Diagnosis and treatment of hypernatremia

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Introduction

Water balance

Hypernatremia is defined as an increase in the plasma Na\(^+\) concentration to >145 mM. Considerably less common than hyponatremia, hypernatremia is however associated with mortality rates of as much as 40–60%. Hypernatremia most commonly occurs in ICUs, mostly developing after admission, and has been associated with increased mortality and prolonged length of ICU stay [1]. A recent study showed that severity rather than duration of the hypernatremia following the ICU admission was associated with increased mortality and increased length of stay (40% and 28% increase, respectively) [2].
Secondary analysis of a recent prospective study in the ICU showed that almost 50% of pre-dialysis patients with acute kidney injury had a dysnatremia, mainly hypernatremia, and that there was an increase in mortality especially with severe hypernatremia (serum sodium ≥156) compared to normonatremic patients (89.1% versus 64.6% respectively) [3]. Preoperative hypernatremia is also associated with increased perioperative 30-day morbidity and mortality [4].

Understanding hypernatremia requires a comprehension of the main body fluid compartments as well as an appreciation of the basic concepts of maintenance of normal body water balance. Total body water (TBW) is a key physiological term in this context. TBW has been estimated to be about 60% of body weight in men and 50% in women; this notably is a simplified estimate. TBW is further divided into two main compartments, an extracellular fluid (ECF) and an intracellular fluid (ICF) compartment. The ECF compartment includes plasma, interstitial and lymph fluid, connective tissue and bone, transcellular fluid within body cavities, and adipose tissue [5].

Tonicity refers to the behavior of cell volume in a given solution and represents the action of effective osmoles across a membrane. Cellular volume expands when cells are bathed in relatively hypotonic solutions and contracts when bathed in relatively hypertonic solutions, due to movement of water in and out of the cell respectively to eventually reach a steady state tonicity. Effective or active osmoles include sodium (and associated anions) and glucose in the extracellular compartment, whereas the ionic osmotic driver in the intracellular compartment is primarily potassium (and associated anions). On the other hand, osmolality represents the sum of both effective and ineffective osmoles in any 1 kg of body fluid. Ineffective osmoles, typically urea and alcohol [6] can cross freely across cell membranes and hence do not generally alter cellular volume. Osmolality is a poor indicator of tonicity given the presence of these ineffective osmoles. While effects of tonicity on cellular size cannot be measured directly, serum sodium can serve as a useful surrogate for tonicity in all body compartments at steady state.

Hypertonicity (dehydration) refers to the loss of total-body water such that cellular volume contracts, whereas volume depletion is a term used to signify loss of extracellular fluid volume. These two distinct conditions have different clinical features as well as different therapeutic responses [6,7].

**Osmoreceptors and thirst**

Vasopressin secretion, thirst, and the renal response to vasopressin collaborate to maintain normal human body fluid osmolality between 280 and 295 mOsm/kg. Thirst and vasopressin secretion are under the control of osmoreceptor neurons within the central nervous system (CNS) (see Fig. 1). Classic canine experiments performed in the 1940s, correlating the effect on urine output of carotid infusion of various osmolytes, led to the postulation of a central “osmoreceptor” [8]. The primary “osmostat” within the CNS is encompassed within the *organum vasculosum* of the *lamina terminalis* (OVLT); this small periventricular region lacks a blood–brain barrier, allowing for direct sensing of the osmolality of circulating blood. Osmoreceptive neurons are however widely distributed within the CNS, such that vasopressin (AVP) release and thirst are controlled by overlapping osmosensitive neural networks [9–12]. Osmosensitive neurons are thus found in the subfornical organ (SFO) and the *nucleus tractus solitarii*, centers which help integrate regulation of circulating osmolality with that of related phenomena, such as extracellular fluid volume [9,10,12] (see Fig. 1).

Osmosensitive neurons from the supraoptic nucleus differ dramatically from hippocampal neurons, in that they demonstrate exaggerated changes in cell volume during cell shrinkage (hypertonic media) or cell swelling (hypotonic media) [13]. In hippocampal neurons, cell swelling evokes a rapid regulatory volume decrease (RVD) response, whereas cell shrinkage evokes a regulatory volume increase (RVI) response. In consequence, if external tonicity is slowly increased or decreased these RVD and RVI mechanisms are sufficient to prevent any change in the cell volume of hippocampal neurons; in contrast, osmosensitive neurons exhibit considerable changes in cell volume during such osmotic ramps [13]. This relative lack of volume regulatory mechanisms maximizes the mechanical effect of extracellular tonicity and generates an ideal osmotic sensor.

