Syndrome of Inappropriate Antidiuretic Hormone Secretion

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Background: Ordinarily, release of antidiuretic hormone (ADH or vasopressin) from the posterior pituitary gland occurs as a physiological response to a drop in plasma volume or an increase in serum osmolality. Nonosmotically driven secretion of ADH in the

Patient Education

absence of a hemodynamic disturbance characterizes the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Specific diagnostic criteria that define SIADH include the following:

- Hyponatremia (serum sodium <135 mEq/L)
- Hypotonicity (plasma osmolality <280 mOsm/kg)
- Inappropriately concentrated urine (>100 mOsm/kg water)
- Elevated urine sodium concentration (>20 mEq/L), except during sodium restriction
- Clinical euvolemia
- Normal renal, adrenal, and thyroid function

Pathophysiology: Sodium serves as the major determinant of serum osmolality and reflects the relative ratio of sodium to water in the blood.

ADH, a water-retaining hormone, promotes water retention by increasing the permeability of nephrons. Elevation in ADH level despite low serum sodium level and decreased osmolality indicates the presence of a nonosmotic stimulus for ADH release. Excess ADH may emerge from the pituitary gland or an ectopic source, such as neoplasms and/or pulmonary tissue.

Neoplastic cells obtained from tumors of patients with SIADH are characterized by the potential to synthesize, store, and secrete ADH (eg, increased levels of ADH found in ~60% of patients suffering from small cell carcinoma of the lung).

Even though hyponatremia accompanying SIADH arises from an increase in total body water, this condition sometimes is referred to, confusingly, as a cause of euvolemic hyponatremia. Patients with SIADH demonstrate relatively normal sodium excretion (if intake is normal), high urine osmolality, and only subtle evidence of volume expansion.

Since most excess body water accumulates intracellularly and not in the intravascular space, evidence of edema, ascites, and heart failure is absent. However, intracellular edema alters cell functions, with the central nervous system (CNS) being the most sensitive to these changes.

Frequency:

- **In the US:** No study specifically has addressed the incidence of hyponatremia in ED patients; however, one study reported an incidence of 1% and prevalence of 2.5% in hospitalized

patients. Additionally, hyponatremia was identified as the most common electrolyte disorder in patients requiring admission. SIADH is the most common cause of hospital-acquired hyponatremia and the most prevalent etiology of euvolemic hyponatremia in children.

Mortality/Morbidity: While the overall rate of mortality due to hyponatremia remains indeterminate, certain trends are notable.

- Morbidity and mortality rates are higher with severe hyponatremia, with acute onset, and in hospitalized patients.
- Hyponatremic hospitalized patients may have up to 60 times the mortality rate of normonatremic hospitalized patients.
- Chronic hyponatremia, with a mortality rate of about 10%, is better tolerated than acute hyponatremia; death in chronic hyponatremia is often attributable to the underlying disease process.
- A significant concern regarding morbidity and mortality rates is that patients with prolonged severe hyponatremia are vulnerable to iatrogenic injury from abrupt increases in serum sodium.

Sex: Premenopausal women may be at greater risk of neurologic complications from hyponatremia than men (controversial).

Age: Studies suggest that the very old and very young develop symptoms with lesser decreases in serum sodium levels than adults. Additionally, animal studies suggest a higher risk of neurologic complications due to hyponatremia in younger animals.

History: Attempt to establish the diagnosis of SIADH in a systematic manner. First, exclude the various disorders that are capable of lowering the plasma sodium without accompanying hypotonicity. These include confounding pathology, such as the CHART diseases (ie, cardiac failure, hepatic dysfunction, adrenal insufficiency, renal disorders, thyroid disease).

- Upon confirming the presence of hypotonic hyponatremia, attempt to identify the responsible mechanism.
  - Attempt to distinguish hypovolemia due to edematous disorders from SIADH.
  - Helpful historical details include information about the patient's diet, fluid intake, gastrointestinal (GI) losses, and medications.

