Do Pharmacists Need to Understand Hyponatremia: Yes or Na+?

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Pharmacist Learning Objectives

- Explain the etiology and pathogenesis of hyponatremia (HN) including the role of arginine vasopressin in the development of HN and the medications that can cause HN.
- List the signs, symptoms, and consequences of HN.
- Explain the importance of understanding the difference between acute and chronic HN, how this affects correction rates, and therapies to treat HN including, fluid restriction, saline replacement, and vasopressin receptor antagonists.

Pharmacy Technician Learning Objectives

- Explain the causes of hyponatremia (HN) including the diseases and medications that can cause HN.
- List the signs and symptoms of HN.
- Explain the role of various therapies to treat HN including fluid restriction, saline replacement, and vasopressin receptor antagonists.

Introduction to Hyponatremia

Definition of Hyponatremia

- Hyponatremia (HN) is the most common electrolyte abnormality in clinical practice[1]
- Commonly Defined as ([Na^+]) <135 mEq/L, but cut-off values vary[2]

Serum [Na+], mEq/L[3]		
<125	125–130	130–135
Severe hyponatremia	Moderate hyponatremia	Mild hyponatremia

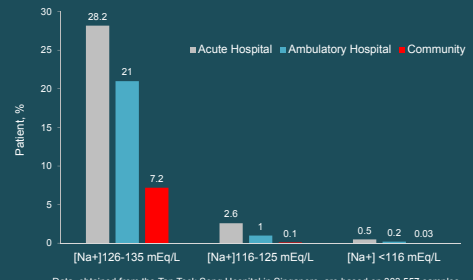
[1]Douglas I. *Cleve Clin J Med.* 2006;73 Suppl [2]Verbalis JG et al. *Am J Med.* 2013;126:S1-S42. [3]Thompson CJ. *Eur J Endocrinol.* 2010;162(suppl 1):S1-3.

Hyponatremia: Incidence

- Occurs in up to 3.2 to 6.1 million persons annually[1]
- Estimated 1 million hospitalizations annually with primary or secondary diagnosis of hyponatremia[1]
  - Up to 15% of hospitalized patients[2]
  - 24.5% of ICU patients[3]
- Increased incidence with increasing age[4]

ICU, intensive care unit.
1. Boscoe A, et al. *Cost Eff Resour Alloc.* 2006 May 31;4:10; 2. Bayliss PH, *Int J Biochem Cell Biol.* 2003;35(11):1495-1499; 3. DeVita MV, et al. *Clin Nephrol.* 1990;34(4):163-8. 4. Hawkins RC. *Clin Chim Acta.* 2003;337(1-2):169-72.

Prevalence of Hyponatremia in the Hospital and in the Community



Data, obtained from the Tan Tock Seng Hospital in Singapore, are based on 303,557 samples from 120,137 patients available for analysis.

Hawkins RC. *Clin Chim Acta.* 2003;337(1-2):169-172.

Incidence of Hyponatremia vs Hypokalemia

Study Population	Hyponatremia, %	Hypokalemia, %
235 British hospitalized AMI patients[1]	45.0	17.9
1558 Swedish subjects aged ≥75 y[2]	9.4	2.5
81 Latino/African-American hospitalized AIDS patients[3]	28.4	17.3
215 Pakistani hospitalized patients with chemotherapy-induced febrile neutropenia[4]	67.9	48.0

- In a study of 204 Greek hospitalized patients with hyponatremia, 45.5% had an additional electrolyte abnormality[5]
  - Hypophosphatemia 17.0%, hypokalemia 15.8%, hypomagnesemia 15.2%, hyperkalemia 5.9%

AMI, acute myocardial infarction.
[1]Fraser CT, Hilton P. *Br Med J.* 1979;1:1242-6; [2]Passare G et al. *Clin Drug Invest.* 2004;24:535-44; [3]Peter SA. *J Nat Med Assoc.* 1991;83:889-91; [4]Shaikh AJ et al. *J Cancer.* 2011;4:62-6; [5]Liamis G et al. *Intern Med.* 2007;46:685-90.

Hyponatremia Is Underreported In the US

- Clinical laboratory values vs ICD-9 codes from 1999 to 2000
- 2632 cases of hyponatremia identified using laboratory data alone
- No accurate ICD-9 code for 66% of patients
  - 94% of moderately hyponatremic patients
  - 87% of severely hyponatremic patients
- Only one-third of cases represented by reported cases of hyponatremia obtained from databases

ICD-9, International Classification of Diseases, Ninth Revision.
Movig K, et al. *J Clin Epidemiol.* 2003;56(6):530-535.

