Optimal Management of Hospitalized Patients with Hyponatremia: Case Scenarios

Presented as a Live Webinar
Wednesday, January 29, 2014
1:00 p.m. – 2:00 p.m. EST

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1. Computer with internet access and basic system requirements. When you register, the webinar system will assess your system to ensure compatibility.
2. Telephone to dial the toll-free number and listen to the presentation (if you choose not to use Voice Over IP [VoIP] via your computer).

Webinar System Requirements
Be sure to view the webinar system requirements for Windows, Mac, iOS, and Android prior to the activity.

Activity Faculty

Amy L. Dzierba, Pharm.D., BCPS, FCCM
Clinical Pharmacist, Adult Critical Care
New York-Presbyterian Hospital
Lecturer
Columbia University School of Nursing
New York, New York

Amy L. Dzierba, Pharm.D., BCPS, FCCM, is a clinical pharmacist in the medical intensive care unit at New York-Presbyterian Hospital (NYPH) in New York. She also serves as Program Director of the postgraduate year 2 (PGY-2) residency program in critical care at NYPH, which she established in 2007. In addition, Dr. Dzierba is a lecturer at the Columbia University School of Nursing and has served as a member of the Investigational Review Board at Columbia University Medical Center for over seven years.

Dr. Dzierba earned both her Bachelor of Science in pharmacy and Doctor of Pharmacy degrees from Midwestern University's Chicago College of Pharmacy in Downer's Grove, Illinois. She completed a postgraduate year 1 (PGY-1) pharmacy residency at Grady Health System in Atlanta, Georgia, and a PGY-2 pharmacy residency in critical care at the University of Washington and Harborview Medical Center in Seattle.

Dr. Dzierba received the Harold Neham Memorial Award from the New York City Society of Health-system Pharmacists in 2011 and was recognized as a fellow of the American College of Critical Care Medicine in 2012. She is an active member of the American College of Clinical Pharmacy, American Society of Health-System Pharmacists, New York State Council of Health-system Pharmacists, and Society of Critical Care Medicine. Dr. Dzierba has presented on topics related to critical care, such as sedation and analgesia, alcohol withdrawal, hyponatremia, and the impact of extracorporeal membrane oxygenation on drug dosing.

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- Jodie L. Pepin, Pharm.D.
- Carla J. Brink, M.S., B.S.Pharm.
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Activity Overview

Hyponatremia remains a frequently overlooked and undertreated electrolyte disorder in hospitalized patients, often with serious clinical and economic outcomes. In this activity, the faculty will use patient case scenarios to illustrate important concepts for managing hyponatremia safely and effectively in different types of hospitalized patients. To set the stage for the patient scenarios, the clinical and economic burden of hyponatremia in hospitalized patients will be presented.

Time for questions and answers from the webinar audience will be provided at the end of the presentation.

Learning Objectives

At the conclusion of this application-based educational activity, participants should be able to

- Describe the impact of hyponatremia on morbidity, mortality, and use of health care resources in hospitalized patients.
- Recommend a strategy for monitoring and managing a patient's hyponatremia based on volume status, clinical presentation, and co-morbidities.

Continuing Education Accreditation

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.0 hour (0.1 CEU) of continuing pharmacy education credit (ACPE activity #0204-0000-14-468-L01-P).

Attendees must complete a Continuing Pharmacy Education Request online and may immediately print their official statements of continuing pharmacy education (CPE) credit following the activity.

Complete instructions for processing CE can be found on the last page of this handout.

Optimal Management of Hospitalized Patients with Hyponatremia: Case Scenarios

Amy L. Dzierba, Pharm.D., BCPS, FCCM
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New York-Presbyterian Hospital
Lecturer
Columbia University School of Nursing
New York, New York

Learning Objectives

After attending this activity, you should be able to

- Describe the impact of hyponatremia on morbidity, mortality, and use of health care resources in hospitalized patients.
- Recommend a strategy for monitoring and managing a patient's hyponatremia based on volume status, clinical presentation, and co-morbidities.

Hyponatremia Definition

- Commonly defined as serum sodium concentration <136 mEq/L, but cut-off values often vary by laboratory
- Degree of severity is associated with serum sodium concentration

Serum Sodium Concentration (mEq/L)		
Mild	Moderate	Severe
131-135	120-130	<120

Upadhyay A et al. *Am J Med*. 2006; 119(Suppl 1):S30-5.
Kumar S et al. *Lancet*. 1998; 352:220-8.

Incidence of Hyponatremia

- Most common electrolyte disorder
  - 6-15% of hospitalized patients at admission and an additional 5% during the hospital stay
- 25% of patients in ICU are hyponatremic
- If not treated appropriately, can lead to significant morbidity, mortality, and costs
- Insufficient data to determine if hyponatremia is a "marker" or "mediator" of adverse outcomes

ICU = intensive care unit

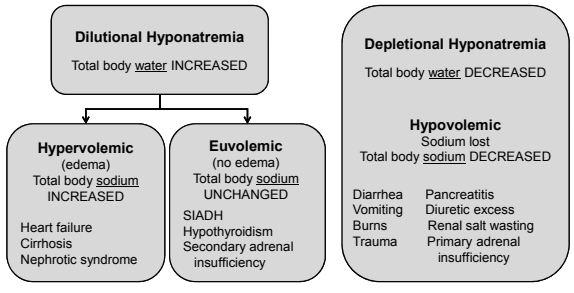
Deitelzweig S el al. *Hosp Prac.* 2011; 39:87-98.
Upadhyay A et al. *Semin Nephrol.* 2009; 29:227-38.

