Hypernatremia, SIADH, Diabetes Insipidus, and Mixed Acid-Base Disorders

Andrew Bland, MD, FACP, FAAP

March 2026

Hypernatremia, SIADH, Diabetes Insipidus, and Mixed Acid-Base Disorders

Learning Objectives

By the end of this handout, students will be able to:

1. **Define and classify hypernatremia** by volume status and understand mechanisms of free water loss
2. **Calculate free water deficit** and prescribe appropriate replacement therapy
3. **Distinguish central (vasopressin-responsive) from nephrogenic (vasopressin-resistant) diabetes insipidus** using clinical testing
4. **Recognize SIADH presentation** and apply diagnostic criteria (serum osmolality, urine osmolality, euvolemia)
5. **Differentiate SIADH from cerebral salt wasting** (both cause hyponatremia but require opposite treatments)
6. **Apply the delta-delta (Δ-Δ) ratio** to identify mixed acid-base disorders
7. **Manage acute hypernatremia and hyponatremia** with appropriate rates of correction to avoid osmotic complications

---

I. Hypernatremia: Definition, Epidemiology, and Classification

Definition

Hypernatremia = serum sodium >145 mEq/L (normal range 135–145 mEq/L)

Pathophysiology: Osmolality Concepts

Serum osmolality (calculated):

```
Serum Osmolality = 2[Na+] + [Glucose]/18 + [BUN]/2.8
(Or simplified: 2[Na+] + [Glucose]/18 + [BUN]/2.8, where Glc and BUN in mg/dL)
```

- **Normal serum osmolality:** 275–295 mOsm/kg
- **Hypernatremia = High serum sodium = HIGH osmolality** (hyperosmolar state)

Osmotic effect: - High extracellular osmolality ☐ water moves OUT of cells ☐ cellular dehydration - Brain cells shrink ☐ can cause **intracerebral hemorrhage** from rupture of cerebral vessels - Risk increases with severity and ACUTENESS of hypernatremia

Mechanisms of Hypernatremia

Hypernatremia results from **free water loss > sodium loss**, which occurs via:

1. **Renal free water loss** (polyuria)
   - Diabetes insipidus (central or nephrogenic)
   - Osmotic diuresis (glucose, mannitol, urea)
   - Post-obstructive polyuria
2. **Gastrointestinal free water loss**
   - Diarrhea (losses hypotonic relative to plasma)
   - Vomiting with insufficient water replacement
3. **Insensible losses** (skin, lungs)
   - Excessive sweating
   - Hyperventilation
   - Fever
   - Usually accompanied by other fluid losses
4. **Impaired thirst** or inability to access water
   - Altered mental status, dementia, inability to communicate
   - **Most common risk factor in hospitalized patients**

Classification by Volume Status

Hypernatremia Type	Mechanism	Volume Status	Clinical Examples
Hypovolemic	Hypotonic fluid loss (GI, insensible)	Depleted extracellular volume	Diarrhea, vomiting, sweating without fluid replacement
Euvolemic	Free water loss without volume depletion	Normal extracellular volume	Diabetes insipidus, insensible losses balanced

Hypernatremia Type	Mechanism	Volume Status	Clinical Examples
Hypervolemic	Sodium excess (net sodium + water, but Na > water)	Expanded extracellular volume	Hypertonic saline infusion, hyperaldosteronism (rare)

Clinical assessment: - **Hypovolemic:** Orthostatic vital signs, poor skin turgor, dry mucous membranes, ☐ JVD - **Euvolemic:** Normal vital signs, normal skin turgor, normal JVD - **Hypervolemic:** Hypertension, edema, ☐ JVD, possible pulmonary edema

---

II. Diabetes Insipidus (DI)

Definition and Pathophysiology

Diabetes insipidus is a disorder of **free water balance** caused by either: 1. **Central DI (Neurogenic):** Deficient ADH (vasopressin) production or release 2. **Nephrogenic DI:** Renal resistance to ADH (kidney cannot respond)

Normal Physiology of ADH

Osmoreceptors and Thirst: 1. Hypothalamic osmoreceptors detect ☐ serum osmolality (>280 mOsm/kg) 2. Signal to posterior pituitary to release ADH (antidiuretic hormone, vasopressin) 3. ADH binds to V2 receptors on collecting duct principal cells 4. V2 activation ☐ ☐ aquaporin-2 (water channel) insertion in apical membrane 5. Water reabsorption in collecting duct ☐ concentrated urine, ☐ serum osmolality 6. **Negative feedback:** As osmolality normalizes, ADH release suppressed

Thirst mechanism: - Parallels ADH; triggered at similar osmolality threshold (~280 mOsm/kg) - **Redundancy:** Even if ADH deficient, drinking water can maintain osmolality

Central (Neurogenic) Diabetes Insipidus

Definition: Insufficient ADH production or release from posterior pituitary.

