depending on response, and stop the drug if access to water is limited.

The answer, of course, is that all of those precautions must be taken. The package labeling tells us not to restrict water intake on Day 1 and the reason is that the initial trials using this drug were done with that precaution. But, it is a wise precaution; one does not know how rapidly the serum sodium will respond in response to an addition of a vasopressin receptor antagonist and in a patient with chronic hyponatremia, one is more worried about the possibility of over rapid correction and osmotic demyelination than one is worried about one additional day with persistent hyponatremia. The only way that one would be able to see the progress of the change in serum sodium is by monitoring the sodium value frequently, particularly during the period just after therapy initiation. I tend to follow serum sodium every 8 hours, at least during the first 24-hour period to get an idea how rapidly the serum sodium is rising and so that I can intervene if necessary, if the rate of rise appears to be too rapid. The drug dose can be titrated up or down, a typical starting dose is 15 mg for tolvaptan, but one can give 30 mg or 60 mg, changing the dose up or down depending upon the sodium response and the sodium goals. Finally, one must remember to stop the drug if access to water is limited. In giving tolvaptan or any vaptan, one is essentially producing chemically-induced nephrogenic diabetes insipidus and the protection against developing hypernatremia in patients with nephrogenic diabetes insipidus is thirst and ingestion of water. If the patient can not either gain access to water or communicate thirst, then that patient would be at risk of developing hypernatremia.

That is what happened in this patient. With the pulmonary deterioration and with continued administration of tolvaptan, the serum sodium rose. Fortunately, that was recognized, tolvaptan was stopped, and a dilute solution consisting of 5% dextrose in water was administered and that brought the sodium back down in a controlled fashion. There were no adverse consequences of the rise in serum sodium.

So, I tried in this case to show you how one may use vaptans and to give an example of the precautions that have to be used when treating a patient with a vaptan.

DISCUSSION 3

Dr. Verbalis: So, Art, this is a very nice illustrative case of a situation in which you could have predicted from the start, based on the urine osmolality and probably based on the urine to plasma ratio, that this patient was unlikely respond to fluid restriction. In fact, the

patient actually had deterioration in the serum sodium concentration. What do you think was the reason for the actual worsening of the hyponatremia with that therapy?

Dr. Greenberg: Well, it has been well described that administration of normal saline to patients with SIADH, particularly in severe SIADH where the urine osmolality is quite high, that those patients are able to generate free water. They are able to excrete the administered salt in a small volume of urine and have net retention of water. And the effect of that is further reduction of serum sodium. And it is not possible with hypertonic saline, which is one of the reasons that with hypertonic saline you can not concentrate the urine enough to excrete the salt from hypertonic saline in the urine and have some water left over for retention to lower the serum sodium.

Dr. Verbalis: An important point is that in some patients, it is not just that standard therapies that are typically employed such as fluid restriction and isotonic saline administration are not just not effective, they can actually worsen the hyponatremia.

Dr. Greenberg: They can. Now the common situation that arises is that the patient's fluid status is indeterminate. Sometimes, you are uncertain whether a patient is euvolemic or has SIADH or is just mildly volume depleted, and in those instances, it can be appropriate to give a trial of volume expansion and how exactly to do that trial of volume expansion depends upon how low the sodium is and what the risk might be of further lowering of sodium. If the patient's just has moderate hyponatremia, then you could do that volume expansion trial with a discrete volume of normal saline, even if you dropped the serum sodium a little bit, in this case it would not put the person at risk. But if the sodium is 114 mmol/L and if there is uncertainty about the patient's volume status, then you might want to do that trial of volume expansion with hypertonic saline so that there is no risk that you would give a liter of isotonic saline and have their sodium drop to 111 or 112 mmol/L.

Dr. Rosner: Can you comment on the risk of over rapid correction with vaptans?