Osmosensitive neurons depolarize after cell shrinkage induced by exposure to hypertonic stimuli, with a marked increase in neuronal spike discharges; the associated current is due to activation of a nonselective cation channel [14], with five-fold higher permeability for Ca²⁺ over Na⁺ [15]. Hypotonic
stimuli in turn hyperpolarize the cells and abolish spike discharges [14]. Depolarization and spike discharges, in the absence of hypertonicity, can also be evoked by suction-induced changes in cell volume during whole-cell voltage recording, suggesting involvement of a stretch-inactivated cation channel [14].

Mechanosensitive, stretch-inactivated cation channels, linked to the cytoskeleton [16], are thought to be key components of the osmoreceptor complex. The TRPV1 channel (transient receptor potential vanilloid channel 1) appears to be a critical component of the mechanosensitive osmoreceptor, with loss of osmoreceptive neuronal depolarization and neuronal activation after hypertonic stimuli in TRPV1−/− mice [17,18]. Specifically, an N-terminal splice variant of TRPV1 has been implicated in this process, with detectable expression of TRPV1 C-terminal exons by RT-PCR in neurons from the SON without detectable expression of N-terminal exons; these AVP-positive neurons also stain positive with a C-terminal TRPV1 antibody, suggesting the involvement of an N-terminal splice-form. More recently, the relevant alternatively spliced isoform (TRPV1dn) has been cloned and characterized; TRPV1dn has an alternative start codon with a truncated N-terminus [19]. TRPV1dn encodes a shrinkage-activated channel and can rescue the phenotype of osmoreceptor neurons from TRPV1−/− mice [19]. The swelling-activated TRPV4 channel is also expressed in osmoreceptor neurons, where it may play an inhibitory role, limiting the thirst response in hypotonicity and perhaps downregulating osmotic-
induced AVP release; however, there are substantial differences in the reported phenotypes of TRPV4 knockout mice [20,21], such that the exact role of TRPV4 is still controversial.

At the neuronal network level, OVLT and adjacent circumventricular regions collaborate to regulate water intake and AVP release, in a number of different species [22,23] (see Fig. 1). In humans, functional magnetic resonance imaging (fMRI) studies have revealed thirst-associated activation of the anterior wall of the third ventricle, encompassing the OVLT, in subjects treated with a rapid infusion of hypertonic saline [24]. In sheep, ablation of the OVLT or SFO alone does not affect osmotic-induced drinking; combined ablation of both regions is more effective, but still only partially effective. Complete abolition of thirst is however seen in sheep after combined ablation of the OVLT, the adjacent median preoptic nucleus (MnPO), and much of the SFO [25]. Similar observations can be made in respect to AVP release, in that combined ablation of the OVLT, SFO, and MnPO is required to fully abolish osmotic-induced release of AVP; notably, “non-osmotic” stimuli such as hemorrhage and fever are still effective in inducing AVP release in these animals [23].

Classically, the onset of thirst, defined as the conscious need for water, was considered to have a threshold of ~295 mOsm/kg, i.e. ~10 mMosm/kg above that for AVP release [26]. However, more recent studies using semi-quantitative visual analog scales to assess thirst suggest that the osmotic threshold is very close to that of AVP release, with a steady increase in the intensity of thirst as osmolality increases above this threshold [27]. Thirst and AVP release share a potent “off” response to drinking, with a rapid drop that precedes any change in circulating osmolality. Teleologically, this reflex response serves to prevent over-hydration [27]. Peripheral osmoreceptors in the oropharynx, upper GI tract, and/or portal vein are postulated to sense the rapid change in local osmolality during drinking, via TRPV4 channels [28], and relay the information back through the vagus nerve and splanchnic nerves [12].

As with AVP release (see below), thirst is stimulated by hypovolemia, although this requires a deficit of 8–10% in plasma volume, versus the 1–2% increase in tonicity that is sufficient to stimulate osmotic thirst [29]. Angiotensin is a particularly potent dipsogenic agent, particularly when infused directly into the brain or, more recently, overproduced in the SFO in transgenic mice [30]. The neuronal effects of angiotensin-II are evidently required for hypovolemic thirst, but not osmotic thirst [31].