Common Symptoms Associated with Severity of Hyponatremia

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

Bagshaw SM et al. *Can J Anaesth*. 2009; 56:151-67.
Ghali JK. *Cardiology*. 2008; 111:147-57.

How is Hyponatremia Classified?

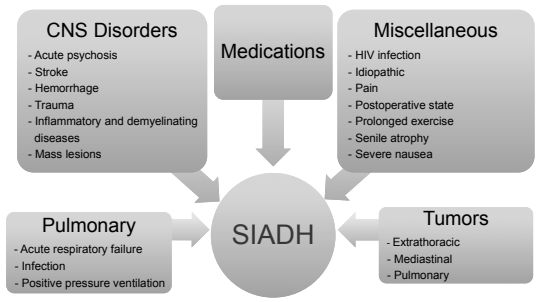


SIADH = syndrome of inappropriate antidiuretic hormone

Cawley MJ. *Ann Pharmacother.* 2007; 41:840-50.

see page 15 for enlarged view

Various Causes of SIADH

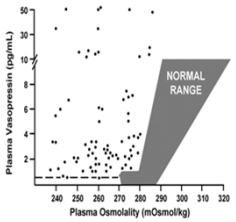


Verbalis JG et al. *Am J Med*. 2013; 126:S1-S42.

see page 15 for enlarged view

Vasopressin Concentrations Inappropriately Elevated in Patients with SIADH

- Caused by excessive levels of vasopressin as a result of disease, drug-induced pituitary release of arginine vasopressin (AVP)
- AVP secretion not suppressed appropriately when plasma osmolality falls below the osmotic threshold
- Inability to suppress AVP secretion results in
  - Impaired renal water excretion
  - Increased total body water
  - Hyponatremia



Zerbe R et al. *Annu Rev Med*. 1980; 31:315-27.

see page 16 for enlarged view

Outcomes Associated with Declining Sodium Concentrations

- Defined – serum sodium concentration <138 mEq/L on admission and further decline < 2 mEq/L over first 48 hours
- This level of decline occurs in 6% of community-acquired hyponatremia patients
- OR for inpatient mortality
  - 2.30 (1.75-3.02) with decline
  - 1.46 (1.31-1.64) with no decline
- OR 1.40 (1.32-1.49) for prolonged length of stay (LOS)
- Sets stage for impact of therapies

OR = odds ratio

Wald R et al. *Arch Intern Med.* 2010; 170:294-302.

Preoperative Hyponatremia in CABG Patients and Outcomes

- Of 4370 patients, 21% had hyponatremia
- Were sicker and had more co-morbid conditions and organ dysfunction
- Adjusted outcomes for patients with hyponatremia
  - 31% higher overall mortality (early and late)
  - 26% increase in length of stay
  - 64% increase in postoperative complications
- Suggests need for optimal preoperative correction of hyponatremia in CABG patients

CABG = coronary artery bypass graft

Crestanello JA et al. *J Surg Res.* 2013; 181:60-6.

Sodium Fluctuations and Outcomes in ICU Patients

- Evaluation of dysnatremia in 11,000 ICU patients from 2004 to 2009 in one ICU
- Dysnatremia either at admission or during ICU stay is associated with higher mortality
- Median fluctuation of sodium in ICU 4 mEq/L (IQR 2-7)
- Sodium fluctuation > 6 mEq/L in normonatremia
  - Higher risk of hospital death (OR 1.5)
  - Possible changes in osmolality in serum and brain
  - First study to implicate serum sodium fluctuations

IQR = interquartile range

Sakr Y et al. *Crit Care Med.* 2013; 41:133-42.

Outcomes of Patients with Hyponatremia*

Variable**	Hyponatremia (*n* = 10,900)	No Hyponatremia (*n* = 187,400)
Hospital mortality (%)	5.9	3.0
Ventilated (%)	5.0	2.8
ICU (%)	17.3	10.9
Median LOS (days)	8.6	7.2
Hospital costs ($)	16,500	13,560

*From a database of 200,000 patients.
**All variables significantly different between groups at $p < 0.001$.

Adjusted incremental hospital cost = $2289

Zilberberg MD et al. *Curr Med Res Opin.* 2008; 24:1601-8.

Cost of Hyponatremia in Patients with Heart Failure

- Association of hyponatremia and adverse outcomes in heart failure well known
- Study of 51,000 patients with heart failure with and without hyponatremia to assess costs
- After adjusting, hyponatremic patients had
  - 21.5% higher hospital LOS
  - 25.6% higher hospital costs
  - 24.6% higher ICU costs
  - Higher all-cause 30-day readmission (OR 5.1)

Amin A et al. *J Med Econ.* 2013; 16:415-20.

