Electrolyte quintet

Sodium

Sumit Kumar, Tomas Berl

Disorders of serum sodium are both the most common and probably most the poorly understood electrolyte disorders in clinical medicine. In the past few years increased knowledge about the non-osmotic release of vasopressin and the cloning of vasopressin receptors and of vasopressin-regulated water channels (AQP2) has enhanced our understanding of these disorders. Also controversies surrounding the treatment of hyponatraemic patients have led to well-accepted therapeutic guidelines.

Control of serum sodium

The renal countercurrent mechanism, in concert with osmoreceptors in the hypothalamus that control secretion of antidiuretic hormone (ADH, vasopressin), maintains a very finely tuned balance of water that keeps the serum sodium concentration or [Na^+] in the very narrow range of 138–142 mmol/L despite great variation in water intake. A defect in the urinary diluting capacity, when coupled with excess of water intake, causes hyponatraemia. A defect in urinary concentration, when not accompanied by adequate water intake, culminates in hypernatraemia (figure 1).

Serum [Na^+] with its accompanying anions accounts for nearly all of the osmotic activity of the plasma, which is calculated, in mosmol/L, as:

$$2\times[Na^+] + \text{urea nitrogen} + \text{glucose, all in mmol/L}$$

There are, however, several clinical settings in which the serum sodium does not predict serum osmolality (figure 1). While an increase in serum [Na^+] always predicts a hypertonic state, a normal or even low serum [Na^+] does not necessarily reflect a euosmotic or hypoosmotic state. The presence of other osmotically active substances can add to the osmolality of body fluids with variable effects on serum [Na^+]. It is the nature of the solute that determines whether serum [Na^+] changes and if an increase in measured osmolality causes an actual increase in "effective" osmolality. Solutes that are permeable across cell membranes such as urea, methanol, ethanol, isopropanol, and ethyleneglycol do not cause water movement—ie, they cause hypertonicity without cellular dehydration. Glucose in the insulinopenic state is not permeant across cell membranes and, by its presence in the extracellular fluid (ECF), causes water to move from cells to extracellular space, leading to cellular dehydration and lowering serum [Na^+]. This hyponatraemia can be viewed as "translocational" since the decrease in serum [Na^+] reflects, not a change in total body water (TBW), but a movement of water from intracellular to extracellular space. Hyperglycaemia accounts for 15% of hyponatraemia in inpatients. Serum [Na^+] falls by 1·6 mmol/L for every 5·6 mmol/L (100 mg/dL) increase in plasma glucose. Other substances causing translocational hyponatraemia are mannitol, maltose, and glycine (which is used as an irrigant solution during transurethral resection of the prostate and in endometrial surgery).[1]

Department of Medicine, University of Colorado School of Medicine, Denver Colorado, USA (S Kumar MD, T Berl MD)

Correspondence to: Dr Tomas Berl, Renal-C281, University of Colorado School of Medicine, 4200E 9th Ave, Denver, CO 80262, USA (e-mail Tomas.Berl@uchsc.edu)

Hypoosmolar hyponatraemia

Once preliminary evaluation reveals that the hyponatraemia is truly hypoosmolar, assessment of ECF volume allows patients to be classed as hypovolaemic, euvolaemic or hypervolaemic hyponatraemia (figure 2).

Underlying all hyponatraemic states is a limitation in urinary dilution. This is most commonly due to secretion of ADH despite serum hypoosmolality, the secretion being stimulated by non-osmotic mechanisms. Less commonly, diminished delivery of fluid to the distal nephron, due to reduced glomerular filtration rate (GFR) and/or an increase in proximal tubular fluid and sodium reabsorption, or a defect in the NaCl transport in the diluting segments of the nephron (thick ascending limb of the loop of Henle and distal tubule), limit urinary dilution.

