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OMG...I DIDN'T KNOW THAT!

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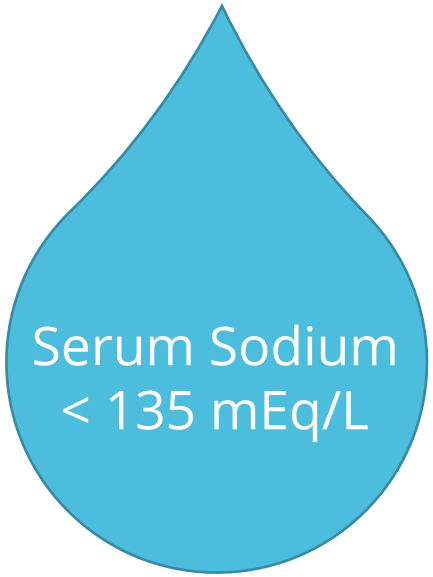
Seven Things to Know About Treating Hyponatremia

PODCAST 2

Hyponatremia

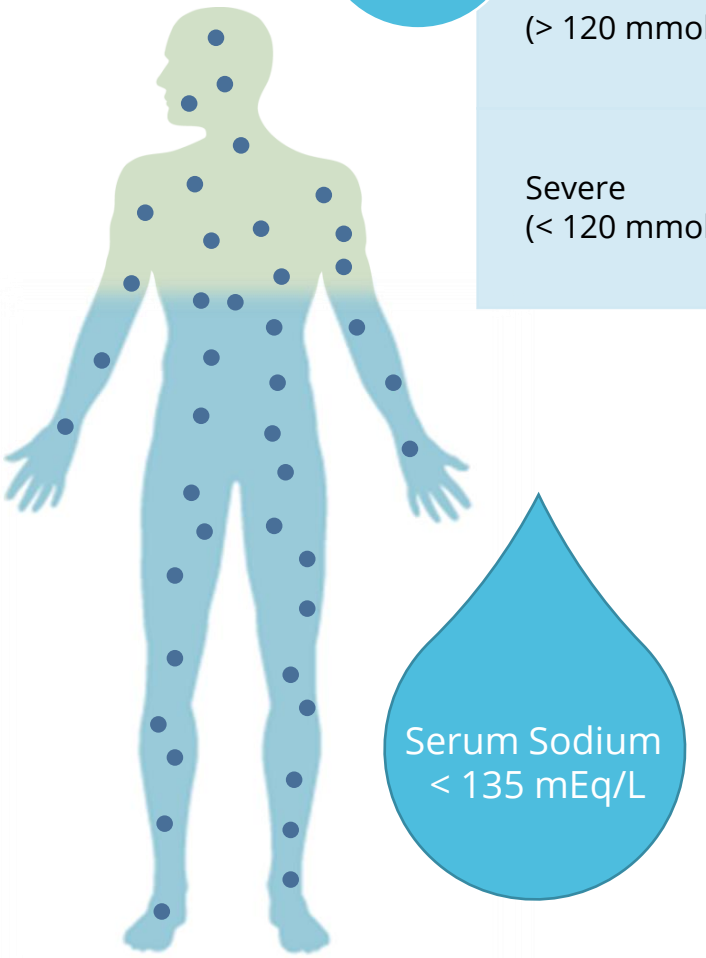
- Most common electrolyte abnormality
- An excess of total body water compared to total body sodium



- Types of hyponatremia may differ depending on effects of total body water and sodium

https://www.ncbi.nlm.nih.gov/books/NBK470386/. Updated January 25, 2021. Accessed June 2, 2021.

Classifications of Hyponatremia



Na^+

- Mild-Moderate (> 120 mmol/L)
- Severe (< 120 mmol/L)

Time

- Acute (< 48 hours)
- Chronic (> 48 hours)

Symptoms

- Present
- Absent

Osmolality

- Hypotonic
- Isotonic
- Hypertonic

Volume Status

- Hypovolemic
- Euvolemic
- Hypervolemic

https://www.ncbi.nlm.nih.gov/books/NBK470386/. Updated January 25, 2021. Accessed June 2, 2021.

Symptomatic Acute Hyponatremia

- Acute hyponatremia
  - Non-specific symptoms can rapidly progress to seizures, respiratory arrest, and permanent or fatal brain injury
    - Headache
    - Nausea and vomiting
    - Drowsiness
    - Mild confusion
  - Brain death from cerebral edema is possible

- Chronic hyponatremia is often asymptomatic, but when symptoms are present, severe neurological complications are unlikely.

Sterns RH, et al. *Chest*. 2013;144(2):672–79.
https://www.ncbi.nlm.nih.gov/books/NBK470386/. Updated January 25, 2021. Accessed June 2, 2021.

Causes of Hyponatremia

Hypovolemic	Euvolemic	Hypervolemic
• Gastrointestinal fluid loss • Third-spacing • Diuretics • Osmotic diuresis • Salt-wasting nephropathies • Cerebral salt-wasting syndrome • Mineralocorticoid deficiency	• Drugs • SIADH • Addison's disease • Hypothyroidism • High fluid intake • Medical testing related to excessive fluids • Iatrogenic	• Renal causes – Renal failure – Nephrotic syndrome • Extrarenal causes – Congestive heart failure – Cirrhosis • Iatrogenic

Drug Causes

- Vasopressin analogs: desmopressin and oxytocin
- Medications that stimulate vasopressin release or potentiate the effects of vasopressin: selective serotonin-reuptake inhibitors (SSRIs) and other antidepressants morphine and other opioids
- Medications that impair urinary dilution: thiazide diuretics
- Medications that cause hyponatremia: carbamazepine or analogs, vincristine, nicotine, antipsychotics, chlorpropamide, cyclophosphamide, nonsteroidal anti-inflammatory drugs
- Illicit drugs: methylenedioxymethamphetamine (MDMA or ecstasy)

https://www.ncbi.nlm.nih.gov/books/NBK470386/. Updated January 25, 2021. Accessed June 2, 2021.