Key Points

- Hyponatremia is common in hospitalized patients
  - Has complex pathophysiology
  - Associated with poor clinical outcomes
  - Have consistent documentation of high economic burden
- Sets stage for appropriate identification and treatment

Patient Case: CD

CD is a 76-year-old woman presenting to ED after hitting her head as a result of a fall. She complains of hip pain, nausea, and dizziness and relates that she has been "unsteady on her feet" over the past few days.

PMH: HTN, hyperlipidemia, DJD (hip and knees), depression
Physical exam: Laceration to right brow, right hip pain, normal skin turgor, and slightly dry oral mucosa
Vitals: temp 98.2^{0}F, BP 150/80 mm Hg, HR 88 bpm
Neuro: Slightly confused; no focal deficits
Head CT: negative
X-ray hip: Evidence of hip fracture
Laboratory data: Sodium 117 mEq/L, potassium 3.9 mEq/L, creatinine 0.9 mg/dL, BUN 10 mg/dL, glucose 102 mg/dL

CD's Home Medications

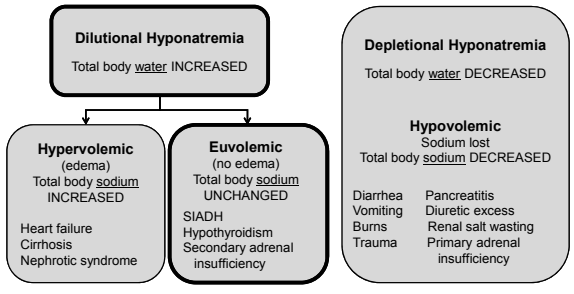
- Lisinopril 40 mg orally daily
- Metoprolol 25 mg orally twice daily
- Aspirin 81 mg orally daily
- Simvastatin 20 mg orally daily
- Citalopram 40 mg orally daily
- Acetaminophen 325 mg orally every 4 hours as needed for pain

Additional Laboratory Results for CD

- Serum osmolality = 240 mOsm/kg
- Urine osmolality = 211 mOsm/kg
- Urine sodium = 45 mmol/L
- TSH = within normal limits
- Cortisol = within normal limits

  – Question:
    - What category of hyponatremia is CD exhibiting?

Hyponatremia: Classification



SIADH = syndrome of inappropriate antidiuretic hormone

Cawley MJ. *Ann Pharmacother.* 2007; 41:840-50.

Features of SIADH

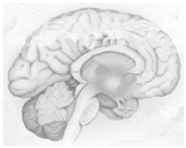
- Hyponatremia
- Urine osmolality > 100 mOsm/kg
- Exclusion of hypovolemia
  - Urine sodium > 20-30 mmol/L
  - No hypotension
  - No edema
- Absence of
  - Adrenal insufficiency
  - Hypothyroidism

Ball SG. *Clinical Medicine.* 2013; 13:291-5.

Which of CD's home medications is most likely to contribute to hyponatremia?

a. Acetaminophen
b. Citalopram
c. Metoprolol
d. Lisinopril
e. Simvastatin

Mechanisms of Drug-induced Hyponatremia

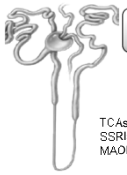


↑ Hypothalamic production of vasopressin

- Antidepressants (TCAs, SSRIs, MAOIs)
- Antipsychotics (phenothiazines, haloperidol)
- Antiepileptics (carbamazepine, valproic acid)
- Antineoplastic agents
- Opiates

↑ Vasopressin effect at renal tubule level

- Antidiabetic drugs (chlorpropamide, tolbutamide)
- Antiepileptics (carbamazepine, lamotrigine)
- IV cyclophosphamide
- Nonsteroidal anti-inflammatory drugs



Alter sodium and water homeostasis

- Thiazide diuretics and indapamide
- Amiloride
- Loop diuretics

TCAs = tricyclic antidepressants
SSRIs = selective serotonin reuptake inhibitors
MAOIs = monoamine oxidase inhibitors

Adapted from Liamis G et al. *Am J Kidney Dis*. 2008; 52:144-53.

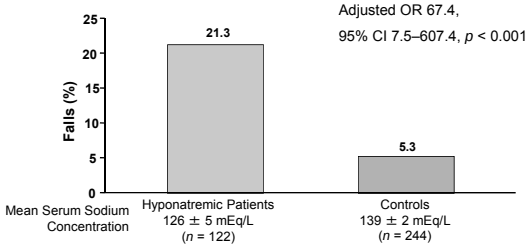
see page 16 for enlarged view

SSRI-induced Hyponatremia

- Incidence 0.5%-32%
- Occurs most often during 1st few weeks
  - Normal serum sodium usually achieved within 2 weeks of discontinuing drug
- Risk factors
  - Older age
  - Concomitant diuretic therapy
  - Low body weight
  - Baseline serum sodium concentration <133 mEq/L

Liamis G et al. *Am J Kidney Dis*. 2008; 52:144-53.
Jacob S et al. *Ann Pharmacother*. 2006; 40:1618-22.
Bouman WP et al. *Int J Geriatr Psychiatry*. 1998; 13:12-5.