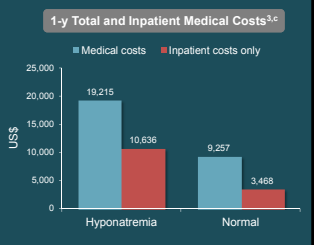
10 Most Common Diagnoses Among Hospitalized Patients With Hyponatremia (Data Collected 2004-2005)

ICD-9-CM Discharge Code		Hyponatremia Present (N = 10,899), %
486	Pneumonia, organism unspecified	6.0
038	Septicemia	5.5
276	Disorders of fluid, electrolyte, and acid-base balance[a]	5.3
428	Heart failure	5.3
250	Diabetes mellitus	5.0
584	Acute renal failure	3.9
410	Acute myocardial infarction	3.2
966	Complications peculiar to certain specified procedures	2.1
518	Other lung diseases	2.0
491	Chronic bronchitis	1.8

[a]Includes the 4-digit code for hyponatremia (276.1).
Zilberberg MD et al. *Curr Med Res Opin.* 2008; 24:1601-8. ©2008, Informa Healthcare. Adapted with permission of Informa Healthcare.

Estimated Cost of Hyponatremia in United States

- Annual direct cost of ~$1.6–$3.6 billion based on low or high prevalence[1,a]
- Incremental per-patient increase in hospital costs[2,b]:
  - $2289 in overall population
  - $3480 in ICU population
- Associated with 46% increase in medical costs[3]



[a]Data from public databases (2002), published literature, and expert consensus panel. [b]data from large administrative database of >198,000 patients (2004–5); [c]data from large managed-care claims database of >167,000 patients in 39 different hospitals (2002–5)
[1]Boscoe A et al. *Cost Eff Resour Alloc.* 2006;31:4:1-11; [2]Zilberberg MD et al. *Curr Med Res Opin.* 2008;24:1601-8; [3]Shea AM et al. *J Am Soc Nephrol.* 2008;19:764-70.

Etiologies

Risk Factors for Hyponatremia

Selected Conditions[1,3]

- CHF
- Cirrhosis
- SIADH
- Very young/old age
- Adrenal insufficiency
- Hypothyroidism
- Renal dysfunction
- CNS impairment
- Surgery or injury

[Na+] <135 mEq/L[3]

Selected Drug Classes[1,2]

- Diuretics
- NSAIDs
- Opiates
- Antidepressants
- Antipsychotics
- Antiepileptic agents
- Anticancer agents
- Antihypertensive agents
- Antidiabetic drugs

[1]Androgué HJ. Consequences of inadequate management of hyponatremia. *Am J Nephrol.* 2005;25:240-9.
[2]Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. *Am J Kidney Dis.* 2008;52:144-53.
[3]Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. *N Engl J Med.* 2007;356:2064-72.

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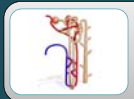
Mechanisms of Drug-Induced Hyponatremia

↑ Hypothalamic production of AVP

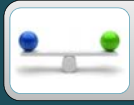
- Antidepressants
- Antipsychotics
- Antiepileptics
- Antineoplastic agents
- Opiates

↑ Effect of AVP at renal tubule level



- Antidiabetic drugs
- Antiepileptics
- IV cyclophosphamide
- NSAIDs

Altered Na/H_2O homeostasis



- Thiazide diuretics/ indapamide
- Amiloride
- Loop diuretics

AVP, arginine vasopressin.
Liamis G et al. *Am J Kidney Dis.* 2008;52:144-53.

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Thiazide-Induced Hyponatremia

- In an observational study, thiazide-induced hyponatremia occurred in 13.7% of treated patients[1]
- Thiazides implicated in 26% of hyponatremia patients[2]
- Thiazides used in 75% of hospitalized hypertensive patients in retrospective analysis[3]
- Risk factors[4]
  - Increasing age
  - Women
  - Low body weight
  - Increased incidence in summer[5]

Note: thiazide-induced hyponatremia may be hypovolemic or euvolemic[6]

[1]Clayton JA et al. Br *J Clin Pharmacol.* 2006;61:87-95. [2]Bissram M et al. *Intern Med J.* 2007;37:149-55. [3]Sharabi Y et al. *J Hum Hypertens.* 2002;16:631-5. [4]Chow KM et al. *J Natl Med Assoc.* 2004;96:1305-8; [5]Gross P, Palm C. *Nephrol Dial Transplant.* 2005;20:2299-301; [6]Hwang KS, Kim G-H. *Electrolyte Blood Press.* 2010;8:51-7.

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SSRI-Induced Hyponatremia

- Incidence: 0.5%–32%[1-3]
- Most cases occur during 1st few weeks of therapy[1-3]
  - Normal serum [Na^+] usually achieved within 2 wk following discontinuation of drug
- Risk factors
  - Older age[2]
  - Concomitant diuretic therapy[2]
  - Low body weight[1]
  - Baseline serum [Na^+] <133 mEq/L[1]

SSRI, selective serotonin reuptake inhibitor.
[1]Liamis G et al. *Am J Kidney Dis.* 2008;52:144-53; [2]Jacob S, Spinler SA. *Ann Pharmacother.* 2006;40:1618-22;
[3]Bouman WP et al. *Int J Geriatr Psychiatry.* 1998;13:12-5.