Dr. Greenberg: Well, in the SALT trials, which were the pivotal trials used to gain approval for the drug, the incidence of over rapid correction was about 4%. Importantly, that was in a very carefully studied population, using a strict protocol, by investigators with experience in the field. So, I would consider that 4% risk as a floor for the risk; it is probably a bit higher in ordinary clinical settings, where a physician administering the drug may

not be as experienced with the use of the drug. That is why I emphasized that the serum sodium should be followed very frequently and then one has an opportunity to intervene if it appears that the rate of rise of serum sodium is going to be too rapid. Again, using that goal of perhaps 6 mEq/L per day rise in a patient with chronic hyponatremia and does not require a rapid increase, then there is opportunity to give 5% dextrose in water and withhold the drug on the second day, and ensure that over rapid correction does not occur or does not progress beyond the time when it is first detected.

Clinical Case Presentation

Dr. Rosner: A 72-year-old male was admitted to the hospital with symptoms of increasing shortness of breath, especially with minor exertion, and worsening peripheral edema. Past medical history is notable for systolic heart failure with an ejection fraction of 25%, type 2 diabetes mellitus, coronary artery disease, and hyperlipidemia. His medications included lisinopril at 20 mg daily, furosemide at 80 mg twice daily, spironolactone at 25 mg daily, carvedilol at 25 mg twice daily, atorvastatin at 10 mg, and daily insulin therapy.

His physical examination included blood pressure at 100/50 mmHg, his pulse was 100 beats/minute and regular. He had jugular venous distention, pulmonary rales, as well as findings consistent with a right-sided pulmonary effusion, and significant lower extremity edema.

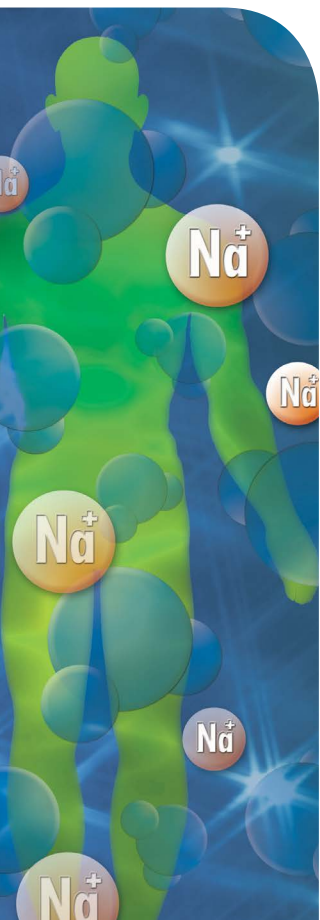
Initial laboratory values, which are notable for a serum sodium of 129 mEq/L, included serum potassium of 3.5 mEq/L, bicarbonate of 30, BUN of 29 mEq/L, creatinine of 1.2 mg/dL, a very elevated N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level of 6900 pg/mL, and a low urine sodium of less than 20 mEq/L which is consistent with a poor output state in congestive heart failure.

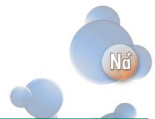
The patient was started on IV furosemide continuous infusion initially at 10 mg which was subsequently increased to 20 mg per hour to treat his significant congestive symptoms. Intermittent metolazone at 5 mg daily was also given to aid diuresis. His urine output significantly increased to 2.2 L per day and his weight began to decrease.

However, on Day 1 his serum sodium was 129 mEq/L and progressively over his first four days of his hospital admission, his serum sodium fell to 120 mEq/L at Day 4.

So, the question that arises is, what is the best option for treating both volume overload and worsening hyponatremia? This is a difficult clinical situation and some of the treatment choices include: 3% saline infusion, addition of sodium chloride tablets, beginning tolvaptan, fluid restriction, or just stopping the diuretic altogether.

Well, let us discuss hyponatremia in heart failure and we will think about the treatment options and come back to the case and what I think is the right course of treatment. In terms of outcomes when hyponatremia is present, in the OPTIME-CHF study where





patients were defined as having left ventricular ejection fraction of less than 40%, nearly 20% of these patients were hyponatremic with serum sodium of less than 135 mEq/L. Those patients were at a high risk of in-hospital death and a 10% increased risk of follow-up mortality. There was a dose-response of the level of serum sodium and the combined risk of death or rehospitalization, so that there was an 8% increased risk of those outcomes for every 3 mEq/L decrease in the admission serum sodium less than 140 mEq/L.