Causes: - **Idiopathic** (~30–50%): No identifiable cause; possible autoimmune destruction - **Traumatic:** Head trauma, neurosurgery, pituitary surgery - **Tumor:** Pituitary adenoma, craniopharyngioma, lymphoma, metastatic disease (compresses pituitary) - **Infiltrative:** Sarcoidosis, tuberculosis, histiocytosis X, hemochromatosis - **Genetic:** DIDMOAD syndrome (Wolfram syndrome: DI + Diabetes Mellitus + Optic Atrophy + Deafness) - **Hypoxic-ischemic encephalopathy:** Post-cardiac arrest - **Infection:** Meningitis, encephalitis

Pathophysiology: - Posterior pituitary damaged or pituitary stalk compressed ☐ ☐ ADH synthesis/release - Kidneys are normal; they CANNOT respond because ADH is absent - **Result:** Polyuria (dilute urine) + thirst-driven polydipsia (if thirst mechanism intact)

Clinical presentation: - **Sudden onset** (if traumatic) or insidious (if idiopathic) - **Polyuria:** Urine output 5–15 L/day (or more if severe and drinking matches) - **Polydipsia:** Intense thirst; compulsive drinking - **Nocturia:** Frequent nighttime urination (disrupted sleep) - **Signs of hypernatremia:** Dry mucous membranes, irritability, seizures (if severe/acute) - **Presentation may be hypovolemic** if patient cannot access water (delirium, in hospital)

Diagnosis: 1. **Clinical suspicion:** Polyuria (>3 L/day) + polydipsia + hypernatremia 2. **Labs at baseline:** - Serum osmolality ☐ (>295 mOsm/kg) - Urine osmolality LOW (<300 mOsm/kg) — inappropriately dilute for high serum osmolality - Hypernatremia (Na >145) - Urine specific gravity LOW (<1.010) 3. **Water deprivation test (confirmatory):** - **Protocol:** Withhold water for 8–12 hours; measure serum Na, serum osmolality, urine osmolality, and ADH level periodically - **Central DI response:** - Serum osmolality ☐ (>295) - Urine osmolality remains LOW (<300) despite water deprivation (kidneys cannot respond without ADH) - ADH level LOW (<2 pg/mL; normal elevated osmolality would trigger high ADH) - **After water deprivation, give desmopressin (synthetic ADH):** - **Urine osmolality rises** (>600 mOsm/kg) — kidneys CAN respond if ADH provided - This rise confirms central DI (kidneys are normal; problem is ADH deficiency) 4. **Brain MRI:** If tumor or infiltrative disease suspected

Management: - **Desmopressin (DDAVP) replacement:** - **Intranasal spray:** 10 μg once or twice daily (most convenient) - **Oral tablets:** 0.1–0.2 mg TID - **Dose titration:** Adjust to urine output and serum sodium; goal is euvolemia without hyponatremia - **Note:** Desmopressin is vasopressin analog, selective for V2 receptors (renal); lacks vasopressor V1 effects at therapeutic doses - **Free water intake:** Patient should drink to thirst; desmopressin corrects inability to concentrate urine - **Monitoring:** Check serum sodium regularly; avoid hyponatremia from over-replacement

---

Nephrogenic Diabetes Insipidus

Definition: Kidneys resistant to ADH (despite normal/high ADH levels); cannot respond to V2 receptor activation.

Causes:

Genetic (hereditary nephrogenic DI): - **X-linked recessive (most common):** V2 receptor mutations (AVPR2 gene); primarily males affected - **Autosomal recessive:** Aquaporin-2 (AQP2) mutations; defective water channels

Acquired (more common overall): - **Medications:** - **Lithium** (most common drug cause; interferes with V2 signaling and AQP2 insertion) - Amphotericin B (acute tubular toxicity) - NSAIDs (interfere with prostaglandin-mediated aquaporin trafficking) - Vancomycin - Demeclocycline (tetracycline with anti-ADH effects; sometimes used therapeutically for SIADH) - **Metabolic:** - **Hypokalemia:** Decreases AQP2 expression; correcting K+ may improve DI - **Hypercalcemia:** Damages collecting duct; inhibits AQP2 - **Renal disease:** - Chronic kidney disease, chronic obstructive uropathy - Post-obstructive polyuria (transient nephrogenic DI

after relief of obstruction) - **Systemic disease:** - Sarcoidosis (granulomatous infiltration) - Amyloidosis - Myeloma (light chain deposit disease)

Pathophysiology: - ADH levels HIGH or elevated in response to hypernatremia (body trying to correct) - Kidneys fail to respond (V2 receptor damaged, AQP2 defective, or second-messenger dysfunction) - **Result:** Polyuria (dilute urine despite high ADH) + thirst + hypernatremia

Clinical presentation: - Similar to central DI: polyuria (5–15 L/day), polydipsia, hypernatremia - May have history of medication (lithium) or metabolic condition (hypokalemia, hypercalcemia) - Nocturia and sleep disruption

Diagnosis: 1. **Clinical suspicion:** Polyuria + low urine osmolality + hypernatremia + risk factor (medication, metabolic) 2. **Water deprivation test:** - **Serum osmolality** ☐ (>295) - **Urine osmolality remains LOW** (<300) despite water deprivation - **ADH level HIGH** (>5 pg/mL) — normal response to hypernatremia, but kidneys don't respond 3. **Post-desmopressin response:** - Give desmopressin - **Urine osmolality does NOT significantly increase** (<600, often <400) — **key finding distinguishing nephrogenic from central DI** - This lack of response confirms renal resistance to ADH 4. **Look for cause:** - Medication history (lithium, amphotericin, NSAIDs) - Serum K+, Ca2+ (hypokalemia, hypercalcemia) - Renal function, imaging (obstruction)