Hyponatraemia with decreased TBNa^+ (hypovolaemic)

These patients have a deficit both in total body sodium (TBNa^+) and water (TBW), the sodium deficit exceeding the water deficit. The underlying mechanism is volume-contraction stimulated secretion of ADH with continued oral or parenteral hypotonic fluid intake. Measurement

Glossary and equation

ADH	Antidiuretic hormone (vasopressin)
AQP2	Gene for vasopressin-regulated water channel in collecting ducts
AVPR2	Arginine-vasopressin type-2 receptor gene
CDI	Central diabetes insipidus
ECF	Extracellular fluid
GFR	Glomerular filtration rate
[Na^+]	Concentration of sodium
NDI	Nephrogenic diabetes insipidus
NO	Nitric oxide
SIADH	Syndrome of inappropriate ADH secretion
TBNa^+	Total body sodium
TBW	Total body water
V_2	Vasopressin type 2 (receptor)

Equation

Osmolality $(2X[Na^+] + (\text{urea nitrogen [mg/dL]}) \div 2{\cdot}8) + (\text{glucose [mg/dL]} \div 18$

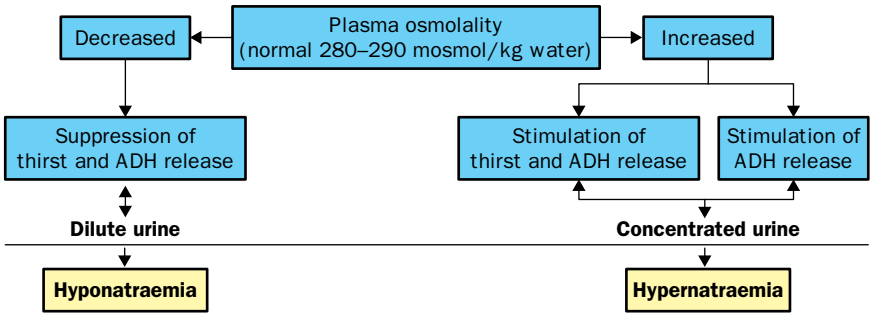

Figure 1: **Relation between plasma osmolality and hyponatraemia and hypernatraemia**
(Modified with permission from Halterman R, Berl T. Therapy of dysnatremic disorders. In: Brady H Wilcox C, eds. Therapy in nephrology and hypertension. Philadelphia: Saunders [in press].)

of urinary [Na^+] helps to differentiate renal and extrarenal sources of fluid loss (figure 2).

Gastrointestinal and third-space losses are associated with avid sodium retention as the kidney responds to volume contraction by conserving NaCl . Urinary [Na^+] is usually less than 10 mmol/L and the urine is hyperosmolar. In some patients with vomiting and metabolic alkalosis, bicarbonaturia occurs, and bicarbonate is a non-resabsorbable anion. This obligates cations to be excreted as well. The urinary [Na^+] in these situations may be greater than 20 mmol/L, despite severe volume depletion. The urinary chloride, however, is less than 10 mmol/L.

Diuretic use is one of the most common causes of hypovolaemic hyponatraemia associated with high urine [Na^+]. Hyponatraemia occurs almost exclusively with thiazide diuretics. Loop diuretics, by inhibiting NaCl reabsorption in the thick ascending limb of the loop of Henle, interfere with the generation of a hypertonic medullary interstitium and urinary concentration as well as dilution. Thiazide diuretics act exclusively in the distal tubule, interfering only with urinary dilution. Underweight elderly women appear to be more prone to this complication, which usually occurs within 14 days of the start of therapy.[2] Several mechanisms for diuretic-induced hyponatraemia have been postulated, including hypovolaemia-stimulated ADH release, interference with urinary dilution in the cortical diluting segment, and a potassium-depletion-mediated alteration in osmoreceptor sensitivity and thirst.

Salt-losing nephropathy occurs in some patients with advanced chronic renal disease who are unable to conserve sodium. This can be associated with medullary cystic disease, polycystic kidney disease, analgesic nephropathy, chronic pyelonephritis, and obstructive uropathy. Patients with proximal type II renal tubular acidosis exhibit renal sodium and potassium wastage despite only moderate renal insufficiency. In these patients, bicarbonaturia obligates urine sodium excretion.

Hyponatraemia with ECF volume contraction in the presence of a urinary [Na^+] higher than 20 mmol/L, especially if associated with a raised serum [K^+], urea, and creatinine, suggests mineralocorticoid deficiency. The decreased ECF volume, rather than deficiency of the hormone per se, provides the non-osmotic stimulus for ADH release.

In osmotic diuresis non-reabsorbable solutes obligate the renal excretion of Na^+ and this results in volume depletion. The continuing intake of hypotonic fluids leads to hypovolaemia and hyponatraemia. The urinary [Na^+] is typically greater than 20 mmol/L. In diabetes the sodium wasting is accentuated by ketonuria, which also causes obligatory Na^+ loss. β-hydroxybutyrate and acetoacetate also obligate urinary electrolyte losses and aggravate the renal sodium wasting seen in diabetic ketoacidosis, starvation, and alcoholic ketoacidosis.