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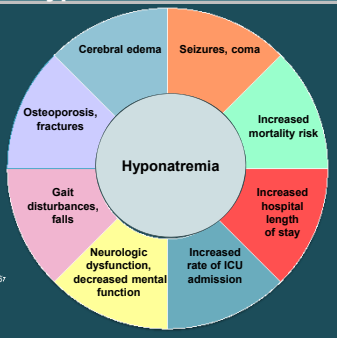
Consequences

Consequences of Hyponatremia

Hyponatremia can have a wide and variable range of consequences[1-5]



[1]Bagshaw SM, et al. *Can J Anesth.* 2009;56(2):151-167
[2]Ghali JK. *Cardiology.* 2008;111(3):147-157;
[3]Kengne FG, et al. *Q J Med.* 2008;101:583-588;
[4]Zilberberg MD, et al. BMC Pulm Med. 2008;8:16;
[5]Patterson JH. Pharmacotherapy 2011;31(5

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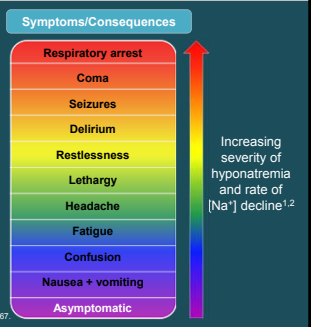
Symptoms Correlate With Severity and Rate of Decline in Serum [Na+]

- Asymptomatic presentation common
- May present with mild, nonspecific symptoms
- Degree of symptomatology is surrogate for duration of hyponatremia
- Symptoms from underlying disease process also common



[1]Bagshaw SM, Townsend D, McDermid R. Can J Anesth 2009;56:151-67.
[2]Ghali J. *Cardiology.* 2008;111:147-57.

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Increased Risk of Falls With Chronic "Asymptomatic" Hyponatremia

Group	n	% Falls	Odds Ratio	Adjusted Odds Ratio*
"Asymptomatic" chronic hyponatremia	122	21.3%	9.45 (2.64–34.09)†	67.43 (7.48–607.42)†
Normonatremic controls	244	5.3%	1.00	1.00

The increased prevalence of falls in patients with hyponatremia, compared to controls, was independent of the severity of hyponatremia, which ranged from 115 to 132 mEq/L.

*Adjusted for age, sex ,and covariates; †P <.001.
Renneboog B, et al. *Am J Med.* 2006; 119:71.e1-71.e8.

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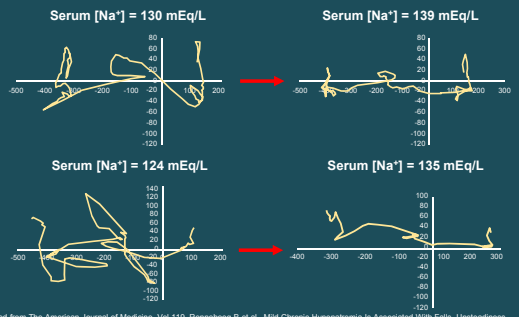
Gait in Patients With Hyponatremia and After Correction



Reprinted from The American Journal of Medicine, Vol 119, Renneboog B et al., Mild Chronic Hyponatremia Is Associated With Falls, Unsteadiness, and Attention Deficits, Pages 7.1.e-e8, Copyright 2006 with permission from Elsevier.

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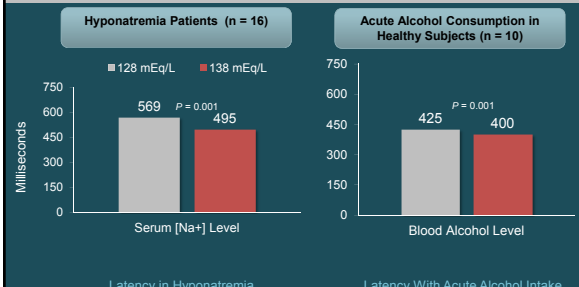
Attention Impairment in Patients With Hyponatremia Compared With Acute Alcohol Ingestion



Latency in Hyponatremia — Latency With Acute Alcohol Intake

Latencies in response time are median values expressed in milliseconds. *P* value between controls and patients with normal serum [Na+] not significant. Four selected attention tests: Go/No Go, intermodal comparison, Phasic Alert 1-4, and Phasic Alert 2-3.

