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Hypernatremia

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Introduction

Background

- Hypernatremia is a common electrolyte problem and is defined as a rise in serum sodium concentration to a value exceeding 145 mmol/L.[1,2]
- Hypernatremia is strictly defined as a hyperosmolar condition caused by a decrease in total body water (TBW)[3] relative to electrolyte content. Hypernatremia is a “water-problem,” not a problem of sodium homeostasis. (See image below and Image 1.)

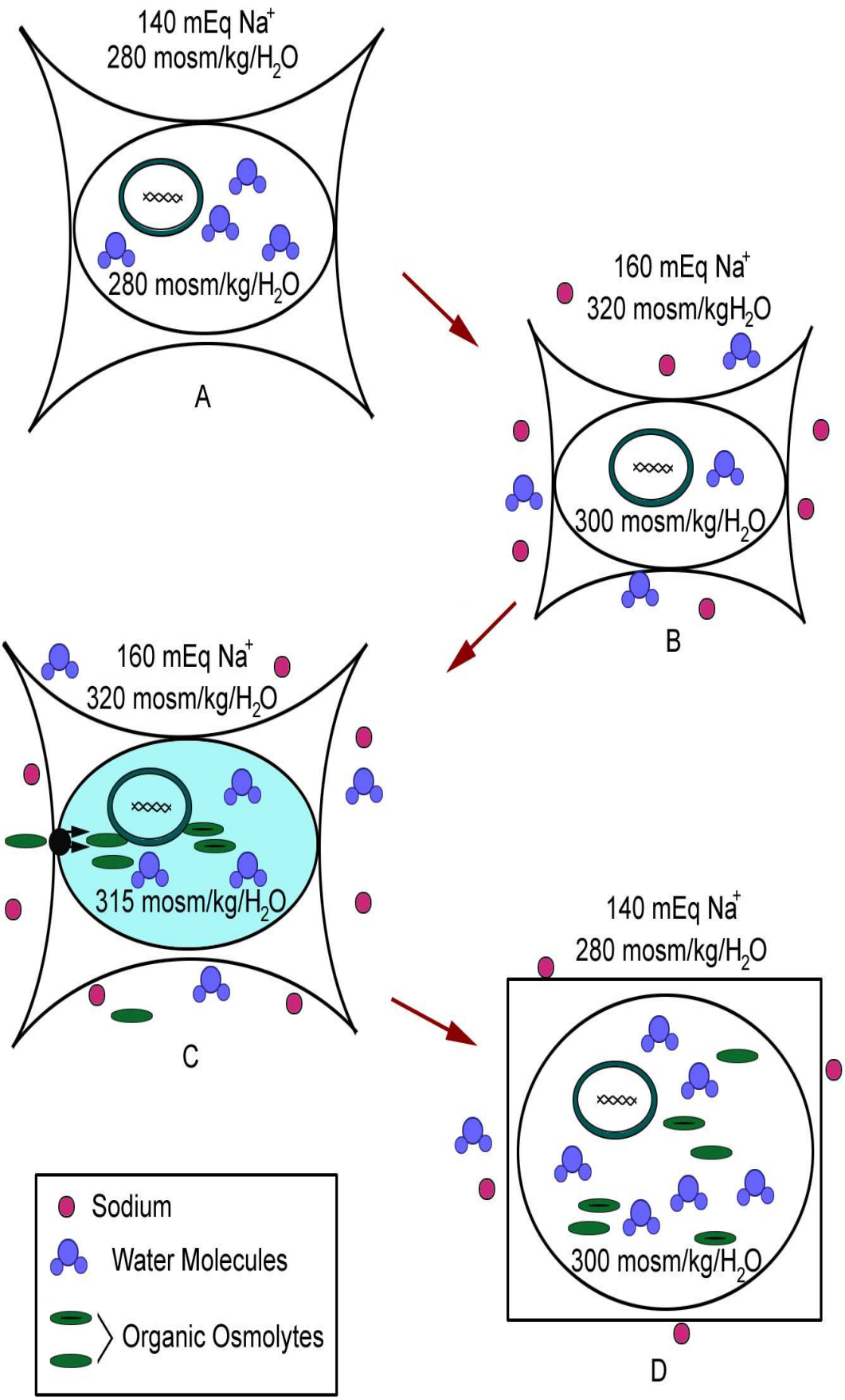


Figure A: Normal cell. Figure B: Cell initially responds to extracellular hypertonicity through passive osmosis of water extracellularly, resulting in cell shrinkage. Figure C: Cell actively responds to extracellular hypertonicity and cell shrinkage in order to limit water loss through transport of organic osmolytes across the cell

membrane, as well as through intracellular production of these osmolytes. Figure D: Rapid correction of extracellular hypertonicity results in passive movement of water molecules into the relatively hypertonic intracellular space, causing cellular swelling, damage, and ultimately death.

- Patients developing hypernatremia outside of the hospital are generally elderly people who are mentally and physically impaired, often with an acute infection. Patients who develop hypernatremia during the course of hospitalization have an age distribution similar to that of the general hospital population. In both patient groups, hypernatremia is caused by impaired thirst and/or restricted access to water, often exacerbated by pathologic conditions with increased fluid loss.
- The development of hyperosmolality from the water loss can lead to neuronal cell shrinkage and resultant brain injury. Loss of volume can lead to circulatory problems (eg, tachycardia, hypotension). Rapid free-water replacement can cause cerebral edema.