Cerebral salt wasting is a rare syndrome described in patients with subarachnoid haemorrhage; it leads to renal salt wasting with volume contraction. The exact mechanism of the natriuresis is not known but one suggestion is that brain natriuretic peptide is released and causes increases in urine volume and sodium excretion.[3]

Hyponatraemia with increased TBNa^+ (hypervolaemic)

Here TBNa^+ is increased but TBW is increased even more, causing hyponatraemia. Clinical settings where this is seen are heart, liver, and kidney failure and nephrotic syndrome.

In congestive heart failure the fall in cardiac output, and frequently mean arterial pressure too, lead to non-osmotic release of ADH.[4] The enhanced renal effect of ADH is also reflected by the recent finding of up-regulation of AQP2, the vasopressin-regulated water channel in collecting ducts in rats with heart failure.[5] Hyponatraemia is further aggravated by the concomitant stimulation of the renin-angiotensin system and catecholamine production. These humoral factors, by decreasing GFR and enhancing tubular Na^+ reabsorption, decrease distal fluid delivery, further contributing to the hyponatraemia. The degree of neurohumoral activation correlates with the clinical severity of left-ventricular dysfunction[6] and the degree of hyponatraemia is also prognostic in these patients.[7]

Patients with hepatic insufficiency and cirrhosis share pathophysiological processes with heart-failure patients. The hallmark of cirrhosis is peripheral and splanchnic vasodilation, leading to renal Na^+ retention. However, these patients have increased cardiac output, mostly because of multiple arteriovenous fistulae in alimentary tract and skin. The vasodilation may be mediated by nitric oxide (NO).[8] Inhibition of NO corrects the arterial hyporesponsiveness to vasoconstrictors[9] and the abnormal water excretion in cirrhotic rats.[8,9] As the cirrhosis becomes more severe (no ascites, ascites, and ascites with hepatorenal syndrome), there is a progressive increase in plasma renin, norepinephrine, and ADH activity. Mean arterial pressure, water excretion, and serum [Na^+] fall. Hyponatraemia is a strong indicator of poor long-term prognosis in these patients. ADH is central to the pathogenesis of the water-excretory defect since cirrhotic rats lacking the hormone do not develop hyponatraemia. Gene expression of ADH-regulated AQP2 had also been shown to be increased in cirrhotic rats.[10]

Patients with nephrotic syndrome, especially those with normal renal function, have intravascular volume contraction. This causes non-osmotic ADH release