**Vasopressin**

Vasopressin is an endogenous peptide that serves multiple regulatory functions related to preservation of blood pressure, water balance, platelet function and thermoregulation [32,33]. Vasopressin is synthesized in magnocellular neurons within the hypothalamus; the distal axons of these neurons project to the posterior pituitary or neurohypophysis, from which AVP is released into the circulation. AVP secretion is stimulated as osmolality increases above a threshold level, beyond which there is a linear relationship between circulating osmolality and AVP (see Fig. 2). The X intercept of this relationship in healthy humans is ~285 mOsm/Kg; AVP levels are essentially undetectable below this threshold.

Changes in blood volume and blood pressure are also potent stimuli for AVP release, albeit with a more exponential response profile (see Fig. 2). Of perhaps greater relevance to the pathophysiology of hyponatremia, extracellular fluid volume strongly modulates the relationship between circulating osmolality and AVP release, such that hypovolemia reduces the osmotic threshold and increases the slope of the response curve to osmolality; *hypervolemia* has an opposite effect, increasing the osmotic threshold and reducing the slope of the response curve [34] (see Fig. 2). A number of other stimuli have potent positive effects on AVP release, including nausea, angiotensin-II, acetylcholine, relaxin, serotonin, cholescytokinin, and a variety of related drugs [35].

The excretion or retention of electrolyte-free water by the kidney is modulated by circulating AVP [36]. AVP acts on renal V2 receptors in the thick ascending limb of Henle and principal cells of the collecting duct (CD), increasing cyclic-AMP and activating protein kinase A (PKA)-dependent phosphorylation of multiple transport proteins. The AVP- and PKA-dependent activation of Na⁺ –Cl⁻ and K⁺ transport by the thick ascending limb of the loop of Henle (TALH) is thus a key participant in the countercurrent mechanism [37]. The countercurrent mechanism ultimately increases the interstitial osmolality in the inner medulla of the kidney, driving water absorption across the renal collecting duct [36]. However, water, salt, and solute transport by both proximal and distal nephron segments
participates in the renal concentrating mechanism. Water transport across apical and basolateral aquaporin-1 water channels in the descending thin limb of the loop of Henle is thus involved [38,39], as is passive absorption of Na\(^{+}\)–Cl\(^{-}\) by the thin ascending limb, via apical and basolateral CLC-K1 chloride channels and paracellular Na\(^{+}\) transport [40,41] (see Fig. 3). Renal urea transport in turn plays important roles in the generation of the medullary osmotic gradient and the ability to excrete solute-free water under conditions of both high and low protein intake [36] (see Fig. 3).

AVP-induced, PKA-dependent phosphorylation of the aquaporin-2 water channel in principal cells stimulates the insertion of active water channels into the lumen of the collecting duct, resulting in transepithelial water absorption down the medullary osmotic gradient. Under “anti-diuretic” conditions, with increased circulating AVP, the kidney reabsorbs water filtered by the glomerulus,

**Fig. 2.** A) A comparison of the response of circulating vasopressin to hemodynamic and osmotic stimulation in healthy adults. The shaded area represents the reference range of plasma arginine vasopressin under normal conditions of hydration with plasma osmolality ranging from 284 to 293 mosmol/kg. (From Baylis PH, “Osmoregulation and control of vasopressin secretion in healthy humans”, Am J Physiol 1987; 253:R671-8, with permission). B) The influence of hemodynamic status on osmotic stimulation of vasopressin release in healthy adults. The heavy oblique line in the center depicts the relationship of plasma vasopressin to osmolality in normovolemic, normotensive subjects. Lighter lines to the left or right depict the relationship when blood volume and/or pressure are acutely decreased or increased by the different percentages indicated in the center circles. (From Robertson GL et al., “The osmoregulation of vasopressin,” Kidney Int 1976; 10:25–37).
equilibrating the osmolality across the collecting duct epithelium to excrete a hypertonic, “concentrated” urine (osmolality of up to 1200 mOsm/kg). In the absence of circulating AVP, insertion of aquaporin-2 channels and water absorption across the collecting duct is essentially abolished, resulting in secretion of a hypotonic, dilute urine (osmolality as low as 30–50 mOsm/kg). Abnormalities in this “final common pathway” are involved in most disorders of water homeostasis, e.g., a reduced or absent insertion of active aquaporin-2 water channels into the membrane of principal cells in both central and nephrogenic diabetes insipidus.