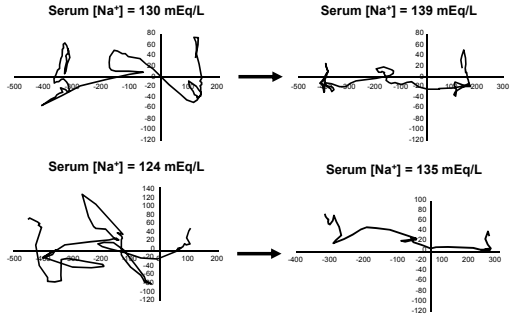
Falls: Common Symptom of Chronic "Asymptomatic" Hyponatremia



Patients with chronic "asymptomatic" hyponatremia admitted for falls significantly more frequently than patients with normal serum sodium

Renneboog B et al. *Am J Med*. 2006;119:71.e1-8.

Gait in Patients Before and After Correcting Hyponatremia



Renneboog B et al. *Am J Med*. 2006;119:71.e1-e8.

Considerations for Treating CD's Hyponatremia

- Chronicity of hyponatremia
- Presence of significant neurologic signs
- Appropriate rate of correction
- Optimal method of raising the plasma sodium concentration

Janicic N et al. *Endocrinol Metab Clin North Am*. 2003; 32:459-81.
Kumar S et al. In Berl T, Bonventre JV, eds. Vol. 1. 1999:1.1-1.22.

Acute versus Chronic Hyponatremia

Acute (≤ 48 hr)	Chronic (> 48 hr)
Symptoms • Cerebral edema • Seizures • Increased mortality risk	**Symptoms** • Nausea and vomiting • Confusion or personality changes • Neurologic dysfunction • Gait disturbances • Seizures (with very low serum sodium levels)
Rapid correction reverses cerebral edema without sequelae	Rapid correction may cause brain dehydration and osmotic demyelination syndrome (ODS)

Ghali JK. *Cardiology*. 2008;1 11:147-57.
Verbalis JG et al. *Am J Med*. 2007; 120(Suppl 1):S1-S21.

Patient CD: Outcomes

- Pharmacist in ED recommended discontinuation of citalopram.
- Pharmacist reminded physician that it may take up to two weeks to completely clear the citalopram and alternate approach would need to be instituted in the mean time.
- Fluid restriction order was written for 1500 mL/day.
- Hospital course (hip fracture surgery and post-operative care)
  Day 1: Citalopram discontinued and NPO for hip surgery. Post-op fluid restriction order – Na+ = 119 mEq/L
  Day 2: Continued fluid restriction – Na+ = 121 mEq/L
  Day 3: Patient mental status improving – Na+ = 123 mEq/L
  Day 4: Discharge to rehab facility with recommendation to continue monitoring sodium – Na+ on discharge = 125 mEq/L

Key Points

- When treating hyponatremia consider chronicity and severity of neurological symptoms
- Consider contribution of home medications to hyponatremia and fall
- Take into account the elimination half-life of the offending drug
  - Many have long half-lives
  - Estimate duration of drug effect on changes in sodium
  - Recommend other interventions during time of drug elimination
- Consider placing pharmacist on falls awareness team

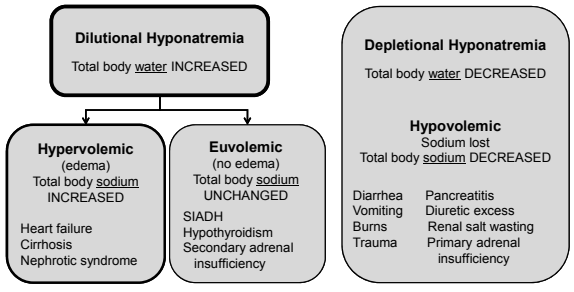
Patient Case: BB

BB is a 66-year-old, 70-kg man presenting to the ED with increasing shortness of breath, fatigue, and marked edema

PMH: DM, CKD (stage II), and CHF (EF 30%)
Physical exam: jugular venous distension and rales
Neuro: alert, following commands
CXR: bilateral pleural effusions, retrocardiac opacity
Vitals: temp 100.4^{0}F, BP 100/60 mm Hg, HR 95 bpm
Laboratory data: sodium 124 mEq/L, creatinine 1.5 mg/dL, urine sodium 7 mEq/L, and plasma osmolality 265 mOsm/kg

What type of hyponatremia does BB exhibit?

Hyponatremia: Classification



SIADH = syndrome of inappropriate antidiuretic hormone

Cawley MJ. *Ann Pharmacother.* 2007; 41:840-50.

Patient Case: BB

ED course:

✓Oxygen saturations began to drop ➔ intubated

BB is transferred to the MICU for further care

Repeat laboratory data: sodium 122 mEq/L

Considerations for Treating BB's Hyponatremia

- Chronicity of hyponatremia
- Presence of significant neurologic signs
- Appropriate rate of correction
- Optimal method of raising the plasma sodium concentration

Janicic N et al. *Endocrinol Metab Clin North Am*. 2003; 32:459-81.
Kumar S et al. In Berl T, Bonventre JV, eds. Vol. 1. 1999:1.1-1.22.

What is the best option for correcting BB's hyponatremia?

a. 0.9% sodium chloride infusion
b. Fluid restriction + furosemide
c. Hypertonic saline infusion + furosemide
d. Conivaptan
e. Tolvaptan

Hyponatremia: Strategies for Correction

Add to the numerator

$$\text{Serum sodium concentration} \sim \frac{Na^+_E + K^+_E}{\text{Body water}}$$

Subtract from the denominator

Verbalis JG et al. *Am J Med*. 2007; 120(Suppl 1):S1-S21.

