Hyponatremia: Diagnosis  
(Teacher’s Guide)

(50 minutes)

I. Objectives

- To learn a diagnostic framework, using examination and laboratory values, for evaluating hyponatremia

II. Cases

Before discussing the cases, review the general diagnostic framework for hyponatremia. Start with the pathophysiology of hyponatremia. Note that most cases of hyponatremia are due to a disorder in water balance, rather than sodium balance.

Which two hormones play the greatest roles in sodium and water balance? How are they regulated? How do they affect urine osmolality and urine sodium?

Antidiuretic hormone (ADH, or vasopressin) is regulated by plasma osmolality and intravascular volume. ADH secretion is stimulated when plasma osmolality is high and inhibited when it is low. Volume depletion is a strong stimulus for ADH secretion, even overriding the inhibitory effect of a low plasma osmolality.

ADH increases water permeability in the collecting tubules of the kidney, increasing water reabsorption, thus increasing urine osmolality. Write the following figure on the board:

\[ \uparrow \text{ADH} \quad \rightarrow \quad \uparrow \text{Urine osmolality} \]

Aldosterone is also regulated by intravascular volume, via the renin-angiotensin system. (Sodium levels also affect aldosterone secretion, though not as strongly as volume.) Aldosterone stimulates the Na\(^+\)-K\(^+\) exchange pump in the distal tubule, increasing sodium reabsorption and decreasing urine sodium. Write the following figure on the board:

\[ \uparrow \text{Aldosterone} \quad \rightarrow \quad \downarrow \text{Urine sodium} \]
Review the diagnostic algorithm for hyponatremia.

Learners will have a blank diagnostic algorithm that they can fill in. (The complete algorithm is in the Appendix.) Start by writing the top of the diagnostic algorithm:

\[
\text{Na}^+ < 135 \text{ mmol/L}
\]

Hyperosmolar  Hypo-osmolar  Iso-osmolar
(Pseudohyponatremia)

Ask team members the most common cause of hyperosmolar hyponatremia. It is hyperglycemia. (Another example would be an osmotic diuretic, such as mannitol.)

Ask someone to explain the pathophysiology behind hyperglycemia-induced hyponatremia. High serum osmoles increase water absorption into the intravascular space, diluting the sodium. Note that this is a true hyponatremia, not a pseudohyponatremia, as sodium concentration is truly decreased. However, once the hyperglycemia is corrected, the sodium will naturally move towards its baseline value.

Now ask team members for the differential diagnosis of pseudohyponatremia. Hypertriglyceridemia and elevated plasma proteins, as in multiple myeloma, cause pseudohyponatremia. The diagnosis in this instance is usually obvious, as the plasma will appear lipemic, or the patient will have a known history of multiple myeloma.

Here is an explanation and illustration of how a serum sodium level can appear falsely low:

Sodium is present only in the aqueous portion of blood, while lipids and proteins are present in the non-aqueous portion. The lab analyzer measures sodium over the entire blood volume, not just the aqueous portion:

**Normal**

\[
\begin{align*}
\text{Non-aqueous} & : \text{Aqueous} \\
\text{Na}^+ & \quad \text{Na}^+ \quad \text{Na}^+
\end{align*}
\]

\[
\begin{align*}
\text{“True” } [\text{Na}^+] &= 154 \text{ mmol/L} \\
\text{Reported } [\text{Na}^+] &= 140 \text{ mmol/L}
\end{align*}
\]

**Pseudohyponatremia**

\[
\begin{align*}
\text{Non-aqueous} & : \text{Aqueous} \\
\text{Na}^+ & \quad \text{Na}^+ \quad \text{Na}^+
\end{align*}
\]

\[
\begin{align*}
\text{Reported } [\text{Na}^+] &= 134 \text{ mmol/L} \\
\text{“True” } [\text{Na}^+] &= 154 \text{ mmol/L}
\end{align*}
\]
The other causes of hyponatremia fall into the hypo-osmolar category. Note that while you can measure serum osmolality to confirm hypo-osmolality, it’s usually not necessary, as hyperosmolar hyponatremia and pseudohyponatremia can often be ruled in or out based upon history and basic labs.

The second portion of the algorithm focuses upon volume status:

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Hypo-osmolar hyponatremia
   ↓
  Hypovolemic   Euvolemic   Hypervolemic
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Note that the above classification refers to extracellular fluid status, not intravascular volume status.

Review hypovolemic hyponatremia:

Ask team members what physical exam and laboratory findings are suggestive of hypovolemia:
- Tachycardia, hypotension
- Orthostatic vital signs
- Dry mucous membranes
- Poor skin turgor
- BUN:creatinine ratio > 20

Note that hypovolemia usually causes hypernatremia. Hyponatremia occurs when the patient takes in hypotonic solutions to make up for their extrarenal losses.