At Risk of Developing Hyponatremia

Risk Disorders
Dialysis
Diabetes
SIADH
Renal failure
Heart failure
Cirrhosis
Cancer

Padhi R, et al. *Indian J Crit Care Med*. 2014;18(2):83-87.
Rhee CM, et al. *Kidney Int Rep*. 2019;4(6):769-80.

U.S. Hyponatremia Treatment Guidelines

	Guideline
Acute or symptomatic hyponatremia	Severe symptoms: Bolus 3% NaCl (100 mL over 10 min × 3 as needed)
	Moderate symptoms: Continuous infusion 3% NaCl (0.5-2 mL/kg per hour)
Chronic hyponatremia	
SIADH	Fluid restriction (first line)
	Vaptans, demeclocycline, or urea (second line)
Hypovolemic hyponatremia	Isotonic saline
Hypervolemic hyponatremia	Fluid restriction
	Vaptans
Correction rates	Minimum: 4-8 mmol/L per day, 4-6 mmol/L per day (high risk of ODS)
	Limits: 10-12 mmol/L per day, 8 mmol/L per day (high risk of ODS)
Management of overcorrection	Baseline $Na^+ \geq 120$ mmol/L: probably unnecessary
	Baseline $Na^+ < 120$ mmol/L: start relowering with electrolyte-free water or desmopressin after correction exceeds 6-8 mmol/L per day

Hoorn EJ, et al. *J Am Soc Nephrol*. 2017;28(5):1340-49.

Treatment of Chronic Hyponatremia: Vaptans

- Vaptans selectively increase solute-free water excretion by the kidneys.
- Vaptans should not be used
  - In hypovolemic hyponatremia
  - In conjunction with other treatments for hyponatremia
  - Immediately after cessation of other treatments for hyponatremia, particularly 3% NaCl
  - In severe, symptomatic hyponatremia
- Monitor serum sodium closely (every 6 - 8 hours) for the first 24 - 48 hours after initiating treatment.
- Maintain ad libitum fluid intake during the first 24 - 48 hours of treatment.
- If overcorrection occurs, consider re-lowering the serum sodium to safe limits.

Verbalis JG, et al. *Am J Med*. 2013;126(10):S1-S42.

Overly Rapid Correction Controversy

- Osmotic demyelination syndrome (ODS) is extremely rare in patients with plasma sodium > 120 mEq/L.
- In patients with plasma sodium ≤ 105 mEq/L, the incidence may be as high as **50%**.
- Controversy exists regarding limits of sodium correction.

10 - 12 mEq/L in the first 24 hours and 18 mEq/L in the first 48 hours

OR

8 mEq/L in any 24-hour period

Rondon-Berrios H. *Clin J Am Soc Nephrol*. 2019;CJN.04880419.

Fluid Restriction

- General recommendations:
  - Restrict all intake, not just water
  - Fluid restriction that is 500 mL/day below the 24-hour urine volume
  - Do not restrict sodium or protein intake
- Predictors of the likely failure of fluid restriction:
  - High urine osmolality (> 500 mOsm/kg H_2O)
  - Sum of the urine Na^+ and K^+ concentrations exceeds the serum Na^+ concentration
  - 24-hour urine volume < 1,500 mL/day
  - Increase in serum Na^+ concentration < 2 mmol/L/day in 24 - 48 hours on a fluid restriction of ≤ 1 L/day

Verbalis JG, et al. *Am J Med*. 2013;126(10):S1-S42.

Vaptans

	Conivaptan	Tolvaptan
Receptor	V1a/V2	V2
Route of administration	IV	Oral
Urine volume	↑	↑
Urine osmolality	↓	↓
Sodium excretion/24 hours	↔	↔
Contraindications	• Hypovolemic hyponatremia • Co-administration with potent CYP3A inhibitors • Anuria • Known corn allergy	• Hypovolemic hyponatremia • Liver disorders • Co-administration with potent CYP3A inhibitors • Anuria • Unable to sense or respond to thirst • Need to raise sodium acutely
Status	FDA-approved	FDA- and EMA-approved

↑ = increased; ↓ = decreased; ↔ = no change; EMA = European Medicines Agency;
FDA = U.S. Food and Drug Administration; IV = intravenous; V1a = vasopressin receptor 1a; V2 = vasopressin receptor 2

Verbalis JG, et al. *Am J Med*. 2013;126(10):S1-S42.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021697s003lbl.pdf. Accessed June 2, 2021.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022275s007lbl.pdf. Accessed June 2, 2021.

Vaptans

- Vaptans are approved for the treatment of hypervolemic and euvolemic hyponatremia.
- Vaptans are not indicated for treatment of hypovolemic hyponatremia.
  - Volume expansion would be expected to lead to prompt aquaresis.
  - Inducing increased renal fluid may worsen hypotension.
  - However, clinically significant hypotension was not observed in either the conivaptan or tolvaptan clinical trials in euvolemic and hypervolemic hyponatremic patients.
- Vaptans are not contraindicated with decreased renal function but these agents generally will not be effective if the serum creatinine is > 2.5 mg/dL.

Verbalis JG, et al. *Am J Med*. 2013;126(10):S1-S42.

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