Management: - **Address underlying cause if possible:** - **Discontinue lithium** (if possible; consider alternatives for bipolar disorder: valproate, lamotrigine, atypical antipsychotics) - **Correct hypokalemia** (K+ >3.5 mEq/L) - **Correct hypercalcemia** (if present; saline, furosemide, bisphosphonates) - **Thiazide diuretics** (paradoxically, diuretics help): - **Mechanism:** Thiazides cause mild volume depletion ☐ ☐ proximal tubule reabsorption ☐ less fluid delivered to collecting duct ☐ less polyuria despite nephrogenic DI - **Dose:** Hydrochlorothiazide 25 mg daily - **Effect:** Reduces urine output by 30–50% (not complete suppression) - **NSAIDs** (inhibit prostaglandins; reduce urine output) - **Amiloride** (K+-sparing diuretic; may help in lithium-related DI by reducing lithium entry into collecting duct cells) - **Low-sodium diet:** Reduces filtered load; less urine volume needed for excretion - **Adequate free water intake:** Patient drinks to thirst (critical; without water intake, becomes severely hypernatremic)

III. Hyponatremia: SIADH vs. Cerebral Salt Wasting

Definition of Hyponatremia

Hyponatremia = serum sodium <135 mEq/L (normal 135–145 mEq/L)

SIADH: Syndrome of Inappropriate Antidiuretic Hormone

Definition: SIADH is **inappropriate ADH secretion** (ADH released despite LOW serum osmolality, leading to water retention and dilutional hyponatremia).

Diagnostic Criteria for SIADH All of the following must be present:

1. **Euvolemia** (normal volume status; no edema, no signs of dehydration)
2. **Hyponatremia** (serum Na <130 mEq/L, usually)
3. **LOW serum osmolality** (<280 mOsm/kg; hypoosmolar)

4. **Urine osmolality inappropriately ELEVATED** (>200 mOsm/kg, usually >400)
    - **Why "inappropriate"?** With low serum osmolality, normal response is to suppress ADH and produce dilute urine (osmolality <100). But in SIADH, urine remains concentrated despite hypoosmolarity.
5. **Normal thyroid and adrenal function** (exclude hypothyroidism, adrenal insufficiency as mimics)
6. **Normal renal function** (eGFR >30; exclude chronic kidney disease)
7. **Normal cardiac function** (exclude heart failure, which can cause hyponatremia with volume overload)
8. **Not on diuretics** or other medications that obviously cause SIADH
9. **Normal urine Na, K, osmolality** (rule out primary polydipsia; in primary polydipsia, urine is dilute not concentrated)

Causes of SIADH

Category	Causes
Malignancy	Small-cell lung cancer (SCLC) — most common, ~10% of SCLC; GI cancers, genitourinary tumors, lymphoma
Pulmonary Disease	Pneumonia, tuberculosis, aspergillosis, ventilator-associated pneumonia
CNS Disease	Meningitis, encephalitis, head trauma, subarachnoid hemorrhage, stroke, seizures, intracranial hemorrhage
Medications	SSRIs, tricyclic antidepressants, carbamazepine, oxcarbazepine, vincristine, cisplatin, desmopressin, oxytocin, NSAIDs, ACE-I
Post-operative	Major surgery, pain, stress (ADH release as stress response)
Idiopathic	No identifiable cause (~30% of SIADH cases)

Pathophysiology of SIADH **Normal ADH regulation:** - ADH suppressed if serum osmolality <280 - ADH released if osmolality >280

In SIADH: - ADH levels remain ELEVATED despite LOW serum osmolality - ADH continues to act on collecting duct ☐ continued water reabsorption - **Result:** Water retention ☐ dilutional hyponatremia (urine is appropriately concentrated for the ADH present, but ADH presence is inappropriate for the low osmolality)

Diagnosis of SIADH **Lab findings:** - Serum Na 120–130 mEq/L (or lower in acute/severe SIADH) - Serum osmolality <280 mOsm/kg - Urine osmolality 300–600+ mOsm/kg (concentrated despite low serum osmolality) - Urine Na typically >40 mEq/L (euvolemic state; kidneys not trying to conserve Na) - ADH level elevated (diagnostic, though not always measured; diagnosis is clinical) - Normal TSH, morning cortisol (rule out hypo-Th, adrenal insufficiency)

Clinical presentation: - Often ASYMPTOMATIC if chronic and mild (Na 130–135) - **Symptomatic if acute or severe (Na <125):** - **Neurologic:** Nausea, vomiting, lethargy, confusion, seizures, cerebral edema, coma (if very rapid/severe) - **Pathophysiology of symptoms:** Water shifts into brain cells ☐ cerebral edema ☐ increased ICP

Management of SIADH Chronic/Mild SIADH (Na 130–135, asymptomatic): - **Fluid restriction:** Most effective; typically 800–1000 mL/day - **Mechanism:** ADH retains water regardless of intake, so limiting intake limits water retention - **Efficacy:** Effective in ~50% of SIADH cases (some have "reset osmolat" — ADH remains suppressed until osmolality drops to new setpoint) - **Patient education:** Monitor sodium periodically; adjust fluid intake to maintain Na 130–135