Figure 35¹⁷

Hyponatremia in Heart Failure: Outcomes

- OPTIME-CHF Study
 - HF defined as LVEF <40%
 - 19.7% hyponatremic ([Na+] <135 mEq/L) at admission
 - 19.5% increased risk of in-hospital death
 - 10% increased risk of follow-up mortality
 - 8% increased risk of death or rehospitalization for each 3 mEq/L decrease in admission [Na+] <140 mEq/L

Georghiadis M, et al. Eur Heart J. 2007;28(8):980-8.

Hyponatremia in heart failure is due to a combination of both sodium retention that is primarily mediated by renal mechanisms due to a decrease in renal blood flow and GFR, an increase in tubular reabsorption of sodium and chloride, elevation of the renin-angiotensin-aldosterone hormonal axis, and inadequate natriuretic mechanisms. Water retention is a parallel process here. There is obligatory water reabsorption that accompanies salt reabsorption, there is elevated angiotensin II levels that stimulate thirst and provokes the release of vasopressin, there is reduced renal tubular renal blood flow which increases free water absorption, and diuretics exacerbate all of these conditions.

Figure 37 shows diagrammatically how initial low cardiac output leads to activation of arterial and ventricular receptors that in turn lead to the nonosmotic stimulation of vasopressin secretion, as well as stimulation of the sympathetic nervous system, and activation of the renin-angiotensin system.

On the right side, renal sodium retention occurs secondary to activation of the renin-angiotensin system. There is also increased peripheral and renal arterial vascular resistance, and also due to the nonosmotic vasopressin stimulation, renal water retention. This is all an attempt to maintain arterial circulation and the integrity of the hemodynamics to maintain end organ perfusion.

Importantly, there is a relationship so that plasma vasopressin levels are increased in patients with lower cardiac indexes.

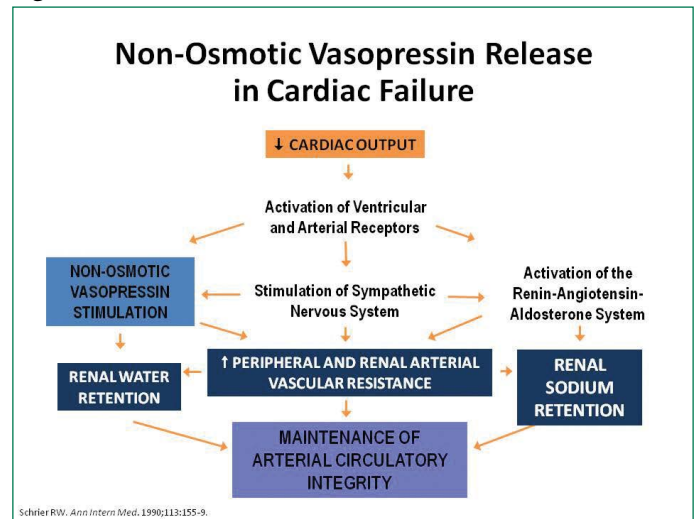
Figure 36¹⁸

Hyponatremia in Heart Failure

- Na+ retention in HF is primarily mediated by renal mechanisms
 - Decrease in renal blood flow and glomerular filtration rate
 - Increase in tubular reabsorption of NaCl
 - Elevation of renin-angiotensin-aldosterone
 - Inadequate natriuretic mechanisms
- Water retention is a parallel process
 - Obligatory water reabsorption accompanies salt reabsorption
 - Elevated angiotensin II stimulates thirst and provokes release of AVP
 - Reduced renal tubular flow increases free-water absorption
 - Diuretics exacerbate this condition