NOT Ideal Therapies for BB

- 0.9% sodium chloride infusion
  - BB is already volume overloaded with symptoms
- Hypertonic saline infusion + furosemide
  - Option if BB was severely symptomatic with rapidly falling serum sodium[1]
- Tolvaptan
  - Decreased bioavailability via NGT administration[2]

[1]Licata et al. *Am Heart J*. 2003; 145:459-66.
[2]McNeely et al. *Am J Health-Syst Pharm*. 2013; 70:1230-7.

Fluid Restriction

- 500-900 mL/day
- Can be used in asymptomatic hyponatremic patients or patients with less serious hyponatremia
- Raises serum sodium approximately 1 to 2 mEq/L/day

Munger MA. *Am J Health-Syst Pharm.* 2007; 64:253-65.
Cawley MJ. *Ann Pharmacother.* 2007; 41:840-50.
Goldsmith SR. *Am J Cardiol.* 2005; 95(Suppl):14B-23B.

Implementation of Fluid Restriction

BB's medication list

Dobutamine 250 mg/250 mL D_5W at 10 mcg/kg/min (1000 mL/day)
Furosemide 100 mg/100 mL D_5W at 25 mg/hr (600 mL/day)
Chlorothiazide (250 mL D_5W / day)
Azithromycin (250 mL D_5W / day)
Ceftriaxone (50 mL D_5W / day)
Vancomycin (1500 mL D_5W / day)
Famotidine (100 mL D_5W / day)
Fentanyl IVP prn for pain
Heparin SQ

~4000 mL per day of free water from medications

Implementation of Fluid Restriction

Alterations to BB's medication list

Dobutamine 250 mg/250 mL D_5W at 10 mcg/kg/min (1000 mL/day)
Dobutamine 1000 mg/250 mL D_5W at 10 mcg/kg/min (250 mL/day)

Furosemide 100 mg/100 mL D_5W at 25 mg/hr (600 mL/day)
Furosemide 500 mg/100 mL D_5W at 25 mg/hr (120 mL/day)

~2000 mL per day of free water from medications

Patient Case: BB

Within 15 minutes after the change in medication concentrations, BB's condition changes

BP: 40/25 mm Hg (MAP= 30 mm Hg)

HR: 180 beats per minute

EKG: PVCs

Problem: infusion pump was not changed to reflect the 4-fold increase in concentration of dobutamine and therefore delivered 40 mcg/kg/min when the same dose was intended

Pitfalls of Fluid Restriction

- Fluid restriction
  - Pharmacist unaware of a fluid restriction order
  - Often 8-12 IV drugs providing daily volume of 4-8 L
  - Cost implications
    - Time to change drug concentration
    - Increase pharmacy workload and drug waste
    - Potential for errors if pump not re-programmed correctly
- Diuretic therapy
  - Electrolyte and acid-base disturbances

Patient Case: BB

Three days after initiating fluid restriction and diuretics, BB is extubated; however, only minimal reduction in total body volume and frequent PVCs are noted on EKG.

Laboratory data: sodium 127 mEq/L, potassium 2.0 mEq/L, creatinine 2.0 mg/dL, urine sodium 9 mEq/L, and plasma osmolality 270 mOsm/kg

Is there a role for conivaptan or tolvaptan?

Vasopressin Receptor Antagonists

Agent	Receptor Selectivity	Formulation	Half-life, hr	Urine Volume	Urine Osmolality	FDA Approval Status
Conivaptan	Mixed (V_{1a}+V_2)	IV	5	↑	↓	Approved 2004
Tolvaptan	V_2	Oral	12	↑	↓	Approved 2009

- Induce highly hypotonic urine and aquaresis without substantially affecting electrolyte excretion
- Can lift fluid restriction

Decaux G et al. *Lancet.* 2008; 371:1624-32.
Lee CR et al. *Am Heart J.* 2003; 146:9-18.

Conivaptan (IV)

- Administer IV via large veins
  - Infusion-site reactions (63–73%), change infusion site every 24 hr
- Available as 20 mg/100 mL premixed in 5% dextrose
- Dosing: 20 mg IV loading dose over 30 min, then 20 mg as continuous infusion over 24 hr
  - Moderate liver impairment: initiate half of normal dose
- Duration of infusion limited to 4 days
- Limited data on IV drug–drug compatibility
- Contraindicated with potent CYP3A4 enzyme inhibitors
  - Examples: ketoconazole, itraconazole, indinavir

Vaprisol (conivaptan hydrochloride) injection prescribing information. 2012 Oct (URL in ref list).

Tolvaptan (Oral)

- Indicated for clinically significant hypervolemic and euvolemic hyponatremia (serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and SIADH
- Available in 15-mg and 30-mg tablets
- Dosing: 15 mg orally once daily
  - May increase at intervals >24 hr to maximum 60 mg once daily
- Limit therapy to 30 days
- Should only be initiated and re-initiated in hospital setting
  - Must review FDA-approved medication guide with every patient
- Contraindicated with potent CYP3A4 enzyme inhibitors
  - Examples: ketoconazole, itraconazole, indinavir

Samsca (tolvaptan) prescribing information. 2013 Apr (URL in ref list).