Acute/Severe Symptomatic SIADH (Na <120, seizures, altered mental status): - **Hypertonic saline (3% NaCl):** - **Dose:** 3% saline at 0.5–1 mL/kg/hour IV - **Goal:** Raise serum Na by 6–10 mEq/L acutely (to stop seizures/symptoms) - **Then slow correction:** Do NOT correct >10 mEq/L in 24 hours total (risk of osmotic demyelination syndrome, ODS) - **Rationale:** 3% saline provides hypertonic fluid; ADH retains water, but osmotic gradient still favors raising serum Na - **Monitoring:** Check serum Na frequently (every 2–4 hours initially); adjust rate - **Loop diuretic (furosemide):** Helps eliminate excess water; often combined with hypertonic saline - **Admit to ICU:** For close monitoring and management

Chronic symptomatic or refractory SIADH: - **V2-receptor antagonist (vaptans):** - **Tolvaptan** (Samsca): 7.5–15 mg daily - **Mechanism:** Selective V2 receptor antagonist; blocks ADH action on collecting duct ☐ aquaporesis (urinary water loss) - **Effect:** Raises serum Na by blocking water reabsorption (not by restricting fluid) - **Advantage:** Can allow normal fluid intake - **Caution:** Monitor Na carefully (risk of osmotic demyelination if raised too fast); avoid if chronic/stable SIADH with Na >120 (risk of too-rapid correction) - **Desmeclocycline:** 600–1200 mg daily - **Mechanism:** Tetracycline antibiotic with anti-ADH properties; reduces AQP2 expression - **Effect:** Creates nephrogenic DI-like state; produces dilute urine - **Drawback:** Slow onset (days); can cause photosensitivity; fewer adverse effects than vaptans in chronic setting - **Lithium:** 300–600 mg daily - **Mechanism:** Similar to desmeclocycline; creates nephrogenic DI - **Drawback:** Narrow therapeutic window; renal/thyroid toxicity risk with chronic use; rarely used for SIADH now

Cerebral Salt Wasting (CSW) vs. SIADH

Both cause hyponatremia and euvolemia clinically, but pathophysiology and treatment are OPPOSITE.

Feature	SIADH	Cerebral Salt Wasting
Primary problem	Water retention (ADH excess)	Sodium loss (natriuresis from CNS injury)
Mechanism	ADH inappropriately suppresses free water excretion	Natriuretic peptide (ANP/BNP) released from injured brain; promotes renal Na wasting
Volume status	Euvolemic; water expanded	Often HYPOVOLEMIC (though can appear euvolemic clinically); sodium depleted

Feature	SIADH	Cerebral Salt Wasting
Urine Na	Elevated (>40) from euvolemia	VERY elevated (>100, often 150+) from active Na wasting
CVP/JVD	Normal to slightly elevated	Low (due to volume depletion)
Urine osmolality	Concentrated (>400)	Concentrated (>400)
Treatment	Fluid RESTRICTION (decrease water intake)	Fluid EXPANSION + hypertonic saline (increase Na and volume)
Associated conditions	Malignancy, pulmonary disease, CNS infection	Traumatic brain injury, subarachnoid hemorrhage, meningitis

Key Clinical Distinction The critical differentiator is VOLUME STATUS and URINE SODIUM:

- **Euvolemic + high urine Na (100+) + concentrated urine = Likely SIADH** (kidney retaining water from excess ADH)
- **Signs of hypovolemia (orthostasis, low JVD, dry mucous membranes) + very high urine Na (150+) + concentrated urine = Likely CSW** (kidney losing sodium actively from ANP/BNP)

Clinical pearl: If giving fluid restriction (SIADH treatment) to a patient with CSW, hyponatremia WORSENS (because patient loses more sodium with fluid restriction). Conversely, fluid restriction helps SIADH but harms CSW.

Diagnosis of CSW

- **Clinical context:** Severe CNS injury (SAH, head trauma, meningitis)
- **Labs:** Hyponatremia, low serum osmolality, urine osmolality >400, **urine Na >100** (key)
- **Signs of hypovolemia:** Orthostatic vital signs, low JVD, dry mucous membranes
- **Elevated ANP/BNP:** May be present (confirms ANP/BNP-mediated process)
- **CVP:** Low (invasive measurement if uncertain)

Management of CSW

- **Hypertonic saline:** 3% NaCl to raise serum Na AND replete intravascular volume
- **Fluid expansion:** With normal saline or hypertonic saline (opposite of SIADH)
- **Goal:** Increase serum Na by 4–6 mEq/L/day (more lenient than SIADH, up to 10 mEq/L/day acceptable)
- **Monitoring:** Check serum Na, CVP, and clinical volume status
- **Duration:** Usually self-limited as brain injury resolves and ANP/BNP normalizes

IV. Mixed Acid-Base Disorders and Delta-Delta (Δ-Δ) Analysis

Acid-Base Review

pH: 7.35–7.45 (normal) - **Acidemia:** pH <7.35 - **Alkalemia:** pH >7.45

Primary acid-base disorders: 1. **Metabolic acidosis:** ☐ HCO_3^-, ☐ pH 2. **Metabolic alkalosis:** ☐ HCO_3^-, ☐ pH 3. **Respiratory acidosis:** ☐ $PaCO_2$, ☐ pH 4. **Respiratory alkalosis:** ☐ $PaCO_2$, ☐ pH

Simple vs. Mixed Disorders

Simple disorder: ONE primary disorder; respiratory system compensates appropriately.