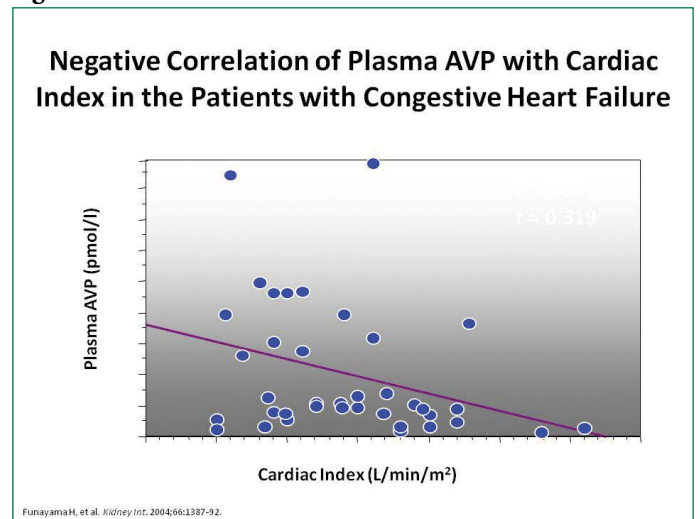
Leier CV, et al. Am Heart J. 1994;128:564-74.

Figure 37¹⁹



Schrier RW. Ann Intern Med. 1996;113:155-9.

Figure 38²⁰



Funayama H, et al. Kidney Int. 2004;66:1387-92.

Figure 38 demonstrates the negative correlation of plasma vasopressin levels with cardiac indices in patients with congestive heart failure. As was discussed earlier, this is a situation in which high vasopressin levels lead to continued retention of water through renal mechanisms.

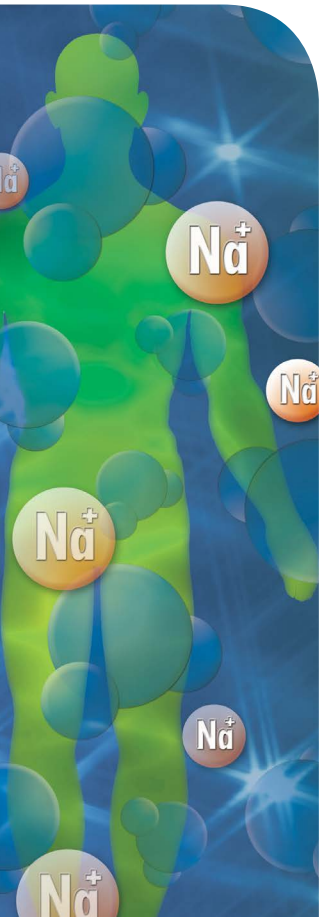
Figure 39²¹

Agent	Considerations
Isotonic saline	- Limited use in setting of edema
Hypertonic saline*	- Limited use in setting of edema + Some recent studies with high dose loop diuretics have shown benefit but requires further study
Loop diuretics	+ May allow for relaxation of fluid restriction + Required to treat congestive symptoms - Potential for volume depletion, and K ⁺ and Mg ⁺ depletion - Potential for worsening hyponatremia
Fluid restriction	+ Inexpensive - Slow and limited response; adherence concerns
Demeclocycline	+ Targets excessive AVP - Slow response; may take 3-6 days to correct - Not FDA approved for hyponatremia - Risk of nephrotoxicity in cirrhosis and heart failure
Salt tablets	- Requires concomitant diuretics
AVP receptor antagonists	+ Target excessive AVP; produces aquaresis + Improves congestion

*Licata G, et al. Am Heart J. 2003;145:459-66.

Coming back to our patient with hyponatremia in the setting of heart failure. Let's investigate the possible therapies. Isotonic saline, if the patient is certainly volume depleted, would be an option. But certainly, in a patient with significant congestive symptoms this would not be a reasonable course of action.

Along with that, hypertonic saline has a very limited use in this setting of edema; but, some recent studies with high-dose loop diuretics in combination with hypertonic saline have shown some benefit. This is very complex, requires careful monitoring, and can be difficult to achieve clinically. Loop diuretics allow for the relaxation of fluid restriction and they are certainly required to treat the congestive symptoms. But as we've seen here, they have a potential for volume depletion, as well as magnesium and potassium depletion, and in this case, for worsening hyponatremia. The major benefit of fluid restriction is that it is inexpensive; but, it has a very slow, limited response and adherence is difficult. Demeclocycline is an option; however, it is not FDA approved for hyponatremia. It does target the excessive vasopressin; but, has a slow response and there is risk for liver toxicity. Salt tablets can be used but