Cerebral adaptation to hypernatremia

Hypernatremia increases osmolality of the ECF, generating an osmotic gradient between the ECF and ICF, an efflux of intracellular water, and cellular shrinkage. Initially, hypernatremia results in a reduced brain volume, which is reversed by cerebrospinal fluid movement into the brain with a subsequent increase in the interstitial volume [42,43], in addition to cellular uptake of solutes by the cell as part of the RVI response [42,44,45]. This RVI process initially involves the uptake of inorganic ions (Na⁺, K⁺, and Cl⁻) via transporters such as NKCC1 [46], followed by a more delayed accumulation of organic osmolytes, primarily myo-inositol, the amino acids glutamine, glutamate, and taurine [44,45,47,48]. Some of the relevant osmolyte transporters are induced in neurons by the osmosensitive transcription factor TonEBP [49], whereas the slow induction of osmolytes transporters in oligodendrocytes and glia likely occurs through transcriptional mechanisms that are independent of TonEBP [48].
Etiology

Hypernatremia is usually the result of a combined water and electrolyte deficit, with losses of H$_2$O in excess of Na$^+$. This imbalance can also result from net water loss, which can be pure water or hypotonic fluid loss, or less frequently from a gain of hypertonic sodium. In order for the hypernatremia to be sustained, there needs to be a defect in the thirst mechanism or a lack of access to water. Notably, hypernatremia in the ICU is the predominant presentation, with the most common causes being a lack of provision of sufficient free water, hypertonic sodium loading that occurs during volume resuscitation or hypertonic bicarbonate administration [50], suboptimal daily free water provision, and impaired renal water conservation due to acute kidney injury and/or diuretic therapy. In the out-of-hospital setting, hypernatremia is most commonly associated with free water losses from non-renal sites [51,52]. The etiologies of hypernatremia are as follows [53]:

Hypernatremia from net water loss

This is the most common cause of hypernatremia and can be further subcategorized into renal and non-renal losses.

Renal water losses

**Neurogenic or central diabetes insipidus**: this can result from traumatic brain injury, space occupying lesions, or infections. Mutations in the AVP gene are associated with hereditary neurogenenic diabetes insipidus (Chapter *).

**Nephrogenic diabetes insipidus**: this can result from renal dysfunction, electrolyte perturbations such as hypercalcemia or hypokalemia, or medication effects such as lithium, foscarnet, amphotericin, vasopressin receptor antagonists, demeclocycline, methoxyflurane. Hereditary causes include loss-of-function mutations in the V2 vasopressin receptor gene, the aquaporin-2 gene, or aquaporin-1 [54] (Chapter**).

Lithium is a particularly common cause of acquired nephrogenic DI (NDI). Lithium causes NDI via direct inhibition of renal glycogen synthase kinase-3 (GSK3), a kinase thought to be the pharmacological target of lithium in psychiatric disease; renal GSK3 is required for the response of principal cells to AVP [55]. Lithium also induces the expression of COX2 in the renal medulla [56]; COX2-derived prostaglandins inhibit AVP-stimulated salt transport by the thick ascending limb [37] and AVP-stimulated water transport by the collecting duct [57], thus exacerbating lithium-associated polyuria. The entry of lithium through the amiloride-sensitive Na$^+$ channel ENaC is required for the effect of the drug on principal cells [58,59], such that combined therapy within lithium and amiloride can mitigate lithium-associated NDI [60]. However, lithium causes chronic tubulointerstitial scarring and chronic kidney disease after prolonged therapy, such that patients may have a persistent cause of NDI long after stopping the drug, with a reduced therapeutic benefit from amiloride [61].

**Renal losses**: loop diuretics, osmotic diuresis.

Non renal water losses

**Hypodyipsia**: affected individuals demonstrate a lack of thirst despite hypertonicity. A variety of infiltrative, neoplastic, vascular, congenital, and traumatic processes in this circumventricular region can be associated with abnormalities in thirst and AVP release. Patients with this “adipsic” or “essential” hypernatremia generally exhibit combined defects in both AVP release and thirst [62]. In some cases, however, thirst is impaired but not AVP release [62], underscoring the functional redundancy and/or plasticity of the osmosensitive neuronal network; alternatively, the intrinsic osmosensitivity of the magnocellular neurons that synthesize and secrete AVP may preserve a residual osmotic-induced AVP release [23].