Safety Warning for Tolvaptan: Prescribing Information Revised

- Serious and potentially fatal liver injury
- Clinical trial, polycystic kidney disease (n = 1400)
  - Significant elevations in liver function tests
  - Reversible following tolvaptan discontinuation
  - Doses of 120 mg/day (higher than in hyponatremia)
- Liver damage not reported in hyponatremia trials
- Precautions
  - Limit use to 30 days
  - Avoid use in patients with underlying liver disease
  - Discontinue if symptoms of liver injury

Samsca (tolvaptan) prescribing information. 2013 Apr (URL in ref list).

Vasopressin Receptor Antagonists

- Some evidence demonstrating impact on morbidity and mortality in heart failure
  - Hyponatremic patients (≤ 135 mEq/L) with a serum sodium improvement on tolvaptan was linked to decrease in 60-day mortality rate[1]
  - Hyponatremic patients (< 130 mEq/L) treated with tolvaptan have a significantly lower combined endpoint of cardiovascular morbidity and mortality[2]

Rossi J et al. *Acute Card Care*. 2007; 9:82-6.
Hauptman PJ et al. *J Card Fail*. 2013; 19:390-7.

Patient Case: BB

- Tolvaptan initiated at 15 mg orally daily for 4 days
- Over that time there was a decrease in total body water and increase in serum sodium
- Tolvaptan discontinued and discharged home

	Serum Sodium (mEq/L)	Δ Serum Sodium from Baseline	SCr (mg/dL)
Day 1	127	0	2.0
Day 2	130	3	1.8
Day 3	131	4	1.8
Day 4	132	4	1.7

Key Points

- Hypervolemic hyponatremia is commonly chronic in nature
- Chronic hyponatremia must be corrected slowly
- Consider volume status of patient in hypervolemia and apply treatments that do not exacerbate condition
- Fluid restriction with diuretics may provide modest improvement in hyponatremia
- Vasopressin receptor antagonists are an attractive alternative in patients with heart failure promoting aquaresis
- Consider safety, need, and resources for outpatient continuation of oral vasopressin antagonist therapy

Patient Case: GH

GH is a 34-year-old, 70-kg woman brought to the ED by EMS with new-onset seizures after being found unresponsive on the ground outside a club

PMH: none

Physical exam: no evidence of fluid overload

Neuro: obtunded

Head CT: negative

Vitals: temp 98.2^{0}F, BP 110/70 mm Hg, HR 80 bpm

Laboratory data: sodium 116 mEq/L, urine sodium 8 mEq/L, and plasma osmolality 266 mOsm/kg

Considerations for Treating GH's Hyponatremia

- Chronicity of hyponatremia
- Presence of significant neurologic signs
- Appropriate rate of correction
- Optimal method of raising the plasma sodium concentration

Janicic N et al. *Endocrinol Metab Clin N Am*. 2003; 32:459-81.
Kumar S et al. In Berl T, Bonventre JV, eds. Vol. 1. 1999:1.1-1.22.

What is the best option for correcting GH's hyponatremia?

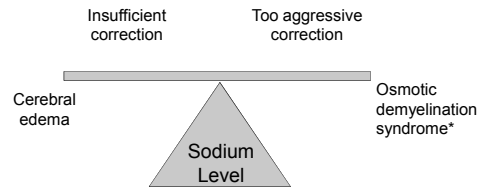
a. 0.9% sodium chloride infusion
b. Fluid restriction + furosemide
c. Hypertonic saline infusion
d. Conivaptan

NOT Ideal Therapies for GH

- 0.9% sodium chloride infusion
- Fluid restriction + furosemide
- Conivaptan

GH is experiencing severe symptoms with a rapidly falling serum sodium

Increase Serum Sodium to More Normal Level at Appropriate Rate



*Patients with severe malnutrition, alcoholism, or advanced liver disease may be especially susceptible, and slower rates of correction may be advisable

Verbalis JG et al. *Am J Med*. 2007; 120(Suppl 1):S1-S21.
Adrogué HJ et al. *N Engl J Med*. 2000; 342:1581-9.

Use of 3% Sodium Chloride in GH

- Equation
  - $\Delta sNa = \{[iNa - sNa\} \div (TBW + 1)$
  - TBW for GH: 0.5 L/kg x 70 kg = 35 L
  - $\Delta sNa = \{[513 - 116\} \div (35 + 1) = 11$ mEq/L
- 1 liter of 3% sodium chloride will correct GH's serum sodium by 11 mEq/L
- Administer 3% sodium chloride @ 90 mL/hr for 5 hours

iNa = infusate sodium; sNa = serum sodium

Patient Case: GH

GH is transferred to the Neuro ICU where she is placed on cEEG monitoring and 3% saline is initiated.