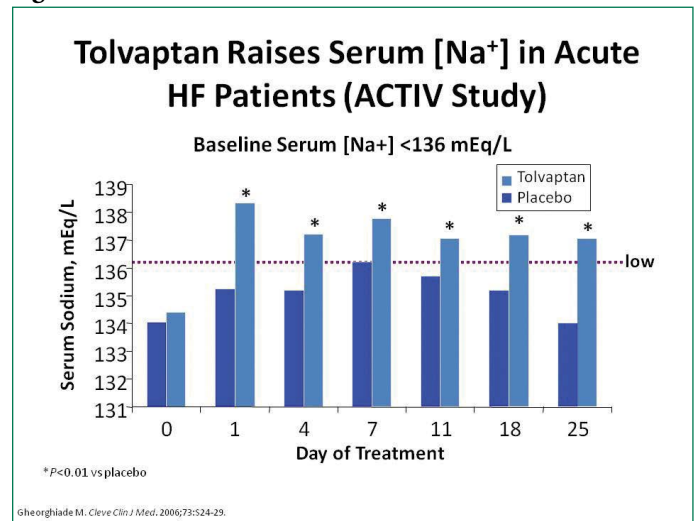
they also require concomitant diuretic use. Another option is the arginine vasopressin receptor antagonists, which we discussed earlier. These target the pathophysiology by targeting the excessive vasopressin; it produces aquaresis and at the same time can improve the congestive symptoms by improving the volume overload.

When hyponatremia develops or worsens with a loop diuretic, a common response is to decrease or stop use of these agents. However, this is problematic and usually undesirable since the treatment of congestion is still of primary concern for the patient's care. So, really this requires other strategies that have to address the congestive symptoms, as well as treating or avoiding hyponatremia.

This leads to a logical discussion that vasopressin receptor antagonists may be an optimal treatment for patients with heart failure and hyponatremia. Essentially, given the primacy of vasopressin in the pathogenesis of water retention, targeting this pathway has great promise and makes pathophysiological sense.

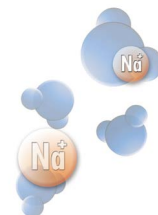
In the ACTIV study, Figure 40 (light blue bars), tolvaptan was given to patients with heart failure, and results showed an increase in serum sodium concentrations on different days of treatment compared with placebo. Overall, you see a significant increase in serum sodium values by Day 1 and sustained throughout the trial up to Day 25, compared with placebo treatment.

Figure 40²²



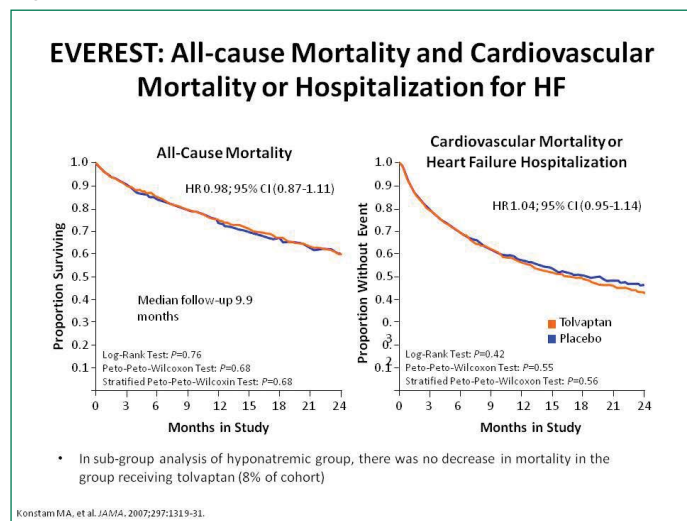
Now, vasopressin receptor antagonists have also been studied in patients with generalized heart failure, including patients that do not have hyponatremia. This was done in the EVEREST study that looked at all-cause mortality as well as cardiovascular mortality and hospitalization for heart failure (Figure 41).