Now review how hypovolemia affects ADH and aldosterone levels, and thus the urine values. Write the following figures on the board:

```
Intravascular volume  ADH  Urine osmolality
↓     ↑  ➔ (> 100 mOsm/L, often > 450 mOsm/L)

Intravascular volume  Aldosterone  Urine sodium
↓     ↑  ➔ (< 20 mmol/L)
```
Now review hypervolemic hyponatremia:

Ask team members to list physical exam and laboratory findings suggestive of hypervolemia:
- Crackles
- Jugular venous distention
- Edema
- Ascites
- Pulmonary edema on chest x-ray
- Elevated B-natriuretic peptide

Now ask them to list the differential diagnosis of hypervolemia:
- Congestive heart failure
- Cirrhosis
- Nephrotic syndrome

Now review how hypervolemia affects ADH and aldosterone levels. Effective circulating volume is decreased. Write the following figures on the board:

\[\Downarrow \text{Intravascular volume} \Rightarrow \Uparrow \text{ADH} \Rightarrow \Uparrow \text{Urine osmolality} (> 100 \text{ mOsm/L}, \text{ usually } > 450 \text{ mOsm/L}) \]

\[\Downarrow \text{Intravascular volume} \Rightarrow \Uparrow \text{Aldosterone} \Rightarrow \Downarrow \text{Urine sodium} (< 20 \text{ mmol/L}) \]

Note that the urine osmolality and urine sodium levels are the same in hypovolemia and hypervolemia. The only way to tell the difference is by clinical exam.

Now review the diagnosis of euvolemic hyponatremia. In euvolemia, there are no signs of hypo- or hypervolemia on exam.

Draw the rest of the algorithm on the board:
Review urine findings in SIADH. The primary problem is inappropriate secretion of ADH, not a reduction in intravascular volume:

![Diagram showing ADH, urine osmolality, intravascular volume, and aldosterone relationships.]

Now review the urine findings in psychogenic polydipsia. The primary problem is increased intravascular volume due to water intoxication:

![Diagram showing intravascular volume, ADH, urine osmolality, and aldosterone relationships.]

Case 1

A 64-year old woman with a past medical history of hypertension and diabetes is brought to the emergency room by her son for several days of nausea, vomiting, headache and fatigue. She is currently taking glipizide, fosinopril and hydrochlorothiazide, which was added about two weeks ago. She has normal vital signs, and her exam is unremarkable. On labs, Na = 123 mmol/L, K = 3.5 meq/L, BUN = 7 mg/dL, creatinine = 0.5 mg/dL and glucose = 304 meq/L. Her urinalysis is specific gravity = 1.015, ph = 6.5, WBC = 3, RBC = 0, trace protein.

What is the most likely cause of this patient’s hyponatremia, and what do you expect her urine studies to show?

Although the patient has hyperglycemia, it is only a minor factor contributing to her hyponatremia. Run through this calculation to estimate the patient’s expected sodium level once her hyperglycemia is corrected.

$$\text{Corrected Na}^+ = \frac{\text{Measured Na}^+ + 2.4 \times (304 - 100)}{100} = 123 + 2.4 \times 2 = 128 \text{ mmol/L}$$

(The traditional correction factor for hyponatremia of 1.6 for every 100 mg/dL of glucose > 100 mg/dL is likely an underestimate.)^2
This is a classic case of SIADH due to a thiazide diuretic. You would expect her urine osmolality to be high (> 300 mOsm/L), because her ADH level is high. Because she has an increased intravascular volume, her aldosterone secretion will be suppressed, causing a high urine sodium (> 20 mmol/L).

Note that the patient’s specific gravity in her urine is a useful reflection of her high urine osmolality. The patient’s low BUN level is also typical in SIADH.

Ask team members to list the differential diagnosis of SIADH:1,2
- Medications (especially thiazide diuretics)
- Pulmonary disease (especially lung cancer)
- Central nervous system disease (especially mass lesions)
- Post-operative state (especially in premenopausal women)
- Nausea, vomiting and pain

Note that there are other conditions that simulate an SIADH picture:1,2
- Adrenal insufficiency (can also present in hypovolemic state)
- Hypothyroidism
- Chronic renal insufficiency

One condition which can produce laboratory abnormalities similar to those seen in SIADH is cerebral salt wasting (CSW) syndrome.2 This syndrome is an infrequent cause of hyponatremia in patients with acute intracranial hemorrhage, such as subarachnoid hemorrhage or traumatic brain injury. It is technically a form of hypovolemic, rather than euvoletic, hyponatremia and can be difficult to differentiate from SIADH in these patients.

Case 2

A 44-year-old man comes to the ER after a week of watery diarrhea, abdominal pain, nausea and vomiting. He has been able to tolerate oatmeal, but says he has been mostly drinking sports drinks in order to replenish his electrolytes. On exam, the patient’s BP = 102/52 mm Hg, P = 111 bpm and T = 99.0°F. His labs reveal Na = 122 mmol/L, K = 2.4 meq/L, BUN = 42 mg/dL and creatinine = 1.2 mg/dL.