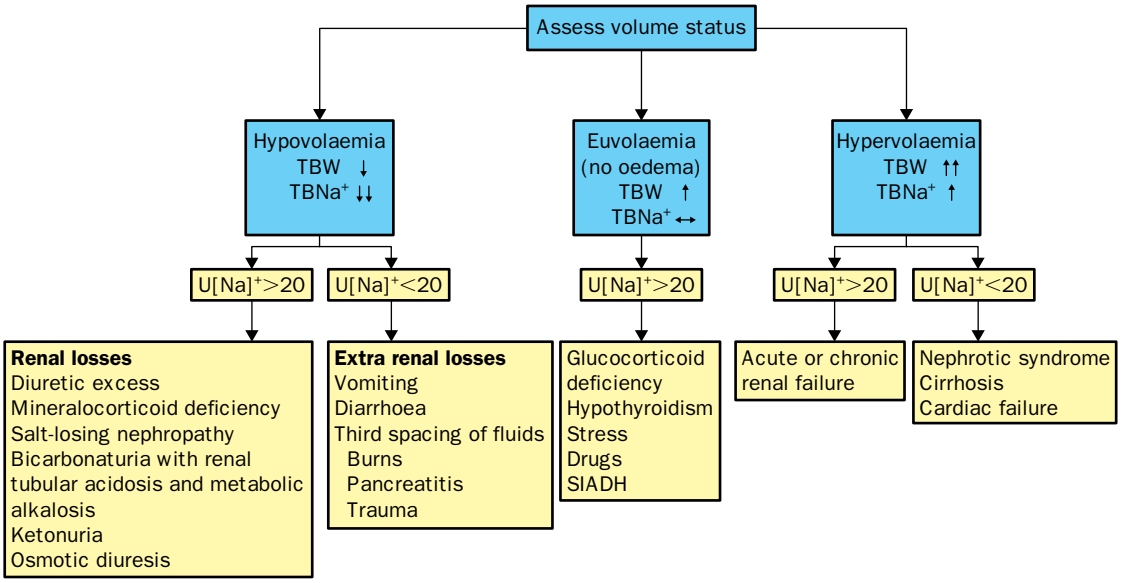

Figure 2: **Diagnostic algorithm for hyponatraemia**
(Modified with permission from Halterman R, Berl T. Therapy of dysnatremic disorders. In: Brady H. Wilcox C, eds. Therapy in nephrology and hypertension. Philadelphia: Saunders, [in print].)

followed by impaired water excretion. In contrast with other water-retaining disorders, in which enhanced AQP2 expression has been found, in rat models of nephrotic syndrome expression of this protein in the renal collecting ducts is decreased.[11] In advanced chronic renal insufficiency, acute or chronic, a profound increase in fractional excretion of sodium keeps the patient in normal salt balance. Oedema usually develops when the sodium ingested exceeds the kidney's capacity to excrete this load. The narrow range of water handling by the diseased kidney is also due in large part to the smaller volumes of fluid that are filtered daily. Even with total suppression of ADH, a limited volume of water is excreted. If daily water intake exceeds this threshold, a positive water balance ensues and hyponatraemia results.

Hyponatraemia with normal TBNa⁺ (euvolaemic)

Euvolaemic hyponatraemia is the most commonly encountered dysnatraemia in hospital patients. No physical signs of increased TBNa⁺ are detected; they may have slight excess of volume but they are not oedematous. Likely clinical causes here include the following.

Glucocorticoid deficiency causes the impaired water excretion of primary and secondary adrenal insufficiency. Raised levels of ADH have been demonstrated even in the absence of volume contraction. ADH-independent factors are also involved since glucocorticoid deficiency is associated with impaired renal haemodynamics.[12] Glucocorticoid deficiency may even increase water permeability in the collecting tubules in the absence of ADH.

Hypothyroidism with myxoedema is associated with hyponatraemia. When ADH is measured in response to water loading some investigators have found increased ADH levels while others have demonstrated neither an increase in ADH nor up-regulation in hypothalamic ADH gene expression in hypothyroid rats.[13] Since cardiac output and GFR are often reduced in severe hypothyroidism, both ADH-mediated and intrarenal mechanisms are probably operating here, with variable contributions in different patients.

Patients with acute psychosis secondary to schizophrenia have a propensity to hyponatraemia. The mechanism may be multifactorial, involving increased thirst perception (leading to polydipsia) a mild defect in osmoregulation that causes ADH to be secreted at lower osmolality, and enhanced renal response to ADH.[14] Antipsychotic drugs may have a role too (see below).

Hyponatraemia is common after surgery and is characterised by high levels of circulating ADH. Infusion of excessive amounts of electrolyte-free water (hypotonic saline or 5% dextrose in water) is to blame here. However, in a recent report it was postulated that hyponatraemia can develop postoperatively despite near-isotonic saline infusion within 24 h of induction of anaesthesia. This occurred mostly by generation of electrolyte-free water by the kidney, much of which was retained because of persistent ADH.16

Drug-induced hyponatraemia is mediated by ADH analogues such as desmopressin or by ADH-release agonists, or agents potentiating the

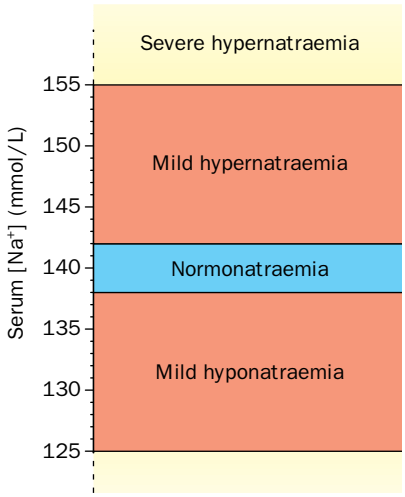

Figure 3: **Normal range for serum [Na⁺]**
Cut-offs are

Panel 1: **Diagnostic criteria for SIADH***

Essential
ECF effective osmolality below 270 mosmol/kg water
Inappropriate urinary concentration (>100 mosmol/kg)
Clinical euvolaemia
Increased urinary [Na^+] while on a normal salt and water intake
Absence of adrenal, thyroid, pituitary or renal insufficiency or diuretic use