Pathophysiology

Hypernatremia results when there is a net water loss or a hypertonic sodium gain and reflects too little water in relation to total body sodium and potassium. Hypernatremia by definition is a state of hyperosmolality, because sodium is the dominant extracellular cation and solute.[4]

The normal plasma osmolality (Posm) lies between 275 and 290 mOsm/kg and is primarily determined by the concentration of sodium salts. (Calculated plasma osmolality: 2(Na) mEq/L + serum glucose (mg/dL)/18 + BUN (mg/dL)/2.8). Regulation of the Posm and the plasma sodium concentration is mediated by changes in water intake and water excretion. This occurs via 2 mechanisms:

- Urinary concentration (via pituitary secretion and renal effects of the antidiuretic hormone arginine vasopressin [AVP])[5,6]
- Thirst

In the normal individual, thirst is stimulated by an increase in body fluid osmolality above a certain threshold and results in increased water ingestion, rapidly correcting the hypernatremic state.

This mechanism is so effective that even in pathologic states in which patients are unable to concentrate their urine (diabetes insipidus) and excrete excessive amounts of urine (10-15 liters per day), hypernatremia will not develop, because thirst is stimulated and body fluid osmolality is maintained at the expense of profound secondary polydipsia.

Thus, sustained hypernatremia can occur only when the thirst mechanism is impaired and water intake does not increase in response to hyperosmolality, or when water ingestion is restricted.

Urinary concentration - AVP and the kidney[7]

Conservation and excretion of water by the kidney depends on the normal secretion and action of AVP and is very tightly regulated. The stimulus for AVP secretion is an activation of hypothalamic osmoreceptors, which occurs when the plasma osmolality reaches a certain threshold (approximately 280 mOsm/kg). At plasma osmolalities below this threshold level, AVP secretion is suppressed to low or undetectable levels.

AVP is synthesized in specialized magnocellular neurons whose cell bodies are located in the supraoptic and paraventricular nuclei of the hypothalamus. The prohormone is processed and transported down the axon, which terminates in the posterior pituitary gland. From there, it is secreted as active AVP hormone into the circulation in response to an appropriate stimulus (hyperosmolality, hypovolemia).

AVP binds to the V2 receptor located on the basolateral membrane of the principal cells of the renal collection ducts. The binding to this G-protein coupled receptor initiates a signal transduction cascade, leading to phosphorylation of aquaporin-2 and its translocation and insertion into the apical (luminal) membrane, creating "water channels" that enable the absorption of free water in this otherwise water-impermeable segment of the tubular system

Thirst

Thirst is the body's mechanism to increase water consumption in response to detected deficits in body fluid. As with AVP secretion, thirst is mediated by an increase in effective plasma osmolality of only 2-3%. Thirst is thought to be mediated by osmoreceptors located in the anteroventral hypothalamus. The osmotic thirst threshold averages approximately 288-295 mOsm/kg.

Of physiologic significance is the fact that this level lies above the osmotic threshold for AVP release and approximates the plasma osmolality at which maximal urine concentration is normally achieved. Thus, under normal physiological conditions, AVP accounts for

the regulation of plasma osmolality within narrow limits and adjusts water excretion to small changes in osmolality. Only when unregulated water intake (beverages) is not enough in the presence of maximal AVP secretion to maintain plasma osmolality will the perceived desire for water (thirst) become crucial.

Significant hypovolemia stimulates AVP secretion and thirst. Blood pressure decreases of 20-30% result in AVP levels many times those required for maximal antidiuresis.

Hypernatremic states can be classified as isolated water deficits (which are generally not associated with intravascular volume changes), hypotonic fluid deficits, and hypertonic sodium gain.

Acute hypernatremia is associated with a rapid decrease in intracellular water content and brain volume caused by an osmotic shift of free water out of the cells. Within 24 hours, electrolyte uptake into the intracellular compartment results in partial restoration of brain volume. A second phase of adaptation, characterized by an increase in intracellular organic solute content (accumulation of amino acids, polyols, and methylamines), restores brain volume to normal. The accumulation of intracellular solutes bears the risk for cerebral edema during rehydration. The brain cell response to hypernatremia is critical; it is illustrated in Image 1.

Frequency

United States

- The overall incidence of hospitalized patients with hypernatremia ranges from 0.3-5.5%. The incidence of patients who have hypernatremia on admission to the hospital is very low, being estimated at 0.12-1.4%. Over 60% of hypernatremia cases are hospital acquired. The prevalence in intensive care units (ICUs) appears to be much higher. Hypernatremia is most prevalent in the geriatric population.

International

- A retrospective, single-center study from Europe, which included 981 patients, found a 9% incidence of hypernatremia at the center's intensive care unit (ICU). However, it was also found that among those patients with hypernatremia, only 23% already had the condition when admitted to the ICU.[8,9]
- A Canadian study of 8000 adult patients identified ICU-acquired hyponatremia in 11% of them and ICU-acquired hypernatremia in 26% of these patients.[9] The report found that the mortality rate in patients with ICU-acquired hyponatremia or hypernatremia was greater than that of study patients with normal serum sodium levels, being 28% versus 16%, p <0.001, and 34% versus 16%, p <0.001, respectively.

Mortality/Morbidity

- Morbidity and mortality estimates in hypernatremic adults range from 42% to more than 70%, with the highest rates being found in the geriatric age group.
- The mortality rate for chronic hypernatremia is approximately 10%, while the mortality rate for severe acute hypernatremia in the ICU setting is as high as 75%.