	Serum Sodium (mEq/L)	Δ Serum Sodium from Baseline	Neurological Exam
1 hour into infusion	119	3	Obtunded
2 hours into infusion	122	6	Obtunded
3 hours into infusion	122	6	Arouses to painful stimuli
4 hours into infusion	123	7	Opens eyes on command
1 hour after infusion discontinued	124	8	Follows commands
2 hours after infusion discontinued	124	8	Follows commands

Monitoring of 3% Sodium Chloride

- Overall goal: Avoid overcorrection
- Monitor
  - Basic metabolic panel
  - Frequent serum sodium levels
  - Neurologic function
  - Serum osmolality
  - Urine osmolality and sodium concentration
  - Fluid intake and output

Verbalis JG et al. *Am J Med.* 2007; 120(Suppl 1):S1-S21.

Managing Overcorrection

- Rapid increase in serum sodium (>12 mEq/L/24 hr) may result in serious neurologic sequelae
  - Withhold current therapies known to increase serum sodium
  - Administer 5% dextrose in water or oral water
  - Consider desmopressin

Perianayagam A et al. *Clin J Am Soc Nephrol*. 2008; 3:331-6.
Sood L et al. *Am J Kidney Dis*. 2013; 61:571-8.

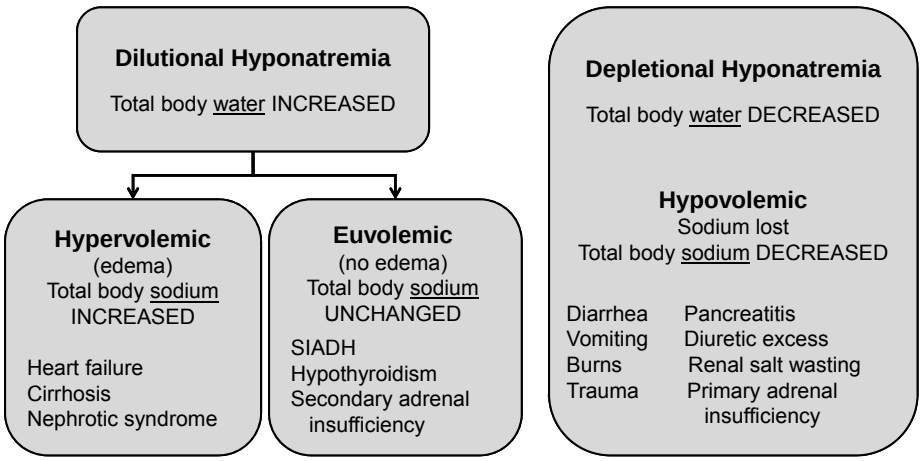
Patient Case: GH's Outcome

- No additional hypertonic saline administered
- Awake and alert on day 4 with no additional seizures
- Serum sodium at discharge: 135 mEq/L

Key Points

- Acute severe hyponatremia can lead to severe symptoms
- Cautious correction of sodium is important to prevent demyelination as fluid leaves the brain
- Hypertonic saline infusion requires vigilant monitoring to avoid overcorrection

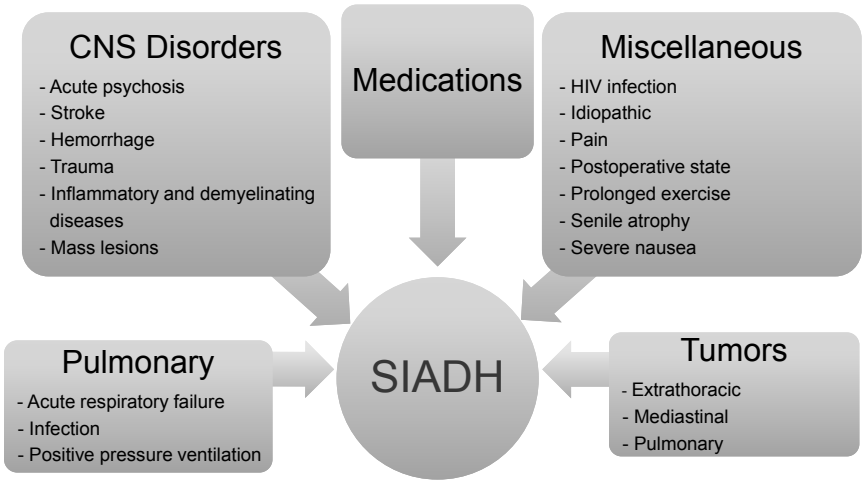
How is Hyponatremia Classified?



SIADH = syndrome of inappropriate antidiuretic hormone

Cawley MJ. *Ann Pharmacother.* 2007; 41:840-50.

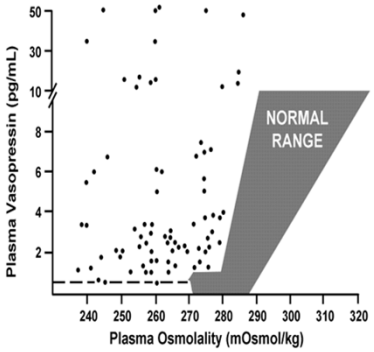
Various Causes of SIADH



Verbalis JG et al. *Am J Med*. 2013; 126:S1-S42.