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

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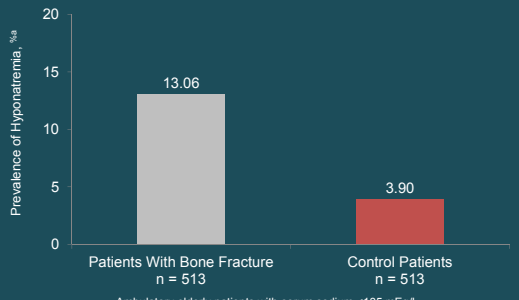
Prevalence of Hyponatremia Significantly Higher in Patients With Bone Fractures Resulting From Falls



Ambulatory elderly patients with serum sodium <135 mEq/L

Kengne FG, et al. *Q J Med.* 2008;101:583-8.

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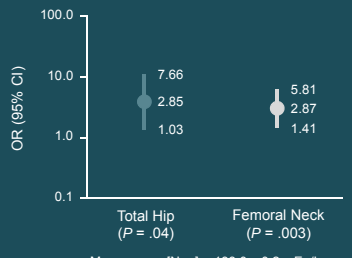
Odds Ratio for Hyponatremia as Predictor of Osteoporosis in NHANES III Database



Mean serum [Na+] = 133.0 ± 0.2 mEq/L

NHANES III, 3rd National Health and Nutrition Examination Survey.
Bone mineral density of hip measured by dual-emission X-ray absorptiometry. Results adjusted for age, sex, body mass index, physical activity, serum vitamin D (ng/mL), and diuretic use.
Verbalis JG, et al. *J Bone Min Res.* 2010;25:554-663.

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Increased Risk of Morbidity and Mortality, and CNS Effects in Geriatric Patients

- Presence of hyponatremia confers increased risk of death for hospitalized geriatric patients[1]
  - In a large cohort study (N = 4123), in-hospital mortality was higher in hyponatremic (16.0%) vs normonatremic (8.0%) patients[1]
- Hyponatremia causes deleterious CNS effects
  - Anorexia, fatigue, lethargy, delirium, seizures, hypothermia, and coma ([Na^+] <125 mEq/L)[1]
  - Falls, unsteadiness, attention deficit, and gait impairment in apparently asymptomatic patients (mean serum [Na^+], 126 mEq/L)[2]

CNS, central nervous system.
[1]Terzian C, et al. *J Gen Intern Med*. 1994;9: 89-91. [2]Renneboog B, et al. *Am J Med*. 2006;119:71.e1-71.e8.

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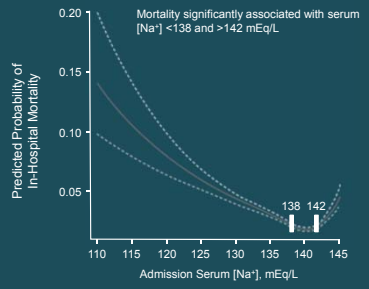
Hospital Admission Serum [Na+] and Estimated In-Hospital Mortality*



*Unadjusted restrictive cubic spline.
Dashed lines represent 95% confidence intervals.
Wald R, et al. *Arch Intern Med*. 2010;170:294-302.

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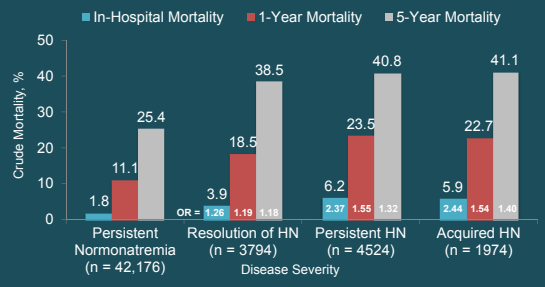
Mortality According to Initial and Final Serum Sodium Concentration



Normonatremia (135–44 mEq/L) and HN (<135 mEq/L) were unadjusted for glucose concentration. ORs and hazard ratios were multivariable-adjusted for age, sex, individual diagnoses, and Deyo-Charlson Index score.
Waikar SS et al. *Am J Med*. 2009;122:857-65.

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Pathophysiology

Arginine Vasopressin (AVP) in the Pathophysiology of Hyponatremia

- AVP, also referred to as Vasopressin or Anti Diuretic Hormone (ADH), is a peptide hormone composed of 9 amino acids
- Synthesized within supra-optic and paraventricular nuclei of hypothalamus
  - Transported from hypothalamus via nerve tracts to neural lobe of pituitary, where it is released into circulation
- Regulates urinary water excretion

[1]Verbalis JG, Berl T. Disorders of water balance. In: Brenner BM. *Brenner and Rector's The Kidney*. 8th ed. Philadelphia, PA: Saunders; 2007:Chap 13.