In the EVEREST study, there was no decrease in all-cause mortality, as well as cardiovascular mortality or heart failure hospitalization as compared with placebo. Now, once again, I want to stress



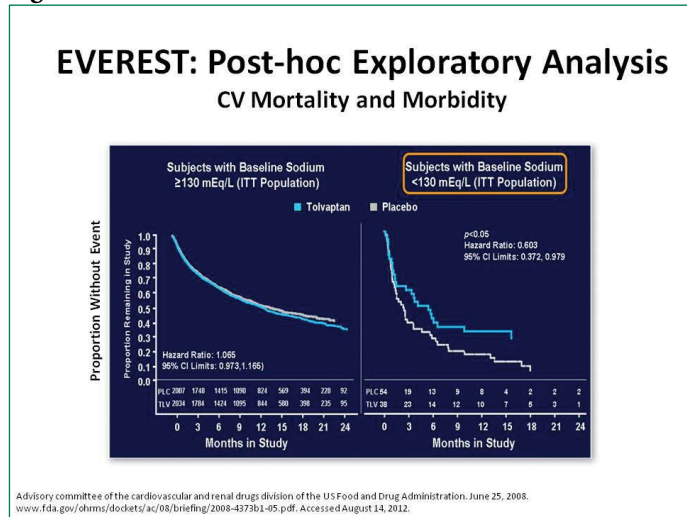
that only a small minority of patients in this trial actually had hyponatremia along with their decompensated heart failure.

Figure 41²³



In fact, in a post-hoc exploratory analysis of cardiovascular mortality and morbidity, when you looked at the subjects with baseline serum sodiums less than 130 mEq/L, you can see that the hazard ratio actually favors treatment with tolvaptan over placebo and actually did show benefit in terms of decreased cardiovascular mortality and morbidity.

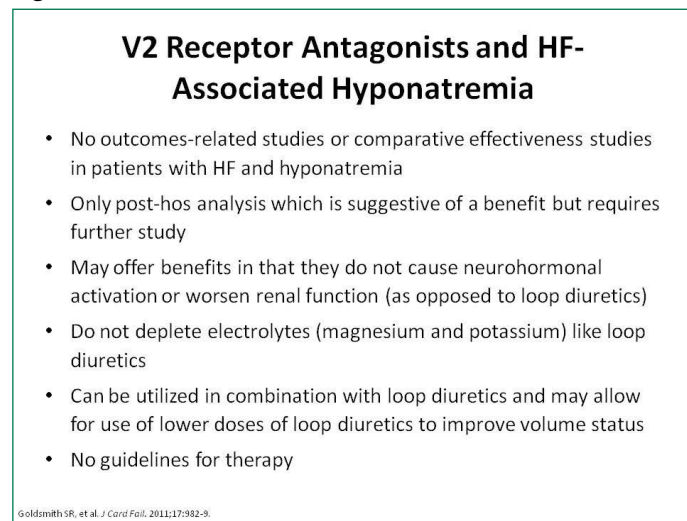
Figure 42²⁴



To summarize the role of vasopressin receptor antagonists in heart failure-associated hyponatremia, there are no outcomes-related studies or comparative effectiveness studies in patients with heart failure and hyponatremia, specifically. There is only the post-hoc analysis, which is suggestive of a benefit; but, certainly requires further study. Importantly, vasopressin receptor antagonists may offer benefits in that they do not cause neurohormonal activation or worsen renal function, as opposed to loop diuretics. They also

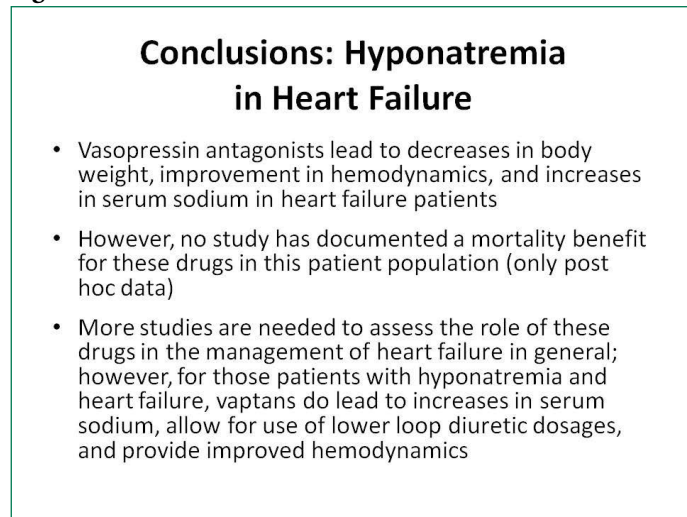
do not deplete electrolytes such as magnesium and potassium, which is so common with loop diuretic therapy. Importantly, they can be utilized in combination with loop diuretics and may allow for use of lower doses of loop diuretics to improve volume status. However, there are no generalized guidelines for therapy at this time.