Unreplaced insensible losses from the respiratory system.

Cutaneous losses: sweating, burns.

Gastrointestinal losses: vomiting, diarrhea, nasogastric drainage, enterocutaneous fistula. Diarrhea is the most common gastrointestinal cause of hypernatremia. Notably, osmotic diarrhea and viral
gastroenteritides typically generate stools with Na\(^+\) and K\(^+\) < 100 mM, thus leading to water loss and hypernatremia; in contrast, secretory diarrhea typically results in isotonic stool and thus hypovolemia +/- hypovolemic hyponatremia.

**Hypernatremia from hypertonic sodium gain**

Sodium bicarbonate infusion. Ampules of sodium bicarbonate are approximately twice as hypertonic as hypertonic saline, such that administration of undiluted ampules leads to marked increases in serum sodium [50].

Feeding.

Oral salt intake.

Sea water ingestion.

Hypertonic enemas.

Hypertonic dialysis.

Primary hyperaldosteronism.

Cushing’s syndrome.

**Diagnosis**

Thorough history, clinical examination and laboratory testing help establish the etiology of hypernatremia.

**History and physical examination**

The history is essential to suggest the possible cause for the hypernatremia and also guide management. Patients who have sustained a traumatic brain injury might suffer from central diabetes insipidus, whereas those with a psychiatric illness with current or prior lithium treatment are more likely to have a nephrogenic diabetes insipidus. History is also crucial in determining the chronicity of hypernatremia, as this will be helpful in making management decisions. Hypernatremia that is thought to have developed within the previous 48 h is considered acute, while patients who have had symptoms for more than 48 h or those with unknown time of start of symptoms are considered to have chronic hypernatremia. Patients with acute hypernatremia will usually have more prominent symptoms than patients in whom hypernatremia develops over a longer period of time. These symptoms can include lethargy, weakness, and irritability and may advance to seizures and coma [63,64]. The sudden shrinkage of brain cells in acute hypernatremia may lead to parenchymal or subarachnoid hemorrhages and/or subdural hematomas; however, these vascular complications are primarily encountered in pediatric and neonatal patients. Osmotic damage to muscle membranes can also lead to hypernatremic rhabdomyolysis [65]. Chronic hypernatremia will have less prominent symptoms, due primarily to the accumulation of intracellular osmolytes within the CNS.

Determining the patient’s volume status is one of the most important steps in management of hypernatremia. The main task is to identify whether there has been an accompanying loss of salt, through history and physical examination. Following the initial assessment, the patients can be categorized into one of the following three groups depending on their volume status:

**Hypernatremia with concomitant loss of salt**

Patients with hypovolemic hypernatremia will have loss of both water and salt but with relatively larger losses of water. The losses are usually from either the kidneys or from the gastrointestinal tract. The presenting symptoms and signs will be those of hypovolemia such as tachycardia, orthostatic hypotension. Measurement of the urine sodium is useful to differentiate these two, as it will be low when there is loss of sodium from the gastrointestinal tract reflecting an intact renal water conserving ability. Notably, this physiology is not clear-cut, given the phenomenon of “dehydration-induced natriuresis”, wherein increases in renal medullary tonicity cause a natriuresis to protect against worsening hypertonicity [66].
Hypernatremia with normal salt content

Euvolemic hypernatremia can result from either renal or extra renal loss of water without any accompanying loss of salt. These patients usually have either impaired sense of taste, inability to administer water, or a neurological or renal pathology that impairs the function of AVP. They will not show any signs of hypo- or hypervolemia on exam. Urine osmolality will be lower than that of plasma in patients with renal losses.

Extra-renal losses.
Renal losses.
Neurogenic diabetes insipidus.
Nephrogenic diabetes insipidus.

Hypernatremia with concomitant gain in salt

This is less common and results from an increase in total body salt that is in excess to an increase in total body water (relative water deficit). Patients in this category develop hypernatremia from hypertonic sodium gain such as sodium bicarbonate administration, hypertonic feeding formulas, oral or intravenous sodium chloride load, seawater ingestion, hypertonic dialysis with inadvertently high sodium baths, and primary hyperaldosteronism [53]. Patients in this group will have signs of volume overload such as edema and some of these patients have conditions that are thought to contribute to salt retention such as liver dysfunction, renal dysfunction, and/or hypoalbuminemia [67].