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Receptor-Mediated Effects of AVP

Receptor Subtype	Sites of Action	Activation Effects
V_{1a}	• Vascular smooth muscle cells • Platelets • Lymphocytes and monocytes • Liver	• Vasoconstriction, myocardial stimulation • Platelet aggregation • Cytokine release • Glycogenolysis
V_{1b} (V_3)	Anterior pituitary	ACTH and β-endorphin release
V_2	Renal collecting duct principal cells	Renal free water absorption

ACTH, adrenocorticotropic hormone.
Verbalis JG. *J Mol Endocrinol*. 2002;29:1-9.

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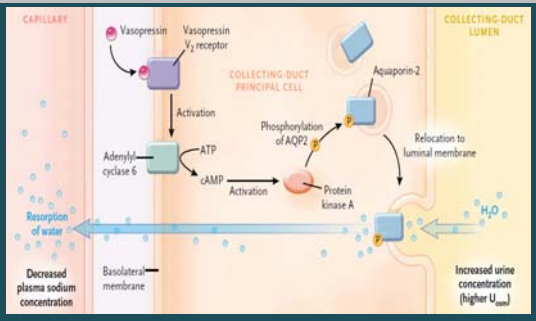
Cellular Pathway of the Hydroosmotic Effect of Vasopressin



[1]Beri T. NEJM 2015; 372:2207-2216

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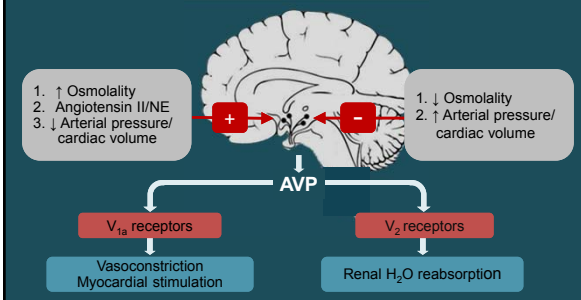
AVP Stimulation and Effects



NE, norepinephrine.
Lee CR et al. *Am Heart J.* 2003;146:9-18.

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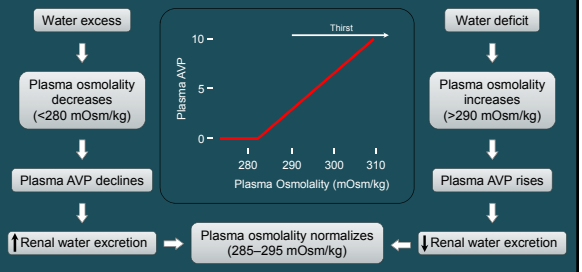
AVP Regulates Water and Electrolyte Balance



[1]Robertson GL et al. *Am J Med.* 1982;72:339-53; [2]Rossi NF et al. *Crit Care Clin.* 1987;3:759-77. [3]Reprinted from *Lancet*, 352, Kumar S et al, Sodium, 220-8, Copyright 1998, with permission from Elsevier.

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Role of Vasopressin in Edematous Disorders

Congestive Heart Failure	Cirrhosis
1. Low cardiac output	1. Decreased peripheral vascular resistance due to splanchnic vasodilatation but high cardiac output
2. Diminished effective arterial blood volume	
3. Nonosmotic stimulus for AVP release	
4. Impaired water excretion leading to ascites and peripheral edema	
5. Increased extracellular fluid volume (hypervolemia)	

Janicic N, Verbalis JG. *Endocrinol Metab Clin North Am.* 2003;32:459-81.

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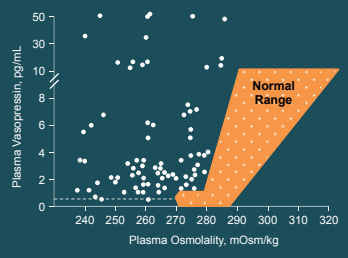
Vasopressin Levels Inappropriately Elevated in Patients With SIADH



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Vasopressin Secretion Independent of Plasma Osmolality

- In patients with SIADH, vasopressin secretion may be independent of plasma osmolality or inadequately suppressed
- Vasopressin levels can be recognized as inappropriate only in relation to the hypotonicity of body fluids

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Diagnosis and Assessment

Acute vs Chronic Hyponatremia

Acute (≤48 hours)	Chronic (>48 hours)
Symptoms include: • Cerebral edema • Seizures • Increased mortality risk[1]	Symptoms include: • Nausea/vomiting[1] • Confusion[1] • Neurologic dysfunction[1] • Gait disturbances[1] • Seizures (with very low serum [Na^+] levels)[2]
Rapid correction reverses cerebral edema without sequelae[1]	Rapid correction may cause brain dehydration and osmotic demyelination syndrome (ODS)[3]

1. Ghali JK. *Cardiology*. 2008;111(3):147-157. 2. Adrogué HJ. *Am J Nephrol*. 2005;25(3):240-249; 3. Verbalis JG, et al. *Am J Med*. 2013;126(10 Suppl 1):S1-42.