Race

- No race predilection exists for hypernatremia.

Sex

- No sex predilection exists for hypernatremia.[10]

Age

- The groups most commonly affected by hypernatremia are elderly people and children.[10]

Clinical

History

Patients developing hypernatremia outside of the hospital setting are generally elderly and debilitated, and often present with an intercurrent acute (febrile) illness. Hospital-acquired hypernatremia affects patients of all ages.

The history should be used to discover why the patient was unable to prevent hypernatremia with adequate oral fluid intake; eg, it should be determined whether the patient is suffering from an altered mental status or whether there are any factors causing increased

fluid excretion (eg, the use of diuretic therapy, the existence of diabetes mellitus, or the occurrence of fever, diarrhea, and vomiting). The history should also cover the symptoms and causes of possible diabetes insipidus (eg, the presence of preexisting polydipsia or polyuria, a history of cerebral pathology, or medication use [lithium]).

It is important to find out if the hypernatremia developed acutely or over time, because this will guide treatment decisions.

Risk factors for hypernatremia include the following:

- Advanced age
- Mental or physical impairment
- Uncontrolled diabetes (solute diuresis)
- Underlying polyuria disorders
- Diuretic therapy
- Residency in nursing home, inadequate nursing care
- Hospitalization
    - Decreased baseline levels of consciousness
    - Tube feeding
    - Hypertonic infusions
    - Osmotic diuresis
    - Lactulose
    - Mechanical ventilation
    - Medication (eg, diuretics, sedatives)

Physical

The examination should include an accurate assessment of volume status and cognitive function. Symptoms can be related to volume deficit and/or hypertonicity and shrinkage of brain cells.

The worsening symptoms associated with hypernatremia may go unnoticed in elderly patients who have a preexisting impairment of their mental status and decreased access to water.

Table 1. Characteristics and symptoms of hypernatremia

Characteristics of hypernatremia	Symptoms related to the characteristics of hypernatremia
Cognitive dysfunction and symptoms associated with neuronal cell shrinkage	Lethargy, obtundation, confusion, abnormal speech, irritability, seizures, nystagmus, myoclonic jerks
Dehydration or clinical signs of volume depletion	Orthostatic blood pressure changes, tachycardia, oliguria, dry oral mucosa, abnormal skin turgor, dry axillae,
Other clinical findings	Weight loss, generalized weakness

In a prospective, case-control, multicenter study, Chassagne and colleagues looked at the symptoms associated with hypernatremia in 150 geriatric patients.[11] The likelihood that patients with hypernatremia would have low blood pressure, tachycardia, dry oral mucosa, abnormal skin turgor, and a recent change in consciousness was significantly greater than that of the controls. The only clinical findings to occur in at least 60% of patients with hypernatremia were orthostatic blood pressure and abnormal subclavicular and forearm skin turgor (poor specificity and sensitivity for all physical findings).

Causes

Several risk factors exist for hypernatremia. The greatest risk factor is age older than 65 years. In addition, mental or physical disability may result in impaired thirst sensation, an impaired ability to express thirst, and/or decreased access to water.[12]

Hypernatremia often is the result of several concurrent factors. The most prominent is poor fluid intake. Normally, an increase in osmolality of just 1-2% stimulates thirst, as do hypovolemia and hypotension. For clinical purposes, hypernatremia can, in a simplified view, be classified on the basis of the concurrent water loss or electrolyte gain and on corresponding changes in extracellular fluid volume:

- Hypotonic fluid deficits (loss of water and electrolytes)
- Nearly pure-water deficits
- Hypertonic sodium gain (gain of electrolytes in excess of water).

Loss of hypotonic fluid (loss of water in excess of electrolytes)

Patients who lose hypotonic fluid have a deficit in free water and electrolytes (low total body sodium and potassium) and have decreased extracellular volume. In these patients, hypovolemia may be more life threatening than hypertonicity. When physical evidence of hypovolemia is present, fluid resuscitation with normal saline is the first step in therapy.

- Renal hypotonic fluid loss - Results from anything that will interfere with the ability of the kidney to concentrate the urine or osmotic diuresis
    - Diuretic drugs (loop and thiazide diuretics)
    - Osmotic diuresis (hyperglycemia, mannitol, urea [tube feeding])
    - Renal salt wasting
    - Postobstructive diuresis
    - Diuretic phase of acute tubular necrosis
- Nonrenal hypotonic fluid loss
    - Gastrointestinal - Vomiting, diarrhea, lactulose, cathartics, nasogastric suction, gastrointestinal fluid drains, and fistulas
    - Cutaneous - Sweating (extreme sports, marathon runs), burn injuries

Pure-water deficits

Patients with pure-water deficits in the majority of cases have a normal extracellular volume with normal total body sodium and potassium. This condition most commonly develops when impaired intake is combined with increased insensible (eg, respiratory) or renal water losses.

Free-water loss will also result from an inability of the kidney to concentrate the urine. The cause of that can be either from failure of the hypothalamic-pituitary axis to synthesize or release adequate amounts of AVP (central diabetes insipidus) or a lack of responsiveness of the kidney to AVP (nephrogenic diabetes insipidus). Patients with diabetes insipidus and intact thirst mechanisms most often present with normal plasma osmolality and serum NA^+, but with symptoms of polyuria and polydipsia.