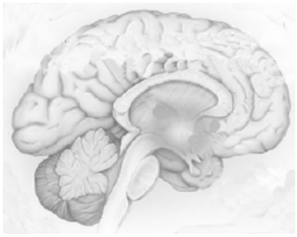
Vasopressin Concentrations Inappropriately Elevated in Patients with SIADH

- Caused by excessive levels of vasopressin as a result of disease, drug-induced pituitary release of arginine vasopressin (AVP)
- AVP secretion <u>not suppressed appropriately</u> when plasma osmolality falls below the osmotic threshold
- Inability to suppress AVP secretion results in
  - Impaired renal water excretion
  - Increased total body water
  - Hyponatremia



Zerbe R et al. *Annu Rev Med*. 1980; 31:315-27.

Mechanisms of Drug-induced Hyponatremia

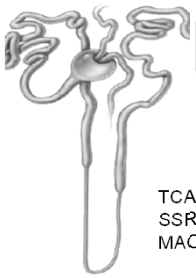


↑ Hypothalamic production of vasopressin

- Antidepressants (TCAs, SSRIs, MAOIs)
- Antipsychotics (phenothiazines, haloperidol)
- Antiepileptics (carbamazepine, valproic acid)
- Antineoplastic agents
- Opiates

↑ Vasopressin effect at renal tubule level

- Antidiabetic drugs (chlorpropamide, tolbutamide)
- Antiepileptics (carbamazepine, lamotrigine)
- IV cyclophosphamide
- Nonsteroidal anti-inflammatory drugs



Alter sodium and water homeostasis

- Thiazide diuretics and indapamide
- Amiloride
- Loop diuretics

TCAs = tricyclic antidepressants
SSRIs = selective serotonin reuptake inhibitors
MAOIs = monoamine oxidase inhibitors

Adapted from Liamis G et al. *Am J Kidney Dis*. 2008; 52:144-53.

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Self-assessment Questions

1. As demonstrated by Zilberberg et al. (2008) in an evaluation of a large database, hospitalized patients with hyponatremia had all of the following outcomes compared with patients without hyponatremia EXCEPT
    a. Increased hospital costs.
    b. Increased mortality.
    c. Higher percentage of patients requiring intensive care.
    d. Smaller percentage of patients requiring mechanical ventilation.

2. BB is a 66-year-old, 70-kg man transported to the ED by ambulance with increasing shortness of breath, fatigue, and marked edema. Past medical history includes diabetes mellitus, stage II chronic kidney disease, and congestive heart failure (ejection fraction 30%). Physical exam shows jugular venous distension and rales. He is alert and following commands, and his vital signs are normal. Laboratory data include serum sodium 124 mEq/L, serum creatinine 1.5 mg/dL, urine sodium 7 mEq/L, and plasma osmolality 265 mOsm/kg. What type of hyponatremia does BB exhibit?
    a. Hypervolemic hyponatremia.
    b. Euvolemic hyponatremia.
    c. Hypovolemic hyponatremia.

3. Which of the following is the best initial option for correcting BB's hyponatremia?
    a. 0.9% sodium chloride infusion.
    b. Fluid restriction and furosemide.
    c. Hypertonic saline infusion and furosemide.
    d. Conivaptan.

4. BB is intubated in the ED as his oxygen saturation began to drop. After being sedated, his blood pressure dropped and he is transported to the medical intensive care unit for further care. Repeat laboratory tests indicate that serum sodium is now 122 mEq/L. Why is tolvaptan not a good option for treating his hyponatremia?
    a. Warning in diabetes mellitus.
    b. Warning in kidney disease.
    c. Decreased bioavailability via nasogastric tube administration
    d. Increased bioavailability via nasogastric tube administration.

5. If a patient admitted to the intensive care unit has no evidence of fluid overload, is experiencing rapidly falling serum sodium, and has severe neurological symptoms, which of the following would be the best option for correcting the patient's hyponatremia?
    a. 0.9% sodium chloride infusion.
    b. Fluid restriction plus furosemide.
    c. Hypertonic saline infusion.
    d. Conivaptan.
    e. Tolvaptan.

Answers

1. d 2. a 3. b 4. c 5. c

List of Abbreviations Used in Presentation

AVP	arginine vasopressin
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
cEEG	continuous electroencephalography
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
CNS	central nervous system
CT	computed tomography
D_5W	dextrose 5% in water
DJD	degenerative joint disease
DM	diabetes mellitus
ED	emergency department
EF	ejection fraction
EKG	electrocardiogram
EMS	emergency medical services
FDA	Food and Drug Administration
HIV	human immunodeficiency virus
HR	heart rate
HTN	hypertension
ICU	intensive care unit
iNa	infusate sodium
IQR	interquartile range
IV	intravenous
IVP	intravenous push
K+	potassium
LOS	length of stay
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure
MICU	medical intensive care unit
Na+	sodium
NGT	nasogastric tube
NPO	nothing by mouth
ODS	osmotic demyelination syndrome
OR	odds ratio
PMH	past medical history
prn	as needed
PVC	premature ventricular contraction
SCr	serum creatinine
SIADH	syndrome of inappropriate antidiuretic hormone
sNa	serum sodium
SQ	subcutaneous
SSRI	selective serotonin reuptake inhibitor
TBW	total body water
TCA	tricyclic antidepressant
TSH	thyroid stimulating hormone

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- - / - - / - -	Optimal Management of Hospitalized Patients with Hyponatremia: Case Scenarios	_ _ _ _ _	1.0

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