What is the most likely cause of this patient’s hyponatremia, and what would you expect from his urine studies?

This is a case of hypovolemic hyponatremia, with continued consumption of hypotonic solutions. (Sports drinks are still hypotonic.) You would expect his urine osmolality to be high (often > 450 mOsm/L in hypovolemia), and his urine sodium to be low.

Although nausea and vomiting can cause SIADH, the signs of dehydration on exam and the elevated BUN point towards hypovolemia.
Case 3

A 51-year-old man with schizophrenia is sent from emergency psychiatric services for evaluation after a routine laboratory check reveals a Na$^+ = 118$ mmol/L. His physical exam is normal. His urine osmolality is 165 mmol/L, and his urine sodium is 41 meq/L.

What is this patient’s diagnosis?

The patient appears euvolemic on exam, which narrows down the diagnosis to SIADH or psychogenic polydipsia. His urine sodium is high, which reflects a high intravascular volume, which again is seen in either SIADH or psychogenic polydipsia.

His urine osmolality is low, but not low enough to be due to pure psychogenic polydipsia (urine osm < 100 mOsm/L). This patient likely has a combination of psychogenic polydipsia and mild SIADH. Many patients with schizophrenia have a mild degree of SIADH, possibly due to their medications, or due to an alteration in their ADH release setpoint.

Note that psychogenic polydipsia is rare in the absence of mental illness, as healthy humans have the capacity to drink 10 - 15 liters of water a day without diluting their sodium.

Case 4

A 65-year-old man with coronary artery disease comes to the emergency room for a one-week history of shortness of breath at rest. He denies any other symptoms. His medications include aspirin, enalapril, metoprolol, furosemide and digoxin. His vitals are BP = 90/45 mm Hg, P = 98 bpm. He has bilateral crackles halfway up on exam, and he has 2+ pitting edema to the knees. His labs show Na = 126 mmol/L, K = 4.8 meq/L, BUN = 23 mg/dL, creatinine = 1.2 mg/dL. His urine osmolality = 548 mOsm/L and urine sodium = 45 mmol/L.

What is the most likely cause of this patient’s hyponatremia?

The patient clearly has congestive heart failure. His elevated urine osmolality is a reflection of his decreased intravascular volume. You would normally expect his urine sodium to be low, but the patient is on furosemide, which increases urine sodium levels.

Note that a low sodium level is a poor prognostic factor in heart failure. However, most of these patients are asymptomatic from their chronically low sodium levels.
III. Questions for Further Discussion

Case 5

A 31-year-old man with Type I diabetes and hypothyroidism comes to the ER with a chief complaint of feeling faint. He reports a 10-lb. weight loss over the last two months, and frequent episodes of hypoglycemia. His medications include insulin and levothyroxine. On exam, he is a thin young man in no apparent distress. His supine vitals are normal, but he is orthostatic by pulse and blood pressure. His labs reveal sodium = 128 mmol/L, K = 5.6 meq/L, glucose = 125 meq/L, BUN = 14 and creatinine = 1.3 mg/dL. His urine osmolality is 472 mOsm/L, and his urine sodium is 96 mmol/L.

What is the most likely cause of this patient’s hyponatremia?

The patient’s urine osmolality and urine sodium are most consistent with an SIADH-like picture. However, his orthostatic vital signs suggest decreased intravascular volume. One diagnosis to consider would be adrenal insufficiency.

Other features of this case that support the diagnosis of adrenal insufficiency include:

- History of other autoimmune endocrine disorders
- History of weight loss and hypoglycemia
- A very high urine sodium, suggesting a mineralocorticoid deficiency
- An elevated serum potassium, also suggesting a mineralocorticoid deficiency
IV.  Key Article


A basic review article on the diagnostic evaluation and management of hyponatremia. Table 1 is a helpful summary of findings in hypo-osmolar hyponatremia.

V.  Reference Article


Review article on the diagnosis and management of SIADH.

VI.  Resources
Appendix: Differential Diagnosis and Urine Studies in Hyponatremia

Serum Na⁺ < 135 mmol/L

Hyperosmolar
- Hyperglycemia
- Mannitol

Hypo-osmolar

Iso-osmolar (Pseudohyponatremia)
- Hypertriglyceridemia
- Hyperparaproteinemia

Hypovolemia
- Diarrhea, vomiting
- Strenuous exercise

Hypervolemia
- Congestive heart failure
- Cirrhosis
- Nephrotic syndrome

Euvolemia

Urine osm > 100 mOsm/L
Urine Na < 20 mmol/L

SIADH (R/O adrenal insufficiency and hypothyroidism)

Psychogenic polydipsia

Urine osm < 100 mOsm/L
Urine Na > 20 mmol/L