- Water intake less than insensible losses
    - Lack of access to water (through incarceration, restraints, intubation, immobilization)
    - Altered mental status (through medications, disease)
    - Neurologic disease (dementia, impaired motor function)
    - Abnormal thirst
        - Geriatric hypodipsia
        - “Essential” hypernatremia with osmoreceptor dysfunction (reset of the osmotic threshold).
        - Injury to the thirst centers by any lesions to the hypothalamus, including from metastasis, granulomatous diseases, vascular abnormalities, and trauma.
    - Loss of pure water through the respiratory tract

Vasopressin (AVP) deficiency (diabetes insipidus)

Central diabetes insipidus[13] can be caused by any pathologic process that destroys the anatomic structures of the hypothalamic-pituitary axis involved in AVP production and secretion. Such processes include the following:

- Pituitary injury - Posttraumatic, neurosurgical, hemorrhage, ischemia (Sheehan’s), idiopathic-autoimmune
- Tumors - Craniopharyngioma, pinealoma, meningioma, germinoma, lymphoma, metastatic disease, cysts
- Aneurysms - Particularly anterior communicating
- Inflammatory states and granulomatous disease - Acute meningitis/encephalitis, Langerhans cell histiocytosis, neurosarcoidosis, tuberculosis

- Drugs - Ethanol (transient), phenytoin
- Genetic - Neurophysin-AVP gene defect

Nephrogenic diabetes insipidus (decreased responsiveness of the kidney to vasopressin)

- Genetic - V2-receptor defects, aquaporin defects (AQP2 and AQP1)
- Structural - Urinary tract obstruction, papillary necrosis, sickle-cell nephropathy
- Tubulointerstitial disease - Medullary cystic disease, polycystic kidney disease, nephrocalcinosis, Sj ö gren's syndrome, lupus, analgesic-abuse nephropathy, sarcoidosis, M-protein disease
- Electrolyte disorders - Hypercalcemia, hypokalemia
- Any prolonged state of severe polyuria - By washing out the renal medullary- intramedullary concentration gradient needed for urinary concentration, and by down-regulating kidney AQP2 water channels
- Medications that induce nephrogenic diabetes insipidus
    - Lithium
    - Amphotericin B
    - Demeclocycline
    - Dopamine
    - Ofloxacin
    - Orlistat
    - Ifosfamide
- Medications that possibly cause nephrogenic diabetes insipidus
    - Contrast agents
    - Cyclophosphamide
    - Cidofovir
    - Ethanol
    - Foscarnet
    - Indinavir
    - Libenzapril
    - Mesalazine
    - Methoxyflurane
    - Pimozide
    - Rifampin
    - Streptozocin
    - Tenofir
    - Triamterene hydrochloride
    - Cholchicine

Gestational diabetes insipidus

In this form of diabetes insipidus, AVP is rapidly degraded by a high circulating level of oxytocinase/vasopressinase. It is a rare condition, because increased AVP secretion will compensate for the increased rate of degradation. Gestational diabetes insipidus occurs only in combination with impaired AVP production.

Hypertonic sodium gain

Patients with hypertonic sodium gain have a high total-body sodium and an extracellular volume overload (rare, mostly iatrogenic). When thirst and renal function are intact, this condition is transient.

- Administration of hypertonic electrolyte solutions - Eg, sodium bicarbonate solutions, hypertonic alimentation solutions
- Sodium ingestion - NaCl tablets, seawater ingestion
- Sodium modeling in hemodialysis

Differential Diagnoses

Cirrhosis
Diabetes Mellitus, Type 1
Hypocalcemia
Hyponatremia

Other Problems to Be Considered

Other problems to consider include all other etiologies for metabolic or drug-induced encephalopathy (eg, cirrhosis, hyponatremia).

Metabolic encephalopathy accompanied by a history of poor oral intake, nursing home residency, the use of certain medications, the presence of appropriate comorbid conditions, increased volume, or insensible loss and obtundation should raise the suspicion of an elevated serum sodium concentration as a possible etiology for mental status changes.

Workup

Laboratory Studies

Diagnosis of hypernatremia is based on an elevated serum sodium concentration (Na^+ >145 mEq/L). It is necessary to obtain the following lab studies:

- Serum electrolytes (Na^+, K^+, Ca^{2+})
- Glucose level
- Urea
- Creatinine
- Urine electrolytes (Na^+, K^+)
- Urine and plasma osmolality
- 24-hour urine volume
- Plasma AVP level (if indicated)

The first step in the diagnostic approach is to estimate the volume status (intravascular volume) of the hypernatremic patient. The associated volume contraction may be mirrored in a low urine Na^+ (usually <10 mEq/L).

In the hypovolemic patient, a hypertonic urine with a UNa^+ <10 mEq/L will point towards extrarenal fluid losses (GI, dermal), whereas an isotonic or hypotonic urine with a UNa^+ >20 mEq/L indicates renal fluid loss (diuretics, osmotic diuresis, intrinsic renal disease).

In the euvolemic patient with preserved intravascular volume, hypernatremia is most likely due to pure-water losses. In the presence of hypernatremia, urine osmolality normally should be maximally concentrated (>800 mOsm/kg H_2O). Measurement of the urine osmolality will allow differentiation of the following:

- Nonrenal causes with appropriately high urine osmolality - Isolated hypodipsia, increased insensible losses
- Renal water loss indicated by inappropriately low urine osmolality - Diabetes insipidus (often U_{osm} <300 mOsm/kg H_2O [central, nephrogenic, partial, gestational diabetes insipidus])

Caveat: Unfortunately, concentrating ability tends to fall with age; the maximum Uosm in an elderly patient may be only 500-700 mOsm/kg.