- The severity of symptoms depends upon the absolute serum sodium level and the rapidity of onset of hyponatremia.
    - Significant symptoms usually do not manifest unless serum sodium is less than 115-120 mEq/L.
    - Rate of decrease of serum sodium greater than 0.5 mEq/L per hour is particularly worrisome.
    - Symptoms associated with chronic hyponatremia tend to be more subtle and vague than those seen with acute water intoxication. CNS symptoms are often the most prominent.
- Acutely, initial symptoms begin to emerge when serum sodium levels fall into the 115-120 mEq/L range.
    - Anorexia
    - Nausea
    - Vomiting
- Early CNS changes associated with hyponatremia include the following:
    - Headache
    - Irritability
    - Disorientation
- Neuromuscular-related complaints include the following:
    - Myalgias or muscle cramps
    - Weakness
- As the serum sodium concentration falls below 110 mEq/L, the following CNS symptoms emerge, usually due to subsequent brain edema; such symptoms suggest severe hyponatremia.
    - Delirium
    - Psychosis
    - Ataxia or gait disturbance
    - Tremulousness/seizures
    - Coma

Physical:

- On the physical examination, carefully check for signs of volume depletion or, conversely, clues to an edematous disorder.
  - For example, pitting edema is almost universally absent in hyponatremia provoked by SIADH.
  - Extreme hyponatremia may impair baroreceptor reflexes, giving rise to postural hypotension and a false impression of volume depletion.
- Attempt to confirm findings that support a normal extracellular fluid volume (euvolemia).
  - Normal blood pressure and pulse, without orthostatic changes
  - Moist mucous membranes
  - Normal skin turgor
  - No edema
- Neurologic abnormalities may occur in severe hyponatremia.
  - Papilledema
  - Hypoactive reflexes
  - Myoclonus
  - Coma
  - Focal neurologic signs

Causes:

- CNS disorders
  - Head trauma
  - Stroke
  - Neonatal hypoxia
  - Brain tumor
  - Hydrocephalus
  - Cerebral abscess

- Meningitis
- Encephalitis
- Subarachnoid hemorrhage
- Delirium tremens
- Guillain-Barré syndrome
- Acute intermittent porphyria

- Malignancy
  - Lung
  - Brain
  - Pancreas
  - Prostate
  - Ovary
  - Lymphoma
  - Leukemia
  - Thymoma
- Pulmonary disease
  - Pneumonia
  - Tuberculosis
  - Empyema
  - Abscess
  - Asthma
  - Chronic obstructive pulmonary disease (COPD)
  - Cystic fibrosis
  - Pneumothorax
  - Acute respiratory failure
  - Positive pressure ventilation

- Endocrine disorders
  - Hypothyroidism/myxedema
  - Glucocorticoid deficiency
- Drugs
  - Analgesics (eg, narcotics, nonsteroidal anti-inflammatory drugs [NSAIDs])
  - Antidepressants (eg, monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors [SSRIs])
  - Antineoplastics (eg, vincristine, vinblastine)
  - Barbiturates
  - Carbamazepine
  - Cyclophosphamide
  - Clofibrate
  - Diuretics (especially thiazides)
  - Neuroleptics (eg, phenothiazines)
  - Oral hypoglycemics (eg, chlorpropamide, tolbutamide)
  - Antibiotics (eg, azithromycin)
- Nausea
- Pain
- Surgery (ie, postoperative period)
- Idiopathic (the most common identified etiology)

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Lab Studies:

- Serum electrolytes, BUN, creatinine, and glucose
  - Hyponatremia (sodium <135 mEq/L) is noted.
  - BUN and serum uric acid levels tend to fall because of plasma dilution and increased excretion of nitrogenous products.
  - Serum potassium and bicarbonate levels are normal in SIADH; hypokalemia and metabolic alkalosis suggest diuretic therapy or vomiting which can be surreptitious.
  - Hyperkalemia and metabolic acidosis coexisting with hyponatremia suggest adrenal insufficiency.
  - Elevated glucose levels decrease the measured serum sodium levels by 1.6 mEq/L for every 100 mg/dL increase in glucose. This results from the osmotic effect of glucose drawing water out of cells, and the serum sodium rises when the hyperglycemia is corrected.
- Serum osmolality low (<280 mOsm/kg)
- Urine
  - Urinary sodium, which is low with some causes of hyponatremia, is elevated (>20 mmol/L) in SIADH.
  - Values <20 mmol/L may be seen with coexisting hypervolemic or hypovolemic states.
  - The urine, which is maximally dilute with some causes of hyponatremia, demonstrates an inappropriately high osmolality; generally, the osmolality is >100 mOsm/L.
- Plasma cortisol level: This is done to exclude adrenal insufficiency, but do not hold back corticosteroid administration pending results if acute adrenal crisis is suspected.
- Pseudohyponatremia occurs with severe hyperlipidemia and with hyperproteinemia (levels >10g/dL, as seen in multiple myeloma).