Laboratory findings

Laboratory testing is required to complete the evaluation of the causative factors, especially in patients who cannot provide history due to depressed level of consciousness, one of the most prominent manifestations of hypernatremia. The urine osmolality, as a function of AVP secretion, is probably the most useful initial test to perform in order to further categorize the etiology and determine whether or not the renal water concentrating ability is preserved. When hypernatremia develops, and in absence of hypothalamic or renal impairment, the concomitant rise in serum osmolality will cause stimulation of AVP secretion. This will result in a rise in the osmolality of urine to more than 600–800 mosmol/kg. Based on the urine osmolality, causes of hypernatremia can be categorized as follows:

Hypernatremia with low urine osmolality

If the urine osmolality is less than 300 mosmol/kg (or less than that of plasma), this suggests either central or nephrogenic diabetes insipidus. In order to differentiate these two disorders, exogenous AVP (usually the pharmacological analog DDAVP, desmopressin acetate) is administered and will result in an increase in urine osmolality in patients with neurogenic diabetes insipidus (see below). However, patients with nephrogenic diabetes insipidus already have maximal AVP secretion with resistance at the kidney level and hence the urine osmolality will not change with DDAVP administration.

Hypernatremia with high urine osmolality

If the urine osmolality is greater than 800 mosmol/kg, this suggests that the secretion and response to AVP are normal. In other words, renal concentrating ability is preserved in this category. This is due to either unreplaced water losses (from GI tract, respiratory tract, or skin) or total body sodium gain.

Hypernatremia with intermediate urine osmolality

If the urine osmolality is between 400 and 800 mosmol/kg, this may reflect partial central diabetes insipidus, partial nephrogenic diabetes insipidus, central diabetes insipidus with volume depletion, or a process of osmotic diuresis. It should be noted in this context that polyuria can result from either an osmotic diuresis or a water diuresis. An osmotic diuresis can be caused by excessive excretion of Na⁺—Cl⁻, mannitol, glucose, and/or urea, with a daily solute excretion of >750–1000 mOsm/day (>15 mOsm/kg body water/day).

Water deprivation testing. Following correction of hypernatremia it may occasionally be appropriate to perform a water deprivation test, followed by administration of DDAVP. This test helps
determine whether an inappropriate water diuresis is caused by central DI or NDI. The patient should be water restricted beginning in the early morning, with careful monitoring of vital signs, weight, and hourly urine output; overnight water deprivation of patients with diabetes insipidus is unsafe and clinically inappropriate, given the potential for severe hypernatremia. Water deprivation is also inappropriate in patients who already have hypernatremia, wherein AVP secretion should already be activated. The serum Na⁺ concentration – more accurate and more immediately available than serum osmolality – should be monitored hourly during water deprivation. A baseline AVP sample should be drawn at the beginning of the test, with a second sample drawn once the serum Na⁺ reaches 148–150 mEq/L. At this point a single 2 µg dose of the V2 vasopressin receptor agonist DDAVP can be administered, followed by ongoing measurement of urine output, serum Na⁺ concentration, in addition to urine and serum osmolality.

During water deprivation testing patients with nephrogenic DI will fail to respond to DDAVP, with a urine osmolality that increases by <50% or <150 mOsm/kg from baseline, in combination with a normal or high circulating AVP level; patients with central DI will respond to DDAVP, with a reduced circulating AVP. Patients may exhibit a partial response to DDAVP, with a >50% rise in urine osmolality that nonetheless fails to reach 800 mOsm/kg; the level of circulating AVP will help differentiate the underlying cause, i.e., nephrogenic versus central DI. Patients with “partial NDI” can thus achieve urine osmolalities of 500–600 mOsm/kg after DDAVP treatment, but will not maximally concentrate their urine to 800 mOsm/Kg or higher.