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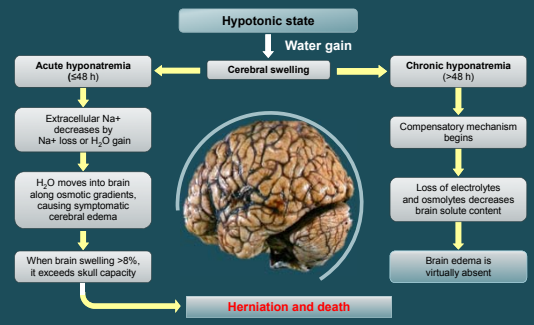
Acute vs Chronic Hyponatremia



[1]Gullans SR, Verbalis JG. *Ann Rev Med*. 1993;44:289-301.

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Dilutional vs Depletional Hyponatremia

Dilutional hyponatremia[1]
- Total body sodium normal or increased
- Total body water increased

Hypervolemic[1] (edema)
- CHF
- Cirrhosis
- Nephrotic syndrome

Euvolemic[1] (no edema)
- SIADH
- Hypothyroidism
- Secondary adrenal insufficiency

Depletional hyponatremia[2]

Hypovolemic
- Sodium lost
- Total body water reduced

➢ Diarrhea
➢ Vomiting
➢ Burns
➢ Trauma
➢ Pancreatitis
➢ Diuretic excess
➢ Renal salt wasting
➢ Mineralocorticoid deficiency

[1]Douglas D. *Cleve Clin Med*. 2006;73:S4-12; [2]Kumar S, Berl T. *Lancet*. 1998;352:2208.
Adapted with permission of OAPI/Phoenix Marketing Solutions.

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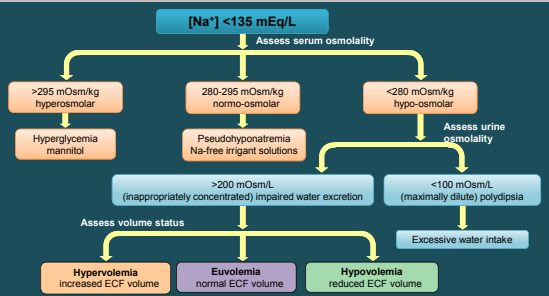
Classification Algorithm



ECF, extracellular fluid.
Cole CD et al. *Neurosurg Focus*. 2004;16:E9; Diringer MN, Zazulia AR. *Neurologist*. 2006;12:117-26; Verbalis JG, et al. *Am J Med*. 2013;126(10 Suppl 1):S1-42

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Assessing Extracellular Fluid Volume

Hyponatremia	Typical Diagnostic Assessments/Findings		
	Physical Exam	Plasma Composition	Urine Electrolytes
Hypovolemia	• Orthostatic decrease in BP, increase in pulse rate • Dry mucous membranes • Decreased skin turgor	• Elevated BUN, creatinine, BUN/creatinine ratio	• [Na^+] <20-30 mEq/L • Low Cl^-
Euvolemia	• No signs of volume depletion • No edema or ascites	• Low BUN • Low serum uric acid	• [Na^+] >20-30 mEq/L
Hypervolemia	• Subcutaneous edema • Pulmonary congestion • Ascites	• Elevated BNP • High BUN	• [Na+] <20-30 mEq/L

BNP, brain (B-type) natriuretic peptide; BUN, blood urea nitrogen.

Palmer BF. *J Hosp Pract*. 2010;5:S1-7; Verbalis JG et al. *Am J Med*. 2013;126:S1-S42.

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Essential Criteria for Diagnosis of SIADH

1. ↓ **Effective osmolality of ECF**
   P_{osm} <275 mOsm/kg H_2O
2. **Inappropriate urinary concentration**
   U_{osm} >100 mOsm/kg H_2O with normal renal function at some level of hypo-osmolality
3. **Clinical euvolemia**
   No signs of hypovolemia (orthostasis, tachycardia, ↓ skin turgor, dry mucous membranes) or hypervolemia (subcutaneous edema, ascites)
4. **Elevated urinary sodium excretion despite normal salt and water intake**
5. **No other potential causes of euvolemic hypo-osmolality** (e.g., hypothyroidism, hypocortisolism, diuretic use)

P_{osm} = plasma osmolality; Uosm = urinary osmolality

[1]Janicic N, Verbalis JG. *Endocrinol Metab Clin North Am*. 2003;32:459-81.