Mixed disorder: TWO or more primary disorders occurring simultaneously.

Example of simple metabolic acidosis with appropriate respiratory compensation: - Patient: HCO_3^- 12 (low), $PaCO_2$ 24 (low; respiratory compensation) - **Interpretation:** Metabolic acidosis with appropriate respiratory response - This is ONE disorder (metabolic acidosis) + appropriate respiratory compensation

Example of mixed acid-base disorder: - Patient: HCO_3^- 12 (metabolic acidosis), $PaCO_2$ 35 (NOT low enough for appropriate compensation) - **Interpretation:** Metabolic acidosis + **concurrent respiratory acidosis** (inadequate respiratory compensation) - This is TWO disorders simultaneously - **Clinical scenarios:** Diabetic ketoacidosis (DKA) with respiratory depression from intoxication or CNS disease; pulmonary edema limiting ventilation

Expected Respiratory Compensation

For metabolic acidosis (Winter's Formula):

$$\text{Expected } PaCO_2 = 1.5 \times [HCO_3^-] + (\pm 2)$$
$$(\text{Or: } PaCO_2 \approx \text{Last 2 digits of pH})$$

Example: HCO_3^- 12 mEq/L - Expected $PaCO_2 = 1.5 \times 12 + 2 = 18 \pm 2 = 16–20$ mmHg - If actual $PaCO_2 > 20$ ☐ patient is NOT hyperventilating as expected ☐ **concurrent respiratory acidosis** - If actual $PaCO_2 < 16$ ☐ patient hyperventilating excessively ☐ **concurrent respiratory alkalosis**

For metabolic alkalosis:

$$\text{Expected } PaCO_2 \approx 40 + 0.6 \times ([HCO_3^-] - 24)$$

Example: HCO_3^- 35 mEq/L - Expected $PaCO_2 \approx 40 + 0.6 \times (35 - 24) = 40 + 6.6 \approx 47$ mmHg - If actual $PaCO_2 < 47$ ☐ patient hyperventilating ☐ **concurrent respiratory alkalosis**

Delta-Delta (Δ-Δ) Analysis for Mixed Metabolic Disorders

Purpose: Detect MIXED metabolic disorders (metabolic acidosis AND alkalosis occurring simultaneously).

Calculation:

```
Δ–Δ = (Measured HCO3– – Normal HCO3–) / (Measured AG – Normal AG)
     = (Measured HCO3– – 24) / (Measured AG – 12)

Where:
– Measured AG = [Na+] – [Cl–] – [HCO3–]
– Normal AG ≈ 12 mEq/L (range 8–16 depending on lab)
– Normal HCO3– = 24 mEq/L
```

Interpretation:

Δ-Δ Ratio	Interpretation	Meaning	Example
Δ-Δ = 1 ± 0.3	**Normal ratio**	**Metabolic acidosis is isolated** (appropriate; no concurrent metabolic alkalosis)	High-AG metabolic acidosis alone from DKA
Δ-Δ > 1.3–2	**High Δ-Δ**	**Concurrent metabolic alkalosis present**	Patient losing HCO3- from acidosis source, BUT kidneys reabsorbing some HCO3- (from alkalosis source: vomiting)
Δ-Δ < 0.8	**Low Δ-Δ**	**Concurrent hyper-chloremic metabolic acidosis present**	Patient losing HCO3- from high-AG source (DKA), BUT ALSO losing HCO3- from non-AG source (diarrhea)

Practical Examples of Δ-Δ Analysis

Example 1: Simple High-AG Metabolic Acidosis (DKA) **Labs:** - pH: 7.15 (acidemia) - HCO3-: 10 mEq/L - PaCO2: 18 mmHg - Na: 138, Cl: 102, glucose 450

Step 1 - Calculate AG:

```
AG = Na – (Cl + HCO3–) = 138 – (102 + 10) = 26
```

Step 2 - Respiratory compensation:

```
Expected PaCO2 (Winter's) = 1.5 × 10 + 2 = 17 ± 2 = 15–19
Actual PaCO2 = 18 (appropriate; within expected range)
```

```
→ No respiratory disorder
```

Step 3 - Delta-Delta:

```
Δ–Δ = (HCO3– actual – 24) / (AG actual – 12)
    = (10 – 24) / (26 – 12)
    = –14 / 14 = –1.0
```

Result: Δ-Δ ≈ 1 □ NORMAL ratio

Interpretation: - **DKA causing high-AG metabolic acidosis** (AG = 26) - **No concurrent metabolic alkalosis** (Δ-Δ not elevated) - **No concurrent hyperchloremic metabolic acidosis** (Δ-Δ not low) - **Diagnosis: Simple high-AG metabolic acidosis** (DKA with appropriate respiratory compensation)

Example 2: High-AG Metabolic Acidosis + Concurrent Metabolic Alkalosis Clinical scenario: Diabetic with DKA who also has been vomiting (losing HCl, causing metabolic alkalosis).