**Treatment**

The treatment of hypernatremia requires a comprehensive understanding of the predisposing mechanism. The most common form of hypernatremia is that due to water loss with impaired thirst mechanism or inability to administer water. Management is targeted towards treating the inciting factor and correcting the hyperosmolality [53]. A stepwise approach is helpful in order to address several considerations and can be summarized by the following points:

Identify and initiate treatment for the predisposing factor

Addressing the inciting factor is key in preventing further loss of water or hypertonic sodium gain. As mentioned in the “diagnosis” section, careful history, clinical examination to determine the volume status and measurement of urine sodium and osmolality will help further elucidate the etiology. Treatment might entail, for example, withholding loop diuretics, administering insulin in the case of hyperglycemia, treating vomiting or diarrhea, withholding/adjusting hypertonic tube feeds, or administering DDAVP for central diabetes insipidus. A key principle however, is that treatment of the cause of the hypernatremia should only be attempted once “eunatremia” has been established through adequate and ongoing free water administration.

Determine whether the hypernatremia is acute or chronic

Attention should be made as to whether the hypernatremia has developed within the preceding 48 h as the rate of correction can possibly be liberalized in patients with acute hypernatremia especially if they are presenting with symptoms. Patients with chronic hypernatremia require slower rates of correction to avoid cerebral edema. Further details on the rate of correction are mentioned below.

Determine the amount of fluid to be replaced

Assess the need for volume resuscitation

Determining the patient’s volume status is one of the most important steps in management of hypernatremia. The main task here is to identify whether there has been an accompanying loss of salt, through history and physical examination as explained above. Patients with hypovolemia on presentation should be resuscitated with 0.9% sodium chloride regardless of the serum sodium level until their vital signs are normal.
Calculate the water deficit

The mainstay of therapy for hypernatremia is to administer fluids that are dilute relative to plasma in order to replace the water deficit. This requires the estimation of the amount of water that has been lost. This can be simplified into the following equations by Adrogué and Madias [53].

Formula (1):

Water deficit = TBW × (plasma[Na+] / 140 - 1)
= (0.4 - 0.5) × lean body weight × (plasma [Na+] / 140 - 1)  

Formula (2):

Change in Na = (infusate Na+ - serum Na) / (TBW + 1)

Assess for any ongoing losses that need to be replaced

Water replacement should address the total body water deficit in addition to any ongoing losses of water. Obligatory water losses from stool and sweat vary but are estimated to be 30–40 mL/h. In addition to insensible water output, ongoing water losses in the urine need to be accounted for when deciding the infusion rate of the replacement fluid and this provides for the most accurate estimate of the sodium level resulting from a given amount of infusate [51]. The amount of pure water lost in urine can be determined by calculating the electrolyte free water clearance (EFWC) [68] using the following equation:

EFWC = urine volume × (1 - [urine Na+ + urine K+] / serum Na)  

If a patient is making 75 mL/h and his urinary sodium and potassium levels are summed to 128 mEq/L with a serum sodium level 160 mEq/L, the electrolyte free water clearance for this patient equals 75 mL/h × (1 - [128 mEq/L / 160 mEq/L]), which is 15 mL/h. In other words, in addition to the water deficit that will need to be replaced, an additional 15 mL per hour of water will have to be administered in order to reach the target sodium level.

Select the type and rate of replacement solution

The choice of replacement solution to be given and the infusion rate are important factors to avoid overcorrection of the hypernatremia [69]. Overcorrection of hypernatremia is associated with increased risk of cerebral edema, due to the CNS response to hypertonicity. Classically, the recommendation is to replace the calculated free water deficit over 48 h. Notably, the plasma Na⁺ concentration should be corrected by no more than 10 mM/day, which may take longer than 48 h in patients with severe hypernatremia (>160 mM). A rare exception is patients with acute hypernatremia (<48 h) due to sodium loading, who can safely be corrected rapidly at a rate of 1 mM/h. As in management of hyponatremia, frequent measurement of serum Na⁺ is critical for monitoring the response to therapy and adjusting the rate or choice of intravenous fluid.