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Management

Management Overview

Most important management factors[1]

- Severity of neurologic symptoms
- Volume status[2]
- Acute vs chronic
- Likely cause of hyponatremia identified
- Serum [Na+] assessment[3]

Principles to guide management[5]

- Weigh risks and benefits[4]
- Neurologic consequences can follow both failure to promptly treat and excessively rapid rate of correction
- Even modest improvement in serum [Na+] has survival benefits
- Monitor serum [Na+] frequently
- Address underlying disease and stop offending medications

1. Adrogue HJ, et al. *N Engl J Med*. 2000;342(21):1581-1589; 2. Ellison DH, et al. *N Engl J Med*. 2007;356(20):2064-2072; 3. Kumar S, et al. *Lancet*. 1998;352(9123):220-228; 4. Lien YH, et al. *Am J Med*. 2007;120(8):653-658; 5. Verbalis JG, et al. *Am J Med*. 2013;126(10 Suppl 1):S1-42.

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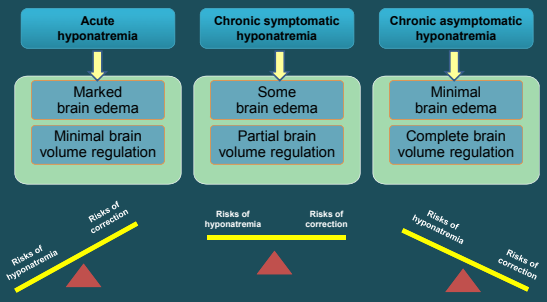
Management of Hyponatremia Requires Balance: Overcorrection vs Risks of Hyponatremia



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Speed of Serum Sodium Concentration Correction

Insufficient correction → *may lead to* → **Cerebral edema**

Too aggressive correction → *may lead to* → **Osmotic demyelination syndrome**

- Symptomatic Acute Hyponatremia—raise [Na+] by 4–6 mmol/L to prevent brain herniation and neurological damage from cerebral ischemia
- Chronic Hyponatremia—raise [Na+] by 4–8 mmol/L per day, with a lower goal of 4-6 mmol/L per day if the risk of ODS is high
- Limits not to exceed—for high risk of ODS 8 mmol/L in any 24-hour period and for normal risk of ODS 10-12 mmol/L in any 24-hour period and 18 mmol/L in any 48-hour period

[1]Adrogue HJ et al. *N Engl J Med*. 2000;342:1581-9; Verbalis JG et al. *Am J Med*. 2013;126(10suppl 1):S1-42.

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Acute Hyponatremia: Treatment Considerations

- For patients with acute symptomatic hyponatremia[1]:
  - Continuous infusion of hypertonic saline (3%) is the mainstay of therapy
  - Furosemide diuresis 20–40 mg IV to treat volume overload
    - Severely symptomatic hyponatremia is uncommon in CHF or cirrhosis, but in theory can be treated with hypertonic saline provided adequate diuresis is established
  - Interrupt management when at least 1 endpoint is reached:
    - Signs and symptoms have resolved
    - Safe serum [Na+] (≥120 mEq/L) is achieved
    - Total magnitude of correction of 18 mEq/L is reached
- Monitor serum sodium levels to ensure total increase over 24 h is not excessive[1]
- In acute hyponatremia, it is only necessary and appropriate to correct serum [Na+] to a safe range, rather than to normal levels[2]

[1]Verbalis JG et al. *Am J Med*. 2007;120:S1-21; [2]Sterns RH et al. *NephSAP*. 2011;10:91-193 .

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Chronic Hyponatremia: Treatment Considerations

- Several treatment options are available for patients with chronic hyponatremia[a]
- Initial management of choice is fluid restriction (only fluid, not sodium)
  - If fluid restriction fails or cannot be maintained by patient, pharmacologic management may be necessary
- Pharmacologic treatment options
  - Demeclocycline[b]
  - Urea[b]
  - Loop diuretics
  - Vasopressin receptor antagonists (vaptans)
- Severe symptoms may require saline administration
- Rapid correction may cause brain dehydration and osmotic demyelination syndrome

[a]For hyponatremic patients with reset osmostat syndrome, no therapy is generally required; [b]not approved in the US for SIADH.
Verbalis JG et al. *Am J Med.* 2007;120:S1-21.

Correcting Hyponatremia

1. Add to numerator

$$\text{Serum } [Na^+] \sim \frac{Na^+_E + K^+_E}{\text{Body water}}$$

2. Subtract from denominator

K^+_E, exchangeable sodium; Na^+_E, exchangeable sodium.
Adrogue HJ et al. *N Engl J Med.* 2000; 342:1581-9.

Management of Hyponatremia

Management	Clinical Issues
Saline infusion	• Rapid response in symptomatic patients • Complex calculations • Not to be used in edema-forming disorders[1]
Fluid restriction	• Inexpensive • Slow and limited response • Adherence concerns[2]
Demeclocycline	• No need to limit water intake • Targets excessive AVP • Slow response • Nephrotoxic in CHF and cirrhosis[2]
Loop diuretics	• Allows relaxation of fluid restriction • May cause volume, K^+, and Mg^+ depletion[2]
AVP receptor antagonists	• Targets excessive AVP • Aquaresis (solute free urine output) • Not to be used in hypovolemic states[2]

[1]Kumar S et al. In: Schrier RW et al (eds). *Atlas of Diseases of the Kidney*. Vol 1. Philadelphia, PA: Current Medicine, Inc; 1999:1.1-.22; [2]Goldsmith SR. *Am J Cardiol.* 2005;95(suppl):14B-23B.