To distinguish between central and nephrogenic diabetes insipidus, first obtain a plasma AVP level and then determine the response of the urine osmolality to a dose of AVP (or preferably, the V2-receptor agonist DDAVP). Generally, an increase in urine osmolality of greater than 50% reliably indicates central diabetes insipidus, while an increase of less than 10% indicates nephrogenic diabetes insipidus; responses between 10% and 50% are indeterminate. Hyperosmolar patients with an elevated AVP level have nephrogenic diabetes insipidus; those with central diabetes insipidus will have inadequately low AVP level.

If the patient has polyuria without hypernatremia and will be evaluated for diabetes insipidus, the plasma sodium has to be above 145 mOsm/kg H_2O prior to testing (via water deprivation test, hypertonic saline).

It is also clinically very useful to calculate the free-water clearance (cH_2O), and it is even more important to calculate the electrolyte – free-water clearance (cH_2Oe), to estimate the ongoing renal losses of hypotonic fluid ($cH_2O = V_{urine}\,[1-(U_{Osm}/S^{Osm)}]$; $cH_2Oe = V_{urine}\,[1-(U_{Na}+U_K)/S_{Na}]$)

An example of the use of above calculations is a follows: An 80-year-old, partially demented man with poor nutritional status is admitted to the hospital because of pneumonia. Hyperalimentation with high protein supplementation is started (containing 30 mEq/L each of Na^+ and K^+). Following 5 days:

- Urine output: 4 L/day
- BUN: 20-88 mg/dL
- Cr: Stable at 1.4 mg/dL
- [Na^+]: From 140 mEq/L up to 156 mEq/L (despite a relatively high fluid intake)
- Posm: 342 mOsm/kg
- Uosm: 510 mOsm/kg
- UNa^+: 10 mEq/L
- UK^+: 42 mEq/L

The free-water clearance is calculated as follows:

cH2O = 4 x (1 - [510 ÷ 342]) = -2 L/day

By this calculation, taking all osmoles into account, the patient retains 2 liters of water, improving hypernatremia; however, he is actually getting worse.

The electrolyte free-water clearance is calculated as follows:

$eCH_2O = 4\,(1 - [(10 + 41) \div 156]) = 2.7$ L/day

The etiology of the hypernatremia is now apparent; the patient is losing approximately 2.7 L of free water per day in his urine, likely secondary to osmotic diuresis from hyperalimentation.

Imaging Studies

- A magnetic resonance imaging (MRI) or computed tomography (CT) scan of the brain may be helpful in cases of central diabetes insipidus eventuating from head trauma or infiltrative lesions.

Histologic Findings

Histologic findings usually are noncontributory (although they may be helpful in central diabetes insipidus).

Treatment

Medical Care

The goals of management in hypernatremia are (1) recognition of the symptoms, when present; (2) identification of the underlying cause(s); (3) correction of volume disturbances; and (4) correction of hypertonicity.[14]

Correcting the hypertonicity requires a careful decrease in serum sodium and plasma osmolality with the replacement of free water, either orally or parenterally. The rate of sodium correction depends on how acutely the hypernatremia developed and on the severity of symptoms.

Acute symptomatic hypernatremia, defined as hypernatremia occurring in a period of less than 48 hours, should be corrected rapidly. Chronic hypernatremia, however, should be corrected more slowly due to the risks of brain edema during treatment (see image below and Image 1). The brain adjusts to and mitigates chronic hypernatremia by increasing the intracellular content of organic osmolytes. If extracellular tonicity is rapidly decreased, water will move into the brain cells, producing cerebral edema (herniation, permanent neurologic deficits, myelinolysis).