Supplemental
Abnormal water load test (inability to excrete at least 90% of 20 mL/kg water load in 4 h and/or failure to dilute urinary osmolality to below 100 mosmol/kg)
Plasma ADH level inappropriately raised relative to plasma osmolality
No significant correction of plasma [Na^+] with volume expansion but improvement after fluid restriction

*Modified from Verbalis, JG. In Schrier RW, Gottschalk CW, eds. Diseases of the kidney 6th edn. Boston: Little Brown, 1997: 2400.

action of ADH. In other instances the mechanism is not known. Drugs causing hyponatraemia include psychoactive agents (fluoxetine, sertraline, thiothixene, haloperidol, and amitriptyline and the amphetamine-related abuse substance "ecstasy"), certain anti-cancer agents (vincristine, vinblastine, and high-dose cyclophosphamide), and carbamazepine, bromocriptine, lorcainide, chlorpropamide, and intravenous vasopressin.

Syndrome of inappropriate ADH secretion (SIADH) is the commonest cause of hyponatraemia in hospital patients yet it is a diagnosis of exclusion. Defective osmoregulation of ADH suppresses plasma ADH concentrations, leading to a urinary concentration that is inappropriate to the degree of hypotonicity (panel 1). The commonest causes are malignancies, pulmonary disease and CNS disorders. CNS bleeds, tumours, infections, and trauma cause SIADH by releasing excess ADH. In cancers (usually small-cell lung, duodenum, and pancreas and olfactory neuroblastoma) there is ectopic ADH production—indeed these tissues can increase ADH secretion in response to osmotic stimulation in vitro.[17]

HIV infection is now leading to a new category of patient with SIADH. Up to 35% of AIDS patients admitted to hospital will have SIADH, and *Pneumocystis carinii* pneumonia, CNS infections, and malignancies are the likely causes.

In one-third of SIADH patients ADH release varies appropriately with the serum [Na^+] but begins at an abnormally low threshold of serum osmolality, suggesting a "resetting of the osmostat". Any ingestion of free water above this threshold would lead to its excretion, maintaining the serum [Na^+].[18] Since hyponatramia can develop as a consequence of both water retention and solute losses the contribution of each to the hyponatraemia of SIADH has been controversial. A natriuresis occurs in the setting of water retention, probably in an effort to restore volume. Thus, while solute depletion contributes to the hyponatraemia most clinically significant hypoosmolar states are due to an increase in TBW.[19] Patients with SIADH cannot excrete a solute-free urine so ingested water is retained, giving rise to moderate non-oedematous volume expansion and dilutional hyponatraemia. However, hyponatraemia is limited by "vasopressin escape". Animal experiments show that, despite simultaneous water and ADH infusion, urine flow rises and urine osmolality decreases. This escape from antidiuresis is caused by marked and selective decrease in the expression of the arginine-vasopressin regulated water channel AQP2, without a concomitant fall in the expression of other water channels.[20]

Management of hyponatraemia

Symptoms depend on the level of hyponatraemia (figure 3) and the rate at which it develops. Above 125 mmol/L symptoms are rare; in the range 125–130 mmol/L, the predominant symptoms are gastrointestinal; neuropsychiatric symptoms dominate once the serum sodium falls below 125 mmol/L. The case fatality rate in untreated severe symptomatic hyponatraemia is high and neurological symptoms in any hyponatraemic patient call for immediate treatment. Signs and symptoms of hyponatraemia are: nausea and vomiting, muscular weakness, headache, lethargy, reversible ataxia, and psychosis and, in severe cerebral oedema, increased intracerebral pressure, seizures, coma, tentorial herniation, and respiratory depression. It is the presence of symptoms and the duration of the hyponatraemia that guide the treatment strategy. Hyponatraemia developing within 48 h carries a greater risk of permanent neurological sequelae from cerebral oedema unless the serum [Na^+] is corrected. However, patients with chronic hyponatraemia are at risk of osmotic demyelination if the correction is excessive or too rapid.[21]