It should be noted that there have been a number of studies revealing that slower rates of correction and persistent hypernatremia are associated with an increased risk of death. Multivariate analysis of a retrospective study of 131 patients hospitalized with severe hypernatremia thus showed that a slower rate of correction of hypernatremia was an independent predictor of 30-day mortality [hazards ratio (HR), 3.85; P < 0.0001] [70]. Another recent retrospective study assessing outcomes in the emergency department of 82 patients with hypernatremia (serum sodium, ≥150) in the emergency room showed that slower rate of sodium correction, rather than the initial severity of the hyperosmorality was associated with an increased risk of death during hospitalization [HR, 10.29; P < 0.001] [71]. Except for hypovolemic patients requiring resuscitation with 0.9% sodium chloride, all other patients should receive either 0.45% sodium chloride or 5% dextrose water infusions to replace the water deficit and ongoing fluid losses.
**Other therapies**

Patients with hypervolemic hypernatremia present a therapeutic challenge as the volume expansion in these patients inhibits the release of AVP, thereby promoting water excretion in the urine. Cessation of the inciting factors and administration of water is usually the initial step in therapy. Treatment with loop diuretics would enhance more aquarexis relative to natriuresis thereby exacerbating the hypertonicity. Infusing dextrose 5% water would address the hypertonicity but worsen the volume overload state. Simultaneous use of intravenous dextrose 5% water and loop diuretics can however be used to lower the serum sodium in addition to achieving a net negative total body water balance. Nguyen and Kurtz derived an equation to determine the amount of dextrose 5% water required to lower the serum sodium to a target level while maintaining a set net negative water balance [72].

Hemodialysis has been used for treatment of hypernatremia, especially in cases where hydration with or without diuresis have failed to bring the sodium level down to the desired target or in patients in whom there are indications for renal replacement therapy [73,74]. Continuous renal replacement therapy has been reported to be useful in situations of hypernatremia and congestive heart failure [75]. A recent retrospective cohort study evaluating 95 patients in the intensive care unit with acute severe hypernatremia revealed that continuous veno-venous hemofiltration led to a greater reduction in serum sodium and was associated with an improved 28-day survival rate compared with conventional therapy using calculation of water deficit and administration of intravenous hypotonic fluids (34.8% vs. 8.7% respectively, P<0.002) [76].

**Specific treatment for neurogenic and nephrogenic diabetes insipidus**

The main treatment modality for patients with central diabetes insipidus is to supplement antidiuretic hormone. This is usually given in the form of DDAVP, a synthetic analog with a longer half-life and mostly V2 receptor agonism, thus with a dominance of antidiuretic rather than pressor effects [77]. DDAVP can be administered by intravenous, subcutaneous, or intranasal routes.

The use of thiazide diuretics in diabetes insipidus has been shown to decrease urine volume and increase urine osmolality [78]. The mechanism of the paradoxical antidiuretic effect of thiazides in diabetes insipidus is thought to be related to volume contraction, leading to an increase in proximal tubular reabsorption of water and sodium thereby decreasing distal delivery of water and subsequent excretion [79,80]. However, it has been shown that volume repletion does not abrogate the antidiuretic effect of thiazides [81]. Thiazides also directly increase water absorption in perfused collecting ducts [82], even in the absence of circulating AVP. In an animal model of lithium-associated NDI, thiazides increase expression of aquaporin-2 [83]. Overall, however, we find very limited clinical utility for thiazides in acquired nephrogenic DI, wherein increased oral free water intake is usually sufficient to prevent hypernatremia and where patients often have chronic kidney disease (CKD) with greater susceptibility to additive diuretic-induced renal insufficiency.

The entry of lithium through the amiloride-sensitive Na⁺ channel ENaC is required for the effect of the drug on principal cells [58,59], such that combined therapy within lithium and amiloride can mitigate lithium-associated NDI [60]. Concomitant therapy with amiloride is thus an attractive option in the management of patients treated with lithium, however this approach has not gained widespread acceptance.

Renal prostaglandins have been shown to play an important role in the pathogenesis of lithium-induced nephrogenic diabetes insipidus. Physiologically, renal prostaglandins exert antagonistic effects on vasopressin mediated osmotic water flow [57]. Animal studies have shown that lithium induces the expression of cyclooxygenase 2 (COX2) in the medullary interstitial cell, via the inhibition of glycogen synthase kinase-3beta (GSK-3beta), leading to increased levels of urinary prostaglandin E2 [56]. COX2 inhibition resulted in a significant reduction in lithium-induced polyuria in this model [56]. Clinical effects for NSAIDs or COX2 inhibitors have also been reported in humans lithium-associated NDI. Again, however, as with thiazides our enthusiasm for COX2 inhibition in lithium-associated DI is minimal, since most patients have associated CKD and most patients can accommodate their defect by increased free water intake.
References


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