Imaging Studies:

- A chest x-ray may provide clues to the underlying cause (eg, pulmonary disease, lung carcinoma).
- CT scan of the head may be appropriate in selected cases.
  - May show evidence of cerebral edema (eg, narrowing of the ventricles) or identify a CNS disorder responsible for SIADH (eg, brain tumor)
  - Helps rule out other potential causes of acute changes in neurologic status

Other Tests:

- Serum ADH levels tend to not be available on a stat basis.

TREATMENT

Prehospital Care: Prehospital treatment is directed toward treatment of symptoms (eg, seizures, arrhythmias) in severely symptomatic patients; the underlying hyponatremia is unlikely to be recognized prior to evaluation in the ED.

Emergency Department Care: Tolerance of hyponatremia is extremely variable. Consider a variety of factors in addition to the serum sodium level, including severity of symptoms, duration of illness, and patient's hemodynamic status.

For asymptomatic or mildly symptomatic hyponatremia, water restriction, started in the ED and continued on an inpatient or outpatient basis, typically is the only necessary therapy. Compliance may be poor, because significant restriction of discretionary water intake (250-500 cc/d) may be required to maintain a negative water balance.

Reserve demeclocycline for patients with chronic SIADH in whom water restriction has failed. This therapy rarely is instituted in the ED.

- Secure the ABCs. Airway, breathing, and cardiovascular stability always take precedence over all other actions, including correction of sodium imbalance.
- Consider naloxone, thiamine, and glucose (N-T-G), as hyponatremia may be a complication in narcotic abusers, diabetics, and chronic alcoholics.
- Severe hyponatremia (sodium <110 mEq/L) or symptomatic hyponatremia (sodium <120 mEq/L) generally requires treatment with isotonic or hypertonic saline.
  - If the adequacy of intravascular volume is in question (eg, patient with tachycardia or hypotension), initiating fluid resuscitation with isotonic saline is usually the best course.
  - Attempts to calculate the precise amount of sodium required to correct hyponatremia generally are doomed to failure.
  - Urine osmolality might guide selection of fluid for replacement. When the urine osmolality is less than 300 mOsm/L, correct with isotonic saline, but if

urine osmolality is greater than 300 mOsm/L, consider hypertonic saline.

- Generally, reserve hypertonic saline (3% or 513 mEq/L sodium chloride) for severely hyponatremic patients who are comatose, seizing, or displaying new-onset, profound changes in mental status.
    - Too rapid correction may result in central pontine myelinosis (CPM).
    - Restrict use of hypertonic saline to 2-3 hours at a maximum rate of 100 cc/h (1 cc/kg/h).
    - For ongoing pediatric seizures, give a 4-6 cc/kg bolus of 3% saline over 10 minutes. On average, 1.2-2.4 cc/kg/h of hypertonic saline raises serum sodium level by 1-2 mEq/L/h.
    - Correction at a rate of 6-8 mmol/L/d is likely to be safe. For patients presenting with severe symptoms of hyponatremia, seizing, or coma, initial increases of 4-6 mmol/L tend to be acceptable. After 2-3 hours, a more conservative approach is safest, limiting the total increase in serum sodium to 12 mmol/L/d.
- Furosemide (1 mg/kg) may be used in conjunction with isotonic or hypertonic saline as it helps maintain urine output and blocks secretion of ADH. Try to maintain a negative urine balance.
- Once normal renal function is ascertained, try to normalize potassium levels prior to or concurrently with the correction of hyponatremia.
- Monitor serum and urine electrolytes. Initially, recheck in 2 hours, then at least every 4 hours until the patient's levels are stabilized.
    - Stop therapy when serum sodium approaches 120-130 mEq/L, symptoms resolve, or serum sodium has increased by 15 mEq/L in 24 hours or less.
    - The total rate of correction should not exceed 10-15 mEq/L in the first 24 hours to minimize the risk of CPM. However, in the presence of risk factors for CPM (eg, hypokalemia, liver disease, malnutrition, large burns), correction should be restricted to 10 mEq/L per 24 hours.