Cerebral adaptation to hypotonicity

Decreases in extracellular osmolality cause movement of water into cells, increasing intracellular volume and causing tissue oedema. Oedema within the cranium raises intracranial pressure, leading to neurological syndromes. To prevent this, a volume-regulatory adaptation comes into play. Early in the course of hyponatraemia, within 1–3 h, cerebral extracellular volume decreases by movement of fluid into the CSF, which is then shunted into the systemic circulation. Thereafter, the brain adapts by losing cellular potassium and organic solutes, which tend to lower the osmolality without substantial gain of water. If hyponatraemia persists, other organic osmolytes such as phosphocreatine, myoinositol, and aminoacids (eg, glutamine and taurine) are lost.[22] The loss of solutes greatly decreases cerebral swelling and it is patients in whom this adaptive response fails who are prone to severe cerebral oedema when they become hyponatraemic (panel 2). Conversely, patients who have had the adaptive response are at risk of osmotic

Panel 2: **Hyponatraemic patients at risk for neurological complications***

Acute cerebral oedema
Postoperative menstruating females
Elderly women on thiazides
Children
Psychiatric polydipsic patients
Hypoxaemic patients

Osmotic demyelination syndrome
Alcoholics
Malnourished patients
Hypokalaemic patients
Burn victims
Elderly women on thiazide diuretics

*Adapted from SM Lauriat, T Berl: The Hyponatremic patients: practical focus on therapy. *J Am Soc Nephrol* 1997; **8:** 1599–1607.

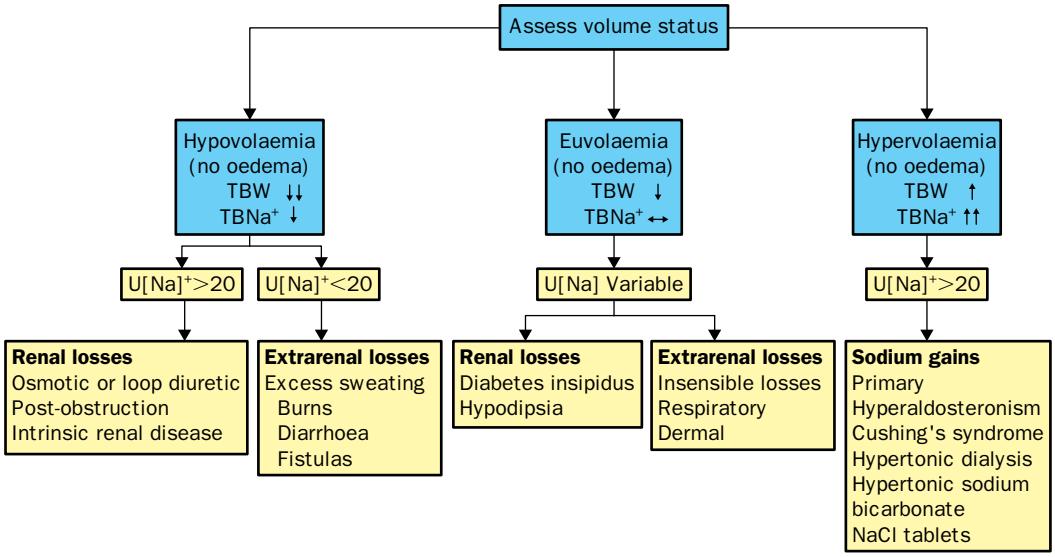

Figure 4: Diagnostic algorithm for hypernatraemia
(Modified with permission from Halterman R, Berl T. Therapy of dysnatremic disorders. In: Brady H. Wilcox C, eds. Therapy in nephrology and hypertension. Philadelphia: Saunders [in press].)

demyelination syndrome if the hyponatraemia is excessively and/or too rapidly corrected. The increase in osmolality seems to cause excessive cerebral water loss in previously adapted brains.

Acute, symptomatic hyponatraemia

Acute symptomatic hyponatraemia, developing in less than 48 h, is almost inevitable in hospital patients receiving hypotonic fluids. Treatment should be prompt because the risk of acute cerebral oedema far exceeds the risk of osmotic demyelination. The aim should be to raise the serum [Na^+] by 2 mmol/L L^{-1} h^{-1} until symptoms resolve. Complete correction is unnecessary, although it is not unsafe. Hypertonic saline (3% NaCl) is infused at the rate of 1–2 mL kg^{-1} h