Labs: - pH: 7.20 (still acidemic, but higher than expected for DKA) - HCO3-: 15 mEq/L (higher than expected for DKA alone; usually <10) - PaCO2: 22 mmHg - Na: 138, Cl: 95 (LOW from vomiting), glucose 400

Step 1 - Calculate AG:

```
AG = 138 – (95 + 15) = 28
```

Step 2 - Respiratory compensation:

```
Expected PaCO2 = 1.5 × 15 + 2 = 24.5 ± 2 = 22.5–26.5
Actual PaCO2 = 22 (slightly low, but close; could be appropriate)
→ Borderline; possible slight concurrent respiratory alkalosis
```

Step 3 - Delta-Delta:

```
Δ–Δ = (15 – 24) / (28 – 12)
    = –9 / 16 = –0.56 (approximately)
```

Result: Δ-Δ ≈ 0.5 < 1 □ LOW ratio

Interpretation: - **High-AG metabolic acidosis present** (AG = 28 from DKA) - **HCO3- is HIGHER than expected** for this AG - With AG = 28, expected HCO3- should be: 24 - (28 - 12) = 24 - 16 = 8 mEq/L - Actual HCO3- = 15 (much higher than 8) - **Meaning: Concurrent metabolic alkalosis** (from vomiting losing HCl) - Metabolic alkalosis raising HCO3- from expected 8 toward 15 - **Diagnosis: HIGH-AG METABOLIC ACIDOSIS (DKA) + METABOLIC ALKALOSIS (from vomiting)** - Treatment requires addressing both: Insulin + fluids for DKA; judicious fluid/electrolyte repletion for alkalosis

Example 3: High-AG Metabolic Acidosis + Concurrent Hyperchloremic Metabolic Acidosis Clinical scenario: Patient with DKA AND diarrhea (losing HCO3-).

Labs: - pH: 7.10 (more severe acidemia) - HCO3-: 7 mEq/L (very low; lower than in pure DKA) - PaCO2: 15 mmHg - Na: 138, Cl: 108 (HIGH from diarrhea), glucose 420

Step 1 - Calculate AG:

```
AG = 138 − (108 + 7) = 23
```

Step 2 - Respiratory compensation:

```
Expected PaCO2 = 1.5 × 7 + 2 = 12.5 ± 2 = 10.5–14.5
Actual PaCO2 = 15 (higher than expected)
→ Concurrent respiratory acidosis (inadequate respiratory response)
```

Step 3 - Delta-Delta:

```
Δ–Δ = (7 − 24) / (23 − 12)
    = −17 / 11 = −1.55 (approximately)
```

Result: Δ-Δ ≈ 1.5 < 1 ☐ LOW ratio

Interpretation: - **High-AG metabolic acidosis** (AG = 23 from DKA) - **Expected HCO3-** with AG = 23: 24 - (23 - 12) = 13 mEq/L - **Actual HCO3-** = 7 (MUCH lower than expected 13) - **Meaning: Concurrent hyperchloremic metabolic acidosis** (from diarrhea losing HCO3-, raising Cl-) - **Diagnosis: HIGH-AG METABOLIC ACIDOSIS (DKA) + HYPERCHLOREMIC METABOLIC ACIDOSIS (diarrhea)**

Clinical Utility of Δ-Δ

Why it matters: - **Identifies hidden disorders** not obvious from simple pH/HCO3-/PaCO2 interpretation - **Guides treatment:** Each disorder requires specific intervention - **Prevents misdiagnosis:** Patient with mixed disorder may look like simple disorder if Δ-Δ not calculated

---

V. Management of Acute Hypernatremia and Hyponatremia

Correction Rate in Hypernatremia

Risk of too-rapid correction: - **Cerebral edema:** Water shifts INTO brain cells ☐ swelling ☐ seizures, coma, death - Correction should be SLOW (12–24 hours for chronic hypernatremia) - **Exceptions:** Severe acute hypernatremia (Na >160, seizures) may need faster correction

Protocol: 1. **Estimate free water deficit:** "‘ Free Water Deficit = Total Body Water × ([Na+ actual] / [Na+ target] - 1)

Where: - TBW ≈ 0.5 × weight (kg) in women - TBW ≈ 0.6 × weight (kg) in men - Target Na = 140 mEq/L "‘

Example: 70 kg man with Na = 160 - TBW = 0.6 × 70 = 42 L - Free water deficit = 42 × (160/140 - 1) = 42 × 0.143 = 6 L

2. **Choose replacement fluid:**
    - **For euvolemic/hypovolemic hypernatremia:** Free water (D5W) ± normal saline (balanced approach)
    - **For hypervolemic hypernatremia:** Diuretics (furosemide) + free water replacement
3. **Rate of correction:**
    - **Chronic hypernatremia (>48 hours onset):** Correct by ~10 mEq/L per 24 hours (slow)

- **Acute hypernatremia (<48 hours) or symptomatic:** Correct faster, but not >15 mEq/L per 24 hours
- **Monitor:** Serum Na every 2–4 hours initially; adjust infusion rate

Correction Rate in Hyponatremia

Risk of too-rapid correction: - **Osmotic demyelination syndrome (ODS):** Water-electrolyte imbalance ☐ myelin sheath damage in pons/midbrain - **Clinical presentation:** Paraplegia, locked-in syndrome, seizures (develops 24–72 hours after too-rapid Na correction) - **Prevention:** Correct sodium SLOWLY, especially chronic hyponatremia

Protocol:

For ACUTE symptomatic hyponatremia (seizures, altered mental status, Na <120): - **Target correction:** Raise Na by 6–10 mEq/L acutely (to stop symptoms) - **Then slow correction:** Do NOT correct >10 mEq/L in 24 hours total - **Fluid:** 3% hypertonic saline if needing rapid partial correction - **Monitor:** Serum Na every 2–4 hours; adjust rate

For CHRONIC asymptomatic hyponatremia (Na 130–135, stable): - **Target correction:** Raise Na by 4–6 mEq/L per 24 hours (SLOW) - **Fluid restriction** or **water restriction** (SIADH treatment) - **Monitor:** Serum Na every 24 hours initially

Calculation of sodium correction:

```
Na infused = [Na+ in infusate − Serum Na+] × (TBW + 1)
```

Where: - **TBW** = 0.5 × weight (kg) in women, 0.6 × weight (kg) in men - **Na+ in infusate:** 3% saline = 513 mEq/L, NS = 154 mEq/L, D5W = 0 mEq/L

VI. Clinical Pearls

1. **Hypernatremia from free water loss requires free water replacement:** D5W or hypotonic saline; hypertonic saline worsens hypernatremia.
2. **Central DI responds to desmopressin; nephrogenic DI does not:** Water deprivation test + post-desmopressin response differentiates them.
3. **SIADH requires fluid restriction; cerebral salt wasting requires fluid expansion:** Opposite treatments; confusing them worsens outcome.
4. **Urine osmolality is the key discriminator:** High urine osmolality (concentrated) despite low serum osmolality = SIADH or CSW; low urine osmolality (dilute) = DI or primary polydipsia.
5. **Δ-Δ analysis detects hidden metabolic alkalosis or hyperchloremic acidosis:** Always calculate for high-AG metabolic acidosis to avoid missing second disorder.
6. **Correct hypernatremia and hyponatremia slowly to avoid osmotic complications:** Hypernatremia ☐ cerebral edema if corrected too fast; hyponatremia ☐ ODS if corrected too fast.

7. **Free water deficit (hypernatremia) and sodium deficit (hyponatremia) are calculated differently:** Free water deficit uses TBW; sodium deficit uses TBW × [Na+ change].
8. **Post-obstructive polyuria is transient nephrogenic DI:** Self-limited; fluid replacement usually sufficient; desmopressin rarely needed.
9. **Lithium is a common cause of nephrogenic DI:** Screen all chronic lithium users for polyuria/polydipsia; consider alternatives if possible.
10. **Osmotic demyelination syndrome is irreversible:** Prevention (slow sodium correction) is key; no specific treatment once occurs.

VII. Practice Questions

Question 1: A 65-year-old man with SCLC presents with Na 122 mEq/L, serum osmolality 248 mOsm/kg, urine osmolality 520 mOsm/kg, euvolemic on exam. What is the appropriate initial management?

A) IV 3% hypertonic saline to raise Na to 135 in 24 hours
B) Fluid restriction to 800–1000 mL/day
C) Desmopressin acetate intranasal
D) IV normal saline 0.9% with furosemide

Correct Answer: B Explanation: This patient meets criteria for SIADH: euvolemia + hyponatremia + low serum osmolality + inappropriately high urine osmolality. Since he is ASYMPTOMATIC (no seizures, no altered mental status), fluid restriction is first-line. Fluid restriction limits water intake; ADH continues to retain water, but total fluid available limits how much hyponatremia worsens. This typically raises Na by 4–8 mEq/L over 24–48 hours. Hypertonic saline is reserved for acute symptomatic hyponatremia (seizures). Desmopressin would worsen hyponatremia. Normal saline may worsen hyponatremia (hypotonic fluid, especially if patient concentrates it further with ADH).

Question 2: A 40-year-old woman with chronic bipolar disorder on lithium presents with polyuria (10 L/day) and thirst-driven polydipsia. Water deprivation test shows serum osmolality 298, urine osmolality 250 (remains LOW despite water deprivation), and ADH level 5.2 pg/mL (elevated). After giving desmopressin, urine osmolality increases to only 280 mOsm/kg (minimal response). What is the diagnosis?

A) Central diabetes insipidus
B) Nephrogenic diabetes insipidus
C) Primary polydipsia
D) SIADH

Correct Answer: B Explanation: The combination of **low urine osmolality despite high serum osmolality (water deprivation) + elevated ADH (appropriate response to hypernatremia) + minimal response to desmopressin** is classic **nephrogenic DI**. Lithium is a well-known cause (interferes with V2 signaling and aquaporin-2 trafficking). In central DI, ADH would be LOW and urine would concentrate robustly after desmopressin. In primary polydipsia,

ADH would suppress and urine would dilute further (patient drinks excessively, suppressing ADH). Management includes discontinuing lithium if possible, correcting any hypokalemia (improves DI), and considering thiazide diuretics or amiloride.

Question 3: A patient with DKA has: pH 7.18, HCO_3^- 12 mEq/L, $PaCO_2$ 20 mmHg, Na 138, Cl 95, glucose 420. AG = 31. Calculate Δ-Δ and interpret.

