Understanding Syndrome of Inappropriate Antidiuretic Hormone (SIADH) and Diabetes Insipidus (DI)

SIADH and DI are both disorders of water regulation affecting the activity or release of antidiuretic hormone (ADH) in the body. ADH secretion is normally inhibited in response to water intake. In SIADH, ADH is not suppressed resulting in water retention and significant electrolyte abnormalities. In DI, there is either decreased production of ADH (central DI), or normal ADH secretion with resistance in the kidneys to its effects (nephrogenic DI). The net result of DI is large volume diuresis of dilute urine.

Pathophysiology
To best understand these complex syndromes, a sound knowledge of the underlying physiology is essential. The kidneys have an important role in fluid and electrolyte homeostasis. In general, homeostasis is achieved by adjustments to urine output and the electrolyte composition of urine and serum. Fluctuations occur with both intake or administration of fluid and solutes (salt, protein) into the body with a subsequent hormonal response/feedback. The release of antidiuretic hormone (ADH) [synonymous with the term arginine vasopressin (AVP)] by the posterior pituitary gland is regulated by a signaling network involving osmosensors, barosensors and volume sensors in the body.

In the renal system, these sensors are located in collecting ducts of the kidney; ADH is the key regulator of water absorption here. The pituitary gland is stimulated to secrete ADH when the body senses hypertonicity allowing the absorption of water back to circulation (or water retention) by means of increased water permeability and Na⁺ absorption in the renal system thereby preventing diuresis (as the name ADH suggests). When this occurs, urine becomes more concentrated and urine output decreases. Alternately, when the body sense hypotonicity, ADH secretion is suppressed, allowing for a less concentrated and higher volume of urine output. ADH secretion also plays a role in the sensation of thirst.

**Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH)**
In SIADH, the body is unable to suppress the secretion of ADH, leading to impaired water excretion and reduced urine output. Normally, when water is ingested, serum tonicity and osmolality decrease and ADH is suppressed, resulting in output of a dilute (less concentrated) urine. This pathway is impaired in SIADH.

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<tr>
<th>Syndrome of Inappropriate Antidiuretic Hormone (SIADH)</th>
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<tbody>
<tr>
<td><strong>Potential Etiologies</strong> (Sterns, 2017)</td>
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<tr>
<td>• CNS disturbances leading to increased ADH release (stroke, hemorrhage, infection, trauma)</td>
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<td>• Malignant tumor production of ADH (common in small cell carcinoma of the lung)</td>
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<td>• Drug-related</td>
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</table>
- Includes but not limited to SSRIs, carbamazepine, chlorpropamide, cyclophosphamide
- Administration of hormones such as vasopressin and desmopressin to treat other medical conditions
  - Surgery
  - Pulmonary disease
    - Pneumonia; less frequently asthma, respiratory failure, atelectasis, pneumothorax
  - Hormone deficiency (hypopituitarism, hypothyroidism)
  - HIV
  - Hereditary
  - Idiopathic

**NOTE:** There is a condition called cerebral salt wasting which may mimic SIADH, but this condition leads to volume depletion, causing a secondary elevation in ADH.

### Clinical Manifestations
**Symptoms** are variable and typically due to hyponatremia and/or specific to the underlying etiology precipitating SIADH.

### Hyponatremia
- Severe (Na⁺ < 120 mEq/L)
  - seizure, poor concentration, speech difficulties, coma, cerebral edema
- Moderate (Na⁺ 120-129 mEq/L)
  - dizziness, gait disturbance, confusion, forgetfulness, lethargy, or asymptomatic
- Mild (Na⁺ 130-135 mEq/L)
  - often asymptomatic

*Note: SIADH may be persistent or transient depending on etiology*

### Common laboratory trends
- Hyponatremia
- Hypoosmolality
- Urine osmolality > 100 mOsm/kg
- Urine sodium typically > 40 mEq/L
- Serum potassium – normal or low normal
- Acid-base status – normal
- Serum uric acid – low

### Treatment
- Treatment of underlying condition/disease
- Prevent further decline in serum Na⁺ concentration
- Goals of treatment may vary depending on clinical acuity and co-morbidities
- Key component of treatment is correcting hyponatremia
  - Fluid restriction
Salt administration (increases solute excretion and urine volume → ↑ Na⁺)
- May be administered with loop diuretics which lowers urine osmolality and increases water excretion
- Urea administration (increases solute excretion and urine volume → ↑ Na⁺)
- Vasopressin receptor antagonists
- Saline or hypertonic saline (3%) in severe, symptomatic hyponatremia

*Persistent SIADH requires ongoing therapy.

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<th>Na⁺ correction rates</th>
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<td>Hyponatremia MUST be corrected slowly. Rapid correction could lead to cerebral fluid shifts and rarely, a life-threatening complication called osmotic demyelination (ODS).</td>
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<td>- In general, rate of correction should 4-6 mEq/L in the first 24 hours and should always be less than 8 mEq/L during this critical period.</td>
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<td>- In those with severe neurologic symptoms, correction rate may be faster, 4-6 mEq/L in the initial 2- to 4-hour period to prevent further neurologic deterioration.</td>
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<td>- Na⁺ should be checked every 2 to 3 hours during initial management.</td>
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Diabetes Insipidus

There are two major types of DI: central (also referred to as neurogenic or neurohypophyseal) and nephrogenic. The common clinical manifestation of the two subtypes is polyuria. In general, polyuria is defined as urine output > 3L/day in adults and > 2L/day in children. Normal expected urine output in adults is 0.8-2L/day; in severe cases of DI, 24-hour urine output could reach up to 10-20L/day. Less common types of DI include gestational DI which is caused by increased metabolism of ADH by the placenta, leading to relative serum ADH deficiency.

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<tr>
<th>Diabetes Insipidus</th>
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<tr>
<td>Central DI</td>
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<tr>
<td>Mechanism</td>
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<tr>
<td>Potential Etiologies (Bichet, 2017)</td>
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</table>
### Pituitary gland/hypothalamus

- Pituitary gland/hypothalamus damage due to trauma, surgery or hypoxic or ischemic encephalopathy
- Familial
- ADH-producing cells

### Congenital
- Hereditary due to genetic defects, most typically presents in childhood

### Acquired
- Chronic lithium use
- Metabolic conditions
  - Hypercalciuria
  - Hypokalemia
  - Obstructive uropathy
  - Craniopharyngioma surgery

### Clinical Manifestations

- Polyuria (possibly nocturia)
- Polydipsia
- Urine output > 50 mL/kg/day
- Hyponatremia
- Urine osmolality less than serum osmolality
- May be partial or complete with range of symptoms
  - Complete: urine output may reach 10-20 L/day
- Clinical signs of dehydration (weight loss, irritability, headache, fatigue, dry skin and mucous membranes)
- In congenital cases, may present as failure to thrive during infancy
- Onset of symptoms
  - Abrupt in central DI
  - Gradual in nephrogenic DI

### Diagnosis

- Evaluation of symptoms and laboratory abnormalities
- Fluid restriction test/water restriction test → induced dehydration
- Measure body weight, plasma osmolality, serum sodium, urine volume and urine osmolality hourly.
- Stop when body weight decreased by 5% OR plasma osmolality/sodium at upper limit of normal (ULN).
- If urine osmolality < 300 mOsm/kg with hyperosmolality, administer desmopressin (0.03μg/kg subcutaneously).
  - Repeat urine osmolality in 1-2 hours.
- Interpretation:
  - An increase in urine osmolality by 50% is seen with severe central DI.
  - No change, or less than 50%, suggests nephrogenic DI.
May be helpful to measure ADH levels before and after fluid restriction to distinguish between central and nephrogenic DI.

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<tr>
<th>Treatment</th>
<th>Desmopressin (DDAVP)</th>
<th>Thiazide diuretic and/or amiloride</th>
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<tr>
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<td>• 1-2 µg subcutaneously daily - BID</td>
<td>• Low sodium diet</td>
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<td>• 10-20 µg via nasal spray BID-TID</td>
<td>• Prostaglandin synthesis inhibitors (indomethacin)</td>
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<td>• 100-400 µg PO BID- TID</td>
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<td>• Recommendation to drink to thirst</td>
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Laboratory Findings

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<th>Typical Laboratory Findings</th>
<th>SIADH</th>
<th>DI</th>
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<tr>
<td>Serum Osmolality</td>
<td>↓ (&lt; 275mOsm/L)</td>
<td>↑</td>
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<tr>
<td>Urine osmolality</td>
<td>↑ (Concentrated urine [&gt; 100 mOsm/L])</td>
<td>↓ (less than serum osmolality)</td>
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<tr>
<td>Serum [Na+]</td>
<td>↓</td>
<td>↑ (serum Na+ &gt; 142 mEq/L due to water loss)</td>
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<tr>
<td>Urine [Na+]</td>
<td>↑ (&gt; 40mEq/L)</td>
<td>↓ (&lt; 30mEq/L)</td>
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<tr>
<td>ADH</td>
<td>↑</td>
<td>↓ in central DI; normal in nephrogenic DI</td>
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<tr>
<td>Total body water (TBW)</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Urine volume/output</td>
<td>↓</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Volume status</td>
<td>↑ (Euvolemic or hypervolemic)</td>
<td>↓ (Euvolemic or hypovolemic)</td>
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References:


