

DISORDERS OF SERUM SODIUM CONCENTRATION

Bruce M. Tune, M.D.
Stanford, California

Regulation of Sodium and Water Excretion

Sodium: glomerular filtration, aldosterone, atrial natriuretic factors, in response to the following stimuli.

1. Reabsorption: hypovolemia, decreased cardiac output, decreased renal blood flow.
2. Excretion: hypervolemia. (Also caused by adrenal insufficiency, renal tubular disease, and diuretic drugs.)

Water: antidiuretic hormone (serum osmolality, effective vascular volume), renal solute excretion.

1. Antidiuresis: hyperosmolality, hypovolemia, decreased cardiac output.
2. Diuresis: hypoosmolality, hypervolemia → natriuresis.

Physiologic changes in renal salt and water excretion are more likely to favor conservation of normal vascular volume than normal osmolality, and may therefore lead to abnormalities of serum sodium concentration. Most commonly,

1. Hypovolemia → salt and water retention.
2. Hypervolemia → salt and water excretion.

• HYPERNATREMIA

Clinical Setting: Sodium excess: salt-poisoning, hypertonic saline enemas
Primary water deficit: chronic dehydration (as in diabetes insipidus)

Mechanism: Dehydration → renal sodium retention, even during hypernatremia
Rapid correction of hypernatremia can cause brain swelling

Management: Slow correction -- without rapid administration of free water
(except in nephrogenic or untreated central diabetes insipidus)

HYPONATREMIAS

Isosmolar

- A. Factitious: hyperlipidemia (triglyceride-plus-plasma water volume).
- B. Other solutes: hyperglycemia, radiocontrast agents, mannitol.

Hypoosmolar

A. Primary water excess

1. Water intoxication
2. Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
3. Acute renal failure

B. Primary salt deficit

1. Renal salt wasting
2. Adrenal mineralocorticoid deficiency
3. Pseudohypoaldosteronism

C. Secondary salt/water imbalance

1. Dehydration
2. Rehydration
3. Edema states

• WATER INTOXICATION

Clinical setting: Excessive intravenous infusion of free water
Infants: swimming, dilute formula (→ excess drinking)

Mechanism: Input >> output → dilutional ↓ $[Na^+]_s$, and hypervolemia → natriuresis

Management: Restricted fluid input
NaCl as needed

• SYNDROME OF INAPPROPRIATE ADH SECRETION (SIADH)

Clinical setting: CNS insults: meningitis, bleeding, trauma
Pulmonary insults: pneumonia, tuberculosis, ventilator therapy
Certain drugs: opiates, IV cyclophosphamide or vincristine

Mechanism: Urine not appropriately dilute
Water retention → hypervolemia → natriuresis
→ escape from hypervolemia (*edema very uncommon*)

Management: Restricted fluid input
NaCl as needed

• ACUTE RENAL FAILURE (ARF)

Clinical setting: Glomerulonephritis, hemolytic uremic syndrome, shock, sepsis
Decreased urine output (oliguria), abnormal urinalysis (blood, protein), elevated serum creatinine

Mechanism: Salt *and* water retention → hypervolemia, edema

Management: Restricted input
Dialysis

• RENAL SALT WASTING

- Clinical setting: Renal dysplasia
Infected hydronephrosis
Miscellaneous tubular injuries
- Mechanism: Primary natriuresis. Note re $[K^+]_s$: $2^\circ \uparrow$ aldo $\rightarrow \downarrow$, but \downarrow GFR $\rightarrow \uparrow$
- Management: Sodium replacement

• ADRENAL (MINERALOCORTICOID) INSUFFICIENCY: $\downarrow [Na^+]_s$, $\uparrow [K^+]_s$ & \downarrow pH

- Clinical setting: Congenital adrenal hyperplasia: young infants, females virilized
Iatrogenic: steroid therapy
Other adrenal cortical disease
- Mechanism: Low distal nephron Na^+/K^+ and Na^+/H^+ exchange \rightarrow
Hyperkalemia and acidosis worsened by decreased GFR
resulting from hypovolemia
- Management: Steroid replacement
Vascular volume expansion
Rx as needed for each electrolyte abnormality

• HYPONATREMIC DEHYDRATION

- Clinical setting: Diarrhea
Cystic fibrosis (sweat losses)
- Mechanism: Urine concentrated, even as hypoosmolality develops
High $H_2O:Na^+$ intake
- Management: Rehydrate with adequate sodium