Consultations: For severe symptomatic hyponatremia, consult an internist or nephrologist for admission.

MEDICATION

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Reserve pharmacologic therapy for patients with SIADH who have chronic hyponatremia (serum sodium concentration <125 mEq/L) or are unable to comply with water restriction or in whom the condition is refractory to water restriction.

Drug Category: *Tetracyclines* -- The tetracycline antibiotic demeclocycline has been used successfully to treat chronic SIADH that is refractory to water restriction or in

patients who are noncompliant with water restriction. This therapy rarely is instituted in the ED and generally is instituted by (or in consultation with) a nephrologist or primary care physician.

Drug Name	Demeclocycline (Declomycin) -- Interferes with action of ADH at renal collecting duct by impairing generation and action of cyclic AMP. This results in picture similar to nephrogenic diabetes insipidus. Onset of action may be delayed by over a week; thus, not indicated for emergency management of symptomatic hyponatremia.
Adult Dose	150 mg PO qid or 300 mg bid
Pediatric Dose	<8 years: Not recommended >8 years: 3-6 mg/lb (6-12 mg/kg), depending upon severity of disease, divided bid or qid
Contraindications	Documented hypersensitivity
Interactions	Antacids containing aluminum, calcium, magnesium, iron, or bismuth subsalicylate may increase bioavailability; may increase hypoprothrombinemic effects of anticoagulants (monitor prothrombin activity); may decrease effects of oral contraceptives, causing breakthrough bleeding and increased risk of pregnancy
Pregnancy	D - Unsafe in pregnancy
Precautions	Photosensitivity may occur with prolonged exposure to sunlight or tanning equipment; reduce dose in renal impairment; consider drug serum level determinations in prolonged therapy; if used during tooth development (last half of pregnancy through age 8 y) can cause permanent discoloration of teeth; Fanconilike syndrome may occur with outdated tetracyclines

Drug Category: *Osmotic diuretic* -- These agents induce diuresis by elevating the osmolarity of the glomerular filtrate, thereby hindering the tubular reabsorption of water (concomitantly, sodium and chloride excretion also increase, but to a lesser extent than water excretion).

Drug Name	Urea (Ureaphil, Aquacare) -- For treatment of SIADH refractory to or in patients noncompliant with alternative therapies. Isosmotic concentration of dextrose or invert sugar is coadministered with urea to prevent hemolysis produced by pure solutions of urea.
Adult Dose	1-1.5 g/kg (0.45-0.68 g/lb) as 3% solution; by slow infusion; not to exceed rate of 4 mL/min or dose of 120 g/d
Pediatric Dose	<2 years: 0.1 g/kg may be adequate >2 years: 0.5-1.5 g/kg
Contraindications	Documented hypersensitivity; severely impaired renal function; active intracranial bleeding; marked dehydration; frank liver failure Infusion into veins of lower extremities in elderly may cause phlebitis and thrombosis
Interactions	May decrease effects of lithium

Pregnancy	D - Unsafe in pregnancy
Precautions	Do not use if intracranial bleeding present, unless prior to surgical intervention to control hemorrhage (reduction of brain edema by urea may result in reactivation of intracranial bleeding); may increase risk of venous thrombosis and hemoglobinuria in hypothermic patients; caution in renal impairment

Drug Category: *Loop diuretic* -- Indicated for the treatment of hypervolemic hyponatremia, which is centered on the correction of the underlying disease and the restriction of both water and salt. For the treatment of SIADH, loop diuretics may be necessary to elicit a loss of free water.