Hypertonic Saline

- When to consider hypertonic saline (3% NaCl)[1]:
  - Symptomatic hyponatremia (seizure, coma)
  - Acute severe hyponatremia (<24 h, <120 mEq/L)
  - Hyponatremia worsening on normal saline (0.9% NaCl)
  - Induced hypernatremic states for prevention/management of cerebral edema
- Discontinue hypertonic saline when serum $[Na^+]$ reaches 120–130 mEq/L
  - Exception: states of cerebral edema with Na^+ augmentation
- Safety concerns: requires ICU monitoring
- No randomized trials performed
- Hypertonic saline may or may not be combined with loop diuretic[2]

[1]Fall PJ. *Postgrad Med.* 2000;107:75-82; [2]Zietse R et al. *NDT Plus.* 2009;2:iii12–iii19.

Fluid Restriction

- Very patient-specific
- Standard procedure: restrict fluid to ~0.8 L/d
- Slow rate of improvement
- Poor patient adherence
- Predictors of failure
  - High urine osmolality (>500 mOsm/kg H_2O)
  - Urine [Na+] and [K+] > serum $[Na^+]$
  - 24-h urine output <1500 mL/d
  - Increase in serum $[Na^+]$ <2 mEq/L in 24 h

Fall PJ. *Postgrad Med.* 2000;107:75-82; Zietse R et al. *NDT Plus.* 2009;2:iii12–iii19.

Demeclocycline

- Demeclocycline is a tetracycline antibiotic
  - Not approved for SIADH treatment
  - Contraindicated in children and pregnant women
- Mechanism of action not entirely understood[1]
  - Inhibits antidiuretic action of AVP by inducing nephrogenic diabetes insipidus[2]
- Slow onset of action[3]
  - Several days to correct serum [Na+]
- Associated with increased risk of nephrotoxicity and renal failure[2,4]

[1]De Troyer A. *JAMA.* 1977;237:2723-6; [2]Goldsmith SR. *Am J Cardiol.* 2005;95:14B-23B; [3]Forrest JN Jr et al. *N Engl J Med.* 1978;298:173-7; [4]Carrilho F et al. *Ann Intern Med.* 1977;87:195-7.

Loop Diuretics

- Block sodium reabsorption in ascending limb of Loop of Henle
  - Bumetanide
  - Furosemide
  - Torsemide
- Cause hypotonic diuresis
- Although serum [NA^+] may increase, total body [NA^+] declines
- Recommended in combination with:
  - Hypertonic (3%) saline in acute hyponatremia
  - Sodium chloride tablets or isotonic saline infusion in chronic hyponatremia
- Promotes excretion of sodium, which may exacerbate hyponatremia

Goldsmith SR. *Am J Cardiol.* 2005;95:14B-23B.

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AVP-Receptor Antagonists

Agent (trade name)	Receptor Selectivity	Formu-lation	Half-life, h	Urine Volume	Urine Osmolality	FDA Approval Status
Conivaptan (Vaprisol®)	Mixed (V_{1a}+V_2)	IV	5	↑	↓	Approved 2004
Tolvaptan (Samsca®)	V_2	Oral	12	↑	↓	Approved 2009
Lixivaptan	V_2	Oral	7–10	↑	↓	No longer being studied

- Nonpeptide AVP-receptor antagonists that induce highly hypotonic diuresis without substantially affecting electrolyte excretion
- Indicated for treatment of euvolemic and hypervolemic hyponatremia only
- Caution: overcorrection of hyponatremia can cause osmotic demyelination and neurologic sequelae

Decaux G et al. *Lancet.* 2008;371:1624-32; Lee CR et al. *Am Heart J.* 2003;146:9-18; Zietse R et al. *NDT Plus.* 2009; 2:iii12-9.

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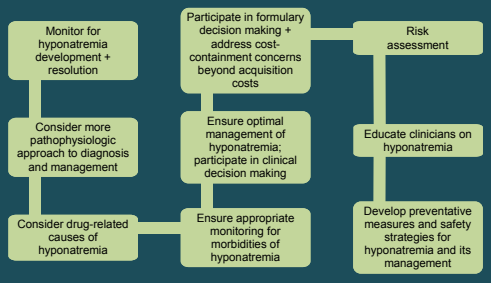
Roles of the Pharmacist

Many Roles of the Pharmacist in the Management of HN



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