• HYPONATREMIC REHYDRATION

- Clinical setting: Underestimate of dehydration or ongoing fluid losses \rightarrow
improper (maintenance) fluid input. [Replacement fluids need
to be isotonic (280-300 mOsm); maintenance fluids are too
dilute.]
- Mechanism: Replacement of isotonic losses with hypotonic fluids
- Management: NaCl

• EDEMA STATES

- Clinical setting: Nephrotic syndrome, hepatic failure, heart failure
- Mechanism: Sodium and water retention
Sodium restriction, diuretic therapy
- Management: Water restriction and/or less diuretic use
Salt administration (rarely)

CLINICAL USE OF URINE SODIUM:	<u>Low</u>	<u>High</u>
Concentration (mEq/l)	< 5-10	> 25-30
Fractional excretion (FENa)		
$\frac{\text{U/P Sodium}}{\text{U/P Creatinine}} \times 100$	< 1%	> 1% (→ 2% in premature infants)

CONDITIONS OF HIGH URINE SODIUM

HYPOVOLEMIC: renal salt wasting, adrenal insufficiency, diuretic use

HYPERVOLEMIC: fluid overload, SIADH, ARF, diuretic use

CONDITIONS OF LOW URINE SODIUM: normal renal and adrenal function, hypovolemia or decreased renal perfusion

Dehydration, hypovolemia

Edema states (untreated)

Diuretics (after drug excretion)

DIAGNOSTIC APPROACH TO HYPONATREMIA

Serum osmolality

Underlying disease state

Total body water/effective vascular volume

Intake/Output

Urinalysis, BUN and serum creatinine

Urine osmolality and urine sodium

Preliminary assessment and response to treatment

IMPORTANT DIFFERENTIAL DIAGNOSES

• SIADH vs.

Acute renal failure

Not useful

Urine osmolality

Urine sodium

Useful*

Edema

Serum creatinine ↑

Abnormal UA

Hyponatremic rehydration

Urine osmolality

Low FENa

Renal salt wasting

Urine osmolality

Response to salt or saline

Natriuresis when

dehydrated

• Salt wasting, adrenal vs. renal

Hyperkalemia

Serum creatinine

Normokalemia

K⁺_s promptly w.n.l.

* Clinical features not found in the first disorder of each differential diagnosis.

MOST COMMON ERRORS IN Dx & Rx

Failure to: 1) assess hydration/volemia, 2) measure urine sodium (FENa), or 3) recognize SIADH with high output or "isotonic" urines.

Use before diagnostic evaluation of: 1) salt, 2) volume expansion, or worse, 3) a diuretic.

READING

1. Gruskin AB, et al: Serum sodium abnormalities in children. In: Pediatric Clinics of North America, Symposium on Pediatric Nephrology. RN Fine (Ed), WB Saunders Co, New York, 1982, pp 907-932. [This comprehensive review has one important fault. It addresses volume in terms of gross assessment of total body water, calling the edema states expanded, when they are physiologically hypovolemic, and calling SIADH euvolemic, which it is not.]
2. Bartter FC, Schwartz WB: The syndrome of inappropriate antidiuretic hormone secretion. Am J Med 42:790, 1967. [Outstanding: The only "classic" article I recommend to students.]

CASE EXAMPLES: All of the following cases are real. In evaluating each of them, do not assume that fluid and electrolyte management was appropriate, or that all of the necessary monitoring was done.