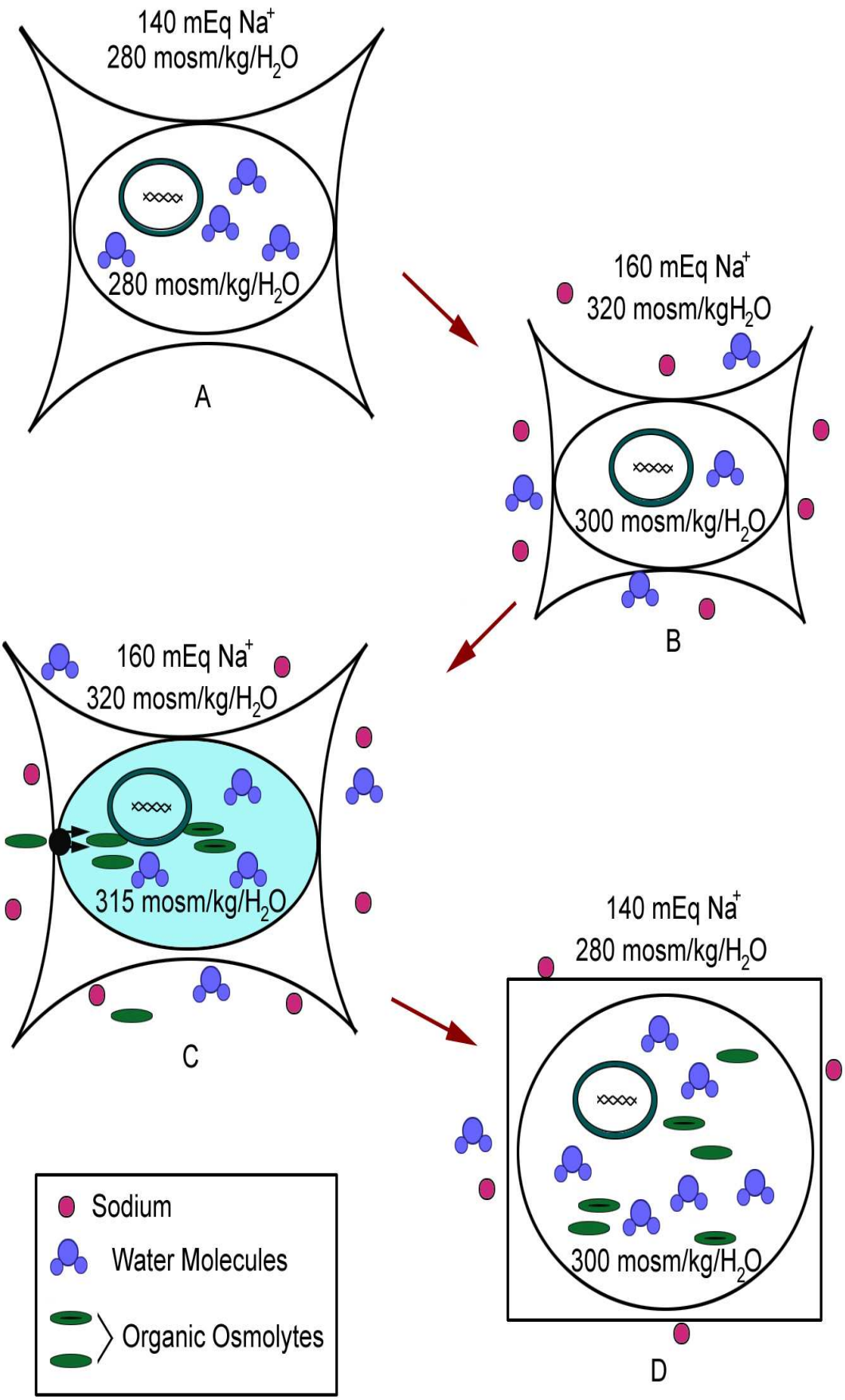


Figure A: Normal cell. Figure B: Cell initially responds to extracellular hypertonicity through passive osmosis of water extracellularly, resulting in cell shrinkage. Figure C: Cell actively responds to extracellular hypertonicity and cell shrinkage in order to limit water loss through transport of organic osmolytes across the cell

membrane, as well as through intracellular production of these osmolytes. Figure D: Rapid correction of extracellular hypertonicity results in passive movement of water molecules into the relatively hypertonic intracellular space, causing cellular swelling, damage, and ultimately death.

Treatment guidelines of symptomatic hypernatremia

- Correct the serum sodium at an initial rate of 1-2 mEq/L/hr
- Replace 50% of the calculated water deficit over the first 12-24 hours
- Replace the remaining deficit over the next 24 hours
- Perform measurements of serum and urine electrolytes every 1-2 hours
- Perform serial neurologic examinations and decrease the rate of correction with improvement in symptoms
- Chronic hypernatremia with no or mild symptoms should be corrected at a rate not to exceed 0.5 mEq/L/h and/or a total of 10 mEq/d (eg, 160 mEq/L to 150 mEq/L in 24 h).
- If a volume deficit and hypernatremia are present, intravascular volume should be restored with isotonic sodium chloride prior to free-water administration.

Estimation of the replacement fluid

The TBW deficit in the hyperosmolar patient that needs to be replaced can be roughly estimated using the formula following formula:

TBW deficit = correction factor x premorbid weight x (1 - 140/Na^+)

Ongoing losses (insensible, renal) need to be added.

However, the formulae below, by Adrogué–Madias, are preferred over the conventional equation for water deficit, because the older equation underestimates the deficit in patients with hypotonic fluid loss and is not useful in situations in which sodium and potassium must be used in the infusate. Formulas used to manage hypernatremia are outlined below.

- Equation 1: TBW = weight (kg) x correction factor
  - Correction factors
    - Children: 0.6
    - Nonelderly men: 0.6
    - Nonelderly women: 0.5
    - Elderly men: 0.5
    - Elderly women: 0.45
- Equation 2: Change in serum Na^+ = (infusate Na^+ - serum Na^+) ÷ (TBW + 1)
- Equation 3: Change in serum Na^+ = ([infusate Na^+ + infusate $K^{+]}$ – serum Na^+) ÷ (TBW + 1)

Equation 2 allows for the estimation of 1 L of any infusate on serum Na^+ concentration. Equation 3 allows for the estimation of 1 L of any infusate containing Na^+ and K^+ on serum Na^+.

Common infusates and their Na^+ contents include the following:

- 5% dextrose in water (D_5 W): 0 mmol/L
- 0.2% sodium chloride in 5% dextrose in water (D_5 2NS): 34 mmol/L
- 0.45% sodium chloride in water (0.45NS): 77 mmol/L
- Ringer's lactate solution: 130 mmol/L
- 0.9% sodium chloride in water (0.9NS): 154 mmol/L

And example of the use of the above calculations is as follows: An obtunded 80-year-old man is brought to the emergency room with dry mucous membranes, fever, tachypnea, and a blood pressure of 134/75. The serum sodium concentration of a 70 kg man is 165 mmol/L. This man is found to have hypernatremia due to insensible water loss.