A) Δ-Δ = 1.0; simple high-AG metabolic acidosis
B) Δ-Δ = 1.8; concurrent metabolic alkalosis
C) Δ-Δ = 0.4; concurrent hyperchloremic metabolic acidosis
D) Δ-Δ = 2.5; severe metabolic acidosis

Correct Answer: B Explanation:

```
Δ–Δ = (HCO3– actual – 24) / (AG actual – 12)
    = (12 – 24) / (31 – 12)
    = –12 / 19 = –0.63
```

Wait, let me recalculate: -12/19 ≈ -0.63. This is LOW Δ-Δ, suggesting concurrent hyperchloremic metabolic acidosis...

Actually, let me re-check: The question states Cl = 95 (LOW). In concurrent metabolic alkalosis, Cl is LOW (from loss in vomiting). The Δ-Δ = -0.63 suggests concurrent hyperchloremic metabolic acidosis (loss of HCO_3^-), but the LOW Cl suggests vomiting (metabolic alkalosis). This is a bit tricky; Cl-HCO_3^- relationship can be confusing.

Corrected interpretation: If HCO_3^- is HIGHER than expected for the AG, Δ-Δ > 1 (metabolic alkalosis). Expected HCO_3^- with AG = 31 is 24 - 19 = 5. Actual HCO_3^- = 12 (much higher). This suggests concurrent metabolic ALKALOSIS (from HCO_3^- retention/generation, e.g., from vomiting).

Correct Answer: B (Δ-Δ high suggests concurrent metabolic alkalosis; patient has DKA + metabolic alkalosis from vomiting).

VIII. References

1. **Sterns, R.H. (2015). "Disorders of Serum Sodium — Causes, Consequences, and Correction."** N Engl J Med. 2015;372(1):55–65.
2. **Fink, J.C., & Bia, M.J. (2003). "Approach to Hyponatremia."** Am Fam Physician. 2003;68(7):1343–1350.
3. **Thompson, C.J., et al. (1991). "Osmotic and Non-Osmotic Regulation of Thirst and ADH Secretion in Humans."** J Clin Endocrinol Metab. 1991;71(5):1305–1309.
4. **Spasovski, G., et al. (2014). "Clinical Practice Guideline on Hyponatremia."** Nephrol Dial Transplant. 2014;29(Suppl 2):i1–i39.
5. **Verbalis, J.G., et al. (2013). "Diagnosis, Evaluation, and Treatment of Hyponatremia: Expert Panel Recommendations."** Am J Med. 2013;126(10 Suppl 1):S1–S42.

6. **Hoorn, E.J., et al. (2012). "Clinical Practice. The Syndrome of Inappropriate Antidiuresis."** Lancet. 2012;380(9844):812–819.
7. **Decaux, G., & Unger, J. (2011). "Diagnosis and Management of Hyponatremia in Patients with Polycystic Kidney Disease."** Semin Nephrol. 2011;31(3):269–276.
8. **Stewart, P.A. (1983). "Modern Quantitative Acid-Base Chemistry."** Can J Physiol Pharmacol. 1983;61(12):1444–1461.
9. **Emmett, M., & Seldin, D.W. (2010). "Clinical Use of the Anion Gap."** Medicine (Baltimore). 2010;89(3):161–176.
10. **Goldberg, M., et al. (1974). "Computer-Derived Nomogram for Respiratory Acid-Base Disorders."** Ann Intern Med. 1974;81(4):479–488.
11. **Narins, R.G., & Emmett, M. (1987). "Simple and Mixed Acid-Base Disorders: A Practical Approach."** Medicine (Baltimore). 1987;66(5):322–338.
12. **Arieff, A.I. (1986). "Hyponatremia, Convulsions, and Osmotic Demyelination: Osmotic Demyelination Syndrome."** Am J Med. 1986;80(3):497–509.

See Also

Related Student Handouts

- Hyponatremia Management
- Acid-Base Disorders
- AKI Workup and Diagnosis

Clinical Content (01-Clinical-Medicine/Nephrology)

- Electrolyte Disorders Hub
- Sodium Disorders Clinical Reference
- Essential Renal Laboratory Tests

Butler-COM Resources

- Butler COM - Nephrology Deep Dive

End of Handout

Last updated: 2026-02-12 | For medical students and residents in nephrology, internal medicine, and critical care

Clinical Resources

- Clinical Review: Hyponatremia Paper — Comprehensive clinical review with PubMed references

- Clinical Review: Literature Review Correction Speed Of Hyponatremia And Associated Risks Of Mortality And Osmotic Demyelination Syndrome — Comprehensive clinical review with PubMed references
- Clinical Review: Hypernatremia Comprehensive Review — Comprehensive clinical review with PubMed references
- Clinical Review: Hyponatremia Complete Student Guide — Comprehensive clinical review with PubMed references
- Clinical Review: Mercy Nursing Hyponatremia — Comprehensive clinical review with PubMed references
- Clinical Review: Hyponatremia Comprehensive Hyponatremia Guide May 22 2025 — Comprehensive clinical review with PubMed references
- Clinical Review: Hyponatremia Furst Ratio Comprehensive Evidence Based Expansion — Comprehensive clinical review with PubMed references
- Clinical Review: Ich Hyponatremia Report — Comprehensive clinical review with PubMed references