Figure 43²⁵



In terms of an overall approach for severely symptomatic patients with a low or rapidly falling serum sodium, treatment can consist of using hypertonic saline combined with a loop diuretic to prevent fluid overload; but, for patients with mild to moderate symptoms, beginning with fluid restriction may be a reasonable alternative. If the serum sodium doesn't correct to the desired level, then lifting the fluid restriction and starting either conivaptan, if an intravenous route is required, or tolvaptan, if oral therapy is preferred. Of note, the FDA has recently recommended that therapy with tolvaptan not be given for more than 30 days at a time due to the risk of liver injury.

Figure 44



CONCLUSIONS

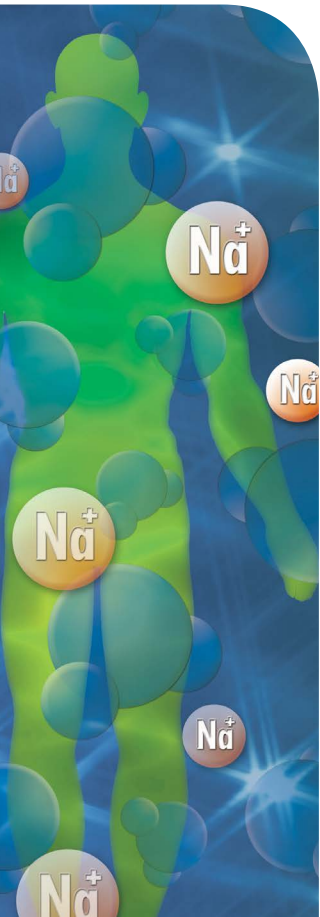
Vasopressin receptor antagonists lead to decreases in body weight, they improve hemodynamics, and increase serum sodium in heart failure patients. However, no study, other than the post-hoc analysis, has demonstrated a mortality benefit for these drugs in this patient population at this time. More studies are needed to assess the role of these drugs in the management of heart failure; however, for those patients with hyponatremia and congestive symptoms, vaptans do lead to increases in serum sodium, they allow for use of lower loop diuretic dosages, and provide improved hemodynamics.

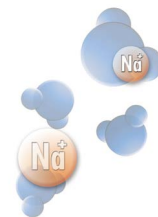
Dr. Verbalis: So, you stress that use of vaptans might allow use of lower doses of loop diuretics because of the combined effects of the diuresis and the aquaresis, but is it not true as well that in some cases they might allow higher use of loop diuretics? In other words, one of the limitations of continuing to use loop diuretics in patients like you presented is to lower the serum sodium to dangerous levels and sometimes that can tie the hands of the cardiologist by not allowing them to give the doses of loop diuretics that they would like to give to relieve congestion. So, by getting the hyponatremia effectively out of the picture with the vaptans, it allows the cardiologist leeway to use either decreased or increased doses of loop diuretics depending on the degree of congestion and volume overload in the patient.

Dr. Rosner: Yes, good point. I think that either can be the case. One thing that you do see when you use combination vaptan plus loop diuretic therapy is that the urine outputs can be quite large over a 24-hour period. So, in fact, you do risk actually almost over-diuresing or aquaresing the patient. You need to have some caution. So, I think you have to be a little bit careful when determining the loop diuretic dose to avoid excessive urine output.

Dr. Greenberg: I just wanted to point out that we talk about the limitation of long-term use of vaptans, but this is a setting where short-term use can be quite helpful and where one may really not need to consider long-term use. As the congestion improves with the combination of therapies used, then the water retentive tendency may be diminished.

Dr. Verbalis: I want to thank Drs. Greenberg and Rosner for these excellent cases that have very well summarized some of the problems and potential solutions of treating hyponatremic patients with a very diverse range of etiologies and therapeutic indications.





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