The man's TBW is calculated by the following:

(0.5 x 70) = 35 L

To reduce the man's serum sodium, D_5 W will be used. Thus, the retention of 1 L of D_5 W will reduce his serum sodium by (0 - 165) ÷ (35 + 1) = -4.6 mmol. The goal is to reduce his serum sodium by no more than 10 mmol/L in a 24-hour period. Thus, (10 ÷ 4.6) = 2.17 L of solution is required. About 1-1.5 L will be added for obligatory water loss to make a total of up to 3.67 L of D_5 W over 24 hours, or 153 cc/h.

- Clinically important: In a study by Lindner and colleagues, the predictive potential of the above formulae (and others) were investigated.[15] The investigators found that all formulae correlated significantly with measured changes in serum sodium in the patient cohort as a total. However the individual variations were extreme. Thus, the above formulae can only guide therapy, but serial measurements of serum sodiumare prudent. These data are no surprise considering that interindividual variables make it difficult to precisely estimate the individual TBW. For example, the degree to which interindividual differences in levels of body fatness affect TBW is very large.[3]

Other treatment considerations

- If hypernatremia is accompanied by hyperglycemia with diabetes, take care when using a glucose-containing replacement fluid. However, the appropriate use of insulin will help during correction.
- Hypernatremia in the setting of volume overload may require dialysis for correction.
- Although water can be replaced by oral and parenteral routes, an obtunded patient requires parenteral treatment. If the deficit is small and the is patient alert and oriented, oral correction may be substituted.
- Once hypernatremia is corrected, efforts are directed at treating the underlying cause of the condition. Such efforts may include free access to water and better control of diabetes mellitus. In addition, correction of hypokalemia and hypercalcemia as etiologies for nephrogenic diabetes insipidus may be required. Vasopressin (AVP, DDAVP) should be used for the treatment of central diabetes insipidus.

Surgical Care

Surgical treatment may be required in the setting of severe central nervous system trauma and associated central diabetes insipidus.

Consultations

- Neurosurgeon (head trauma)
- Endocrinologist (diabetes insipidus or diabetes mellitus)
- Nephrologist (nephrogenic etiologies for hypernatremia)

Diet

Diet should be altered as applicable to diabetes mellitus and increased water intake during increased insensible loss. A low-sodium diet will reduce oral solute intake and therefore diminish renal water loss.

Activity

Activity alterations are applicable only as related to free access to water.

Medication

Some patients with nephrogenic diabetes insipidus—particularly those in whom it is mild or incomplete—may benefit from diuretic therapy (ie, thiazides) in an effort to increase proximal tubular reabsorption and decrease delivery to diluting segments where water may be lost. Inhibition of cyclooxygenase by nonsteroidal anti-inflammatory drugs (NSAIDs) may attenuate the polyuria in these patients. In addition, any medications that may cause nephrogenic diabetes insipidus (such as lithium) may require discontinuation.

In patients with central diabetes insipidus, desmopressin administered orally or intranasally may be used. Pharmacologic agents can be used in partial central diabetes insipidus to increase circulating AVP. These drugs include chlorpropamide, clofibrate, and carbamazepine.

Diuretics

These drugs may be used to enhance sodium excretion.

Hydrochlorothiazide (Esidrix, HydroDIURIL, Microzide)

Inhibits the reabsorption of sodium in the distal tubules, causing increased excretion of sodium and water, as well as of potassium and hydrogen ions.

Dosing

Adult

25-100 mg PO qd; not to exceed 200 mg/kg/d

Pediatric

<6 months: 1-3 mg/kg/d PO divided bid, total range 12.5-37.5 mg/d
6 months to 2 years: 1-2 mg/kg/d PO divided qd/bid, total range 12.5-37.5 mg/d
2-12 years: 1-2 mg/kg/d PO divided qd/bid, not to exceed 37.5-100 mg/d

Interactions

Thiazides may decrease effects of anticoagulants, antigout agents, and sulfonylureas; thiazides may increase toxicity of allopurinol, anesthetics, antineoplastics, calcium salts, loop diuretics, lithium, diazoxide, digitalis, amphotericin B, and nondepolarizing muscle relaxants

Contraindications

Documented hypersensitivity; anuria; renal decompensation

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Caution in renal disease, hepatic disease, gout, diabetes mellitus, and erythematosus

Vasopressin analogs

These agents may enhance sodium excretion.

Desmopressin (DDAVP)

Increases cellular permeability of collecting ducts, resulting in the reabsorption of water by the kidneys.

Dosing

Adult

2-4 mcg IV/SC divided bid
Alternatively, 2-4 mcg/kg/dose intranasally

Pediatric

<3 months: Not established
3 months to 12 years: 5-30 mcg/d intranasally qd or divided bid
Alternatively, 2-4 mcg/dose intranasally
>12 years: Administer as in adults

Interactions

Coadministration with demeclocycline and lithium decreases effects; fludrocortisone and chlorpropamide increase effects of desmopressin

Contraindications

Documented hypersensitivity; platelet-type von Willebrand disease

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Avoid overhydration in patients using desmopressin to benefit from its hemostatic effects

Follow-up

Further Inpatient Care

- Inpatient care is appropriate only as it relates to the correction of underlying diseases that may lead to hypernatremia (diabetes mellitus).