- 1) A 7 month-old healthy boy, hospitalized for repair of a cleft lip, was resuscitated after a hypoxic episode and cardiac arrest in the operating room. He was returned to the ward extubated and with good blood pH, PO₂ and PCO₂. The next afternoon he had a seizure. Preoperative BUN, serum creatinine, and electrolytes had all been within normal limits. A routine electrolyte panel showed a fall of serum sodium from 142 to 128 mEq/l over the 24 hours following the arrest. The consultant called to evaluate the infant made an immediate tentative choice between two possible causes of this child's hyponatremia. a) What were the possibilities; b) which of the two could be diagnosed without further laboratory testing; and c) how?
- 2) A 13 year-old girl with a slowly growing brain tumor had been under home care with chronic nasogastric feeding. She was hospitalized after several weeks of feeding difficulty, with regurgitation of formula and increasing irritability. Admission physical examination showed subcutaneous tissue wasting and mild dehydration. Admission laboratory included the following: BUN 32 mg/dl, serum creatinine 1.9 mg/dl, serum sodium 126 mEq/l, urine osmolality 460 mOsm/l, urine sodium 68 mEq/l (FENa 2.2%). a) Based upon her history, physical examination, and laboratory findings, what two causes of hyponatremia seem most likely; b) which was the more likely of the two; and c) how could one confirm this conclusion?
- 3) A 14 month-old boy was diagnosed as having acute bacterial meningitis after a one-day history of vomiting and increasing irritability. All appropriate cultures were taken, and intravenous fluids and antibiotics started. The next day the boy had a seizure, and was found to have a serum sodium of 126 mEq/l (down from 140). BUN was 24 mg/dl (down from 36), urine SG was 1.018, and urine sodium was 5 mEq/l, at a time of 0.75 ml/kg/hr urine output. a) What were the two most likely causes of the hyponatremia; b) which was the more likely of the two; and c) which laboratory test best enabled you to distinguish between the two choices?
- 4) A 16 year-old unmarried mother brought her 4 month-old daughter to the emergency department shortly after a generalized convulsion. The baby was afebrile and alert, but thin and irritable. An LP showed no abnormality of cell count, glucose, or protein. A blood glucose was 76 mg/dl; BUN was 8 mg/dl; serum creatinine was 0.3 mg/dl; and electrolytes were Na 121, K 3.3, Cl 97, and HCO₃ 22 mEq/l, respectively. Urinalysis was benign, with a SG of 1.003; 1 hour later the urine osmolality was 220 mOsm/l and urine sodium was 4 mEq/l; 6 hours later urine osmolality and sodium were 320 mOsm/l and 28 mEq/l. Cultures of blood, CSF, and urine later proved to be negative, and no abnormality was found by EEG. The baby's serum sodium responded appropriately to 5 mEq/kg BW hypertonic saline and subsequent intravenous therapy with maintenance volumes of half-isotonic saline. Her serum sodium remained normal on subsequent PO feeding. What do you think caused her hyponatremia?
- 5) A 5 day-old full-term infant with septicemia was on ventilatory support in the ICN. Her serum sodium had drifted down from 140 to 124 mEq/l, while BUN and serum creatinine remained normal. An increase of her intravenous sodium replacement from 0.2% to 0.45% at maintenance IV rates and then to 0.45% at 1.5X maintenance rates resulted in serum sodium levels of 128 and then 124 mEq/l. Urine sodium went from 35 to 83 to 124 mEq/l (FENa ?? to 3.2 to 4.7%). Urine osmolality varied between 250 and 350 mOsm/l. BUN and serum creatinine remained normal, but potassium decreased to the point of requiring extra replacement. At no time did the infant appear dehydrated or overhydrated. GU ultrasound showed no abnormality. a) What was the most likely cause of the hyponatremia; b) why; and c) how could one document this diagnosis?

ANSWERS TO CASES:

- 1) a) SIADH (postoperative, post-arrest) vs. ARF (post-hypoxic cardiac arrest); b) ARF; c) SIADH rarely presents with edema, because of a natriuretic response to hypervolemia. ARF does not allow this escape from volume retention. ARF, therefore, presents with gross fluid overload (edema in this case) when there is enough fluid excess to produce this much hyponatremia.
- 2) a) SIADH (brain tumor) vs. renal salt wasting (malnutritional); b) renal salt wasting (SIADH is a state of fluid excess, and the patient appeared dehydrated); c) if uncertain about dehydration, restrict fluid input under close observation (the natriuresis of SIADH would resolve, that of renal salt wasting would not).
- 3) a) SIADH (meningitis) vs. hyponatremic rehydration (history of vomiting and unclear information about admission state of hydration and choice of intravenous fluids suggest inadequate attention to fluid management); b) hyponatremic rehydration; c) urine sodium, which was very low in a marginally oliguric state (i.e., presumed low FENa). The falling BUN ruled against ARF, a third conceivable choice. A low urine sodium almost always indicates hypovolemia, resulting in this case from inadequate extracellular rehydration 2° inadequate replacement of sodium.
- 4) Detailed dietary history revealed that the mother had no guidance in the feeding of the infant, and had been preparing a very dilute formula, especially recently because of lack of funds. The infant was a vigorous feeder, taking very large quantities of formula in an effort to meet her nutritional needs. However, this effort was inadequate, as indicated by her poor weight gain, and produced a state of mild malnutrition, sodium and potassium deficiency, and (as documented by her dilute urine) water intoxication. The confirmatory diagnostic evidence disappeared quickly as sodium was administered and appropriate fluid volumes given. A retrospective analysis of the data suggested the diagnosis, which was supported by further questioning of the mother.
- 5) a) The urine losses of sodium were impressive, and the house staff requested a renal consult because of urinary salt wasting. They had not seriously considered SIADH because of the urine osmolalities in the 250-350 range. However, although renal salt wasting due to hypoplastic kidneys was a possibility, the normal BUN, serum creatinine, and renal ultrasound ruled against this diagnosis. b) SIADH is one of the most common causes of hyponatremia in an ICU setting, and is the most likely process to behave in this manner. Although we are accustomed to seeing urine SG ≥ 1.015 and urine Osm ≥ 450 in SIADH, the normal physiologic response to hyponatremia in a well-hydrated patient is to dilute the urine fully (osmolality $\leq 100-150$ mOsm/l). Urine osmolalities of 250-350 were inappropriately concentrated in this patient. She was wasting sodium in her urine because she had SIADH. Giving her still more sodium and then more fluid volume predictably worsened the natriuresis and did not resolve the hyponatremia. c) Of all of the causes of hyponatremia, SIADH stands out as the one in which natriuresis is most sensitive to restriction of fluid volume. Water intoxication may respond similarly, but the medical record and the urine osmolality $\geq 100-150$ ruled out that diagnosis.

PROBLEMS

Four pairs of entities causing hyponatremia (1-4) and four sets of clinical information (A-D) are listed below. For each differential diagnosis (left), select the clinical information (right) that most promptly and most specifically allows one to distinguish between the two entities.

- | | |
|---|--|
| 1. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) vs. renal salt-wasting _____. | A. Serum cortisol, aldosterone. |
| 2. SIADH vs. hyponatremic dehydration _____. | B. Presence of gross overhydration; abnormal urinalysis, serum creatinine. |
| 3. SIADH vs. acute renal failure _____. | C. Baseline urine sodium excretion (FeNa). |
| 4. Primary renal vs. adrenal-mediated salt-wasting _____. | D. Natriuresis resolves with restricted fluid input. |

ANSWERS TO PROBLEMS

1. D. The natriuresis of SIADH is caused by hypervolemia and will resolve with decreased fluid input; that of renal salt-wasting is not and will not. "A" is an acceptable but impractical second choice answer (aldosterone increase due to hypovolemia in renal salt-wasting); serum aldosterone measurements are not available for 1-2 weeks (vs. 1-2 hours for FeNa).
2. C. SIADH is a natriuretic state, while dehydration is a state of low urine sodium. "A" is an acceptable second choice answer, but impractical for the reason given above.
3. B. Of the two entities, only acute renal failure will show the abnormalities listed.
4. A. Adrenal insufficiency is diagnosed by finding subnormal blood levels of adrenal steroid hormones; renal salt-wasting causes hypovolemia, which increases renin and secondarily aldosterone release. An earlier sign will be the frequent finding of normal or even low serum potassium in renal (but not adrenal) salt-wasting, or the prompt normalization of serum potassium in those cases of renal salt-wasting with hyperkalemia due to hypovolemia and prerenal azotemia.

DIFFERENTIAL DIAGNOSIS OF HYPONATREMIA IN CHILDREN

	CONDITION	BODY WEIGHT	URINE VOLUME	URINE S.G. & Osm	URINE [Na ⁺]	OTHER FEATURES
PRIMARY WATER EXCESS	Water intoxication	↑ (slightly)	polyuria	≤ 1.005 & ≤ 100	Low, but FENa may be > 1%*	I & O leads to Dx
	Inappropriate ADH secretion	↑ (slightly)	oliguria or normal	not maximally dilute	FENa > 1%*	Acute (occ. chronic) CNS or pulmonary disease, some drugs
	Acute renal failure	↑↑ (edema common)	oliguria with abnormal sediment	1.010 to ↑ & 300 to ↑	FENa > 1%* (except early in AGN)	Rising BUN & serum creatinine [K ⁺] may be ↑ Acidosis (±)
PRIMARY SODIUM LOSS	Adrenal insufficiency (& pseudohypoaldosteronism)	↓ (may be slight)	normal	1.010 to ↑ & 300 to ↑	↑↑	Adrenal functions [K ⁺]s ↑↑ Acidosis BUN may be ↑ Hypoglycemia ±
	Salt losing renal disease	↓ (may be slight)	normal	1.010 to ↑ & 300 to ↑	↑↑	BUN may be ↑ [K ⁺]s normal, ↑, or ↓ Ease of correction with NaCl
SECONDARY NA ⁺ /H ₂ O IMBALANCE	Hyponatremic dehydration	↓	decreased	↑↑	FENa < 1%*	Gastroenteritis Cystic fibrosis
	Hyponatremic rehydration	↓, normal, or ↑	decreased or normal	↑	FENa < 1%*	Underestimated dehydration Ongoing losses or pooling
	Edema states	↑ to ↑↑	normal to ↓	varies	varies	Salt restriction Diuretic therapy

* 1-2% in premature infants.