Drug Name	Furosemide (Lasix) -- Increases excretion of water by interfering with chloride-binding cotransport system that, in turn, results in inhibition of sodium and chloride reabsorption in ascending loop of Henle and distal renal tubule. Its action on distal tubule is independent of any inhibitory effect it may have on either carbonic anhydrase or aldosterone. Dose must be individualized to patient. Depending on response, administer at increments of 20-40 mg, no sooner than 6-8 h after previous dose, until desired diuresis occurs. When treating infants, titrate with 1 mg/kg/dose increments until satisfactory effect achieved. In children, if diuretic response after initial dose is not satisfactory, increase dosage by 1 mg/kg, no sooner than 2 h after previous dose, until desired effect obtained. Doses >6 mg/kg not recommended.
Adult Dose	40 mg IV over 1-2 min initial; if response not satisfactory, increase to 80 mg IV (administered over 1-2 min) or 20-80 mg/d PO qd maintenance
Pediatric Dose	1 mg/kg IV/IM slowly under close supervision; not to exceed 6 mg/kg
Contraindications	Documented hypersensitivity; hepatic coma; anuria; severe electrolyte depletion
Interactions	Metformin decreases concentrations; interferes with hypoglycemic effect of antidiabetic agents and antagonizes muscle-relaxing effect of tubocurarine; aminoglycosides increase risk of auditory toxicity—hearing loss of varying degrees may occur; may enhance anticoagulant activity of warfarin; may increase plasma lithium levels and toxicity
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Perform frequent serum electrolyte, carbon dioxide, glucose, creatinine, uric acid, calcium, and BUN determinations during first few months of therapy and periodically thereafter

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Further Inpatient Care:

- Indicated for severe symptomatic hyponatremia or the underlying disease

Further Outpatient Care:

- Water restriction (severe, 500-1000 cc/d) is the treatment of choice.
- Treat the underlying cause when known and treatable.
- Careful follow-up is essential, as some malignancies may not become clinically apparent for months.

In/Out Patient Meds:

- For refractory cases of SIADH, consider pharmacologic therapy.
  - Demeclocycline, 300-600 mg PO bid
  - Oral urea, 0.5-1.0 g/kg PO qd
  - Furosemide, 40 mg PO qd; maintain a high-sodium diet or provide sodium chloride supplementation when using furosemide for treatment of chronic SIADH.

Transfer:

- Only indicated when the underlying pathology cannot be managed adequately at the receiving facility

Complications:

- CPM is the most feared complication of excessive, overly rapid correction of hyponatremia.
  - Patients with cerebral disease or underlying metabolic disorders (eg, alcoholism, liver disease, malnutrition, hypokalemia, large burns) are at increased risk for CPM. Premenopausal patients undergoing surgery, especially gynecologic or related procedures, also may have an increased risk.
  - CPM is more likely in patients with long-standing, severe hyponatremia that is corrected too rapidly.
  - Risk is minimal if hyponatremia develops over less than 48 hours, even with rapid correction.
  - Onset of CPM may be delayed, manifesting 1-2 days after correction, despite initial clinical improvement.

Prognosis:

- Ultimately, the prognosis of SIADH best correlates to the underlying cause.
- Rapid and complete recovery tends to be the rule for recovery from drug-induced SIADH when the offending agent is withdrawn.
- Similarly, successful treatment of pulmonary or CNS infection lead to correction of SIADH.
- Unfortunately, notwithstanding the correction of the hyponatremia associated with malignancies, the final outlook relies on the course of the cancer.

Patient Education:

- Emphasize the importance of compliance with fluid restriction.
  - Patients must understand that a typical diet may contain 750-1000 cc of water before accounting for free water intake.
  - Voluntary fluid intake may have to be limited to 250-500 cc (ie, 1-2 glasses) per day.

MISCELLANEOUS

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Medical/Legal Pitfalls:

- Correcting hyponatremia too rapidly may result in CPM with permanent neurologic deficits.
- Given the strong association with small cell carcinoma of the lung, some authorities recommend an aggressive workup for occult small cell carcinoma in patients without an alternative explanation for their SIADH.
- Do not neglect to consider laboratory error as a cause of hyponatremia.

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