Further Outpatient Care

- Outpatient care is related to water intake and medication treatment.

Transfer

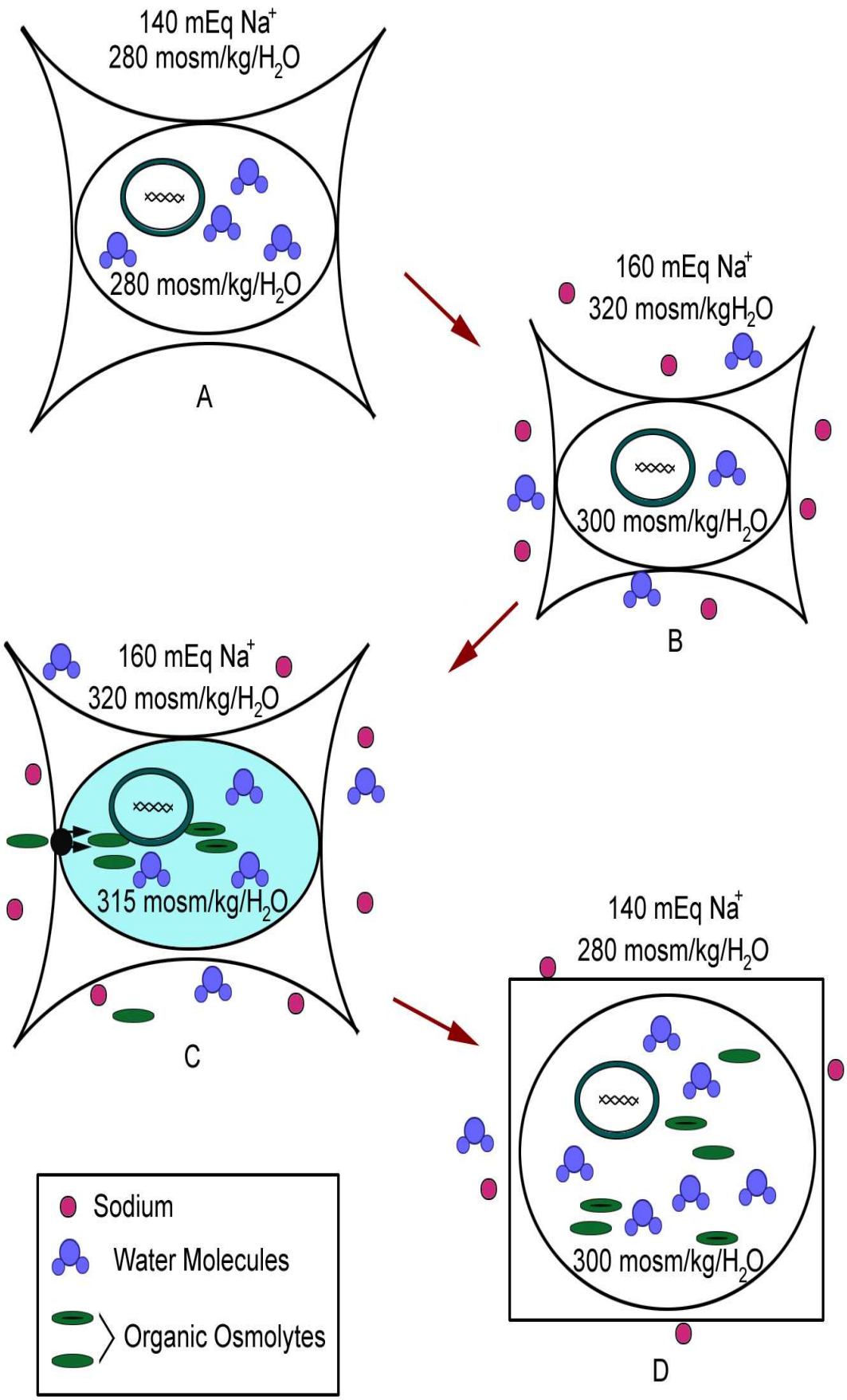
- Transfer may only be necessary in the setting of severe head trauma with central diabetes insipidus.

Miscellaneous

Medicolegal Pitfalls

- Failure to treat volume contraction during hypotension prior to free-water replacement
- Correction of chronic hypernatremia too quickly, leading to cerebral edema or myelinolysis
- Failure to treat central diabetes insipidus with vasopressin during severe water loss

Multimedia



Media file 1: Figure A: Normal cell. Figure B: Cell initially responds to extracellular hypertonicity through passive osmosis of water extracellularly, resulting in cell shrinkage. Figure C: Cell actively responds to extracellular hypertonicity and cell shrinkage in order to limit water loss through transport of organic

osmolytes across the cell membrane, as well as through intracellular production of these osmolytes. Figure D: Rapid correction of extracellular hypertonicity results in passive movement of water molecules into the relatively hypertonic intracellular space, causing cellular swelling, damage, and ultimately death.

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Keywords

hypernatremia, sodium, potassium, dehydration, electrolyte, electrolytes, sodium potassium, diabetes, diabetes insipidus, diabetes mellitus, vasopressin, high sodium, electrolyte imbalance, antidiuretic, antidiuretic hormone, sodium level, blood sodium, hyperosmolar, serum sodium, sodium concentration, sodium in blood, symptoms sodium, blood salt, high blood sodium, hypertonic, hypotonic, hyperosmolality, inadequate fluid intake, water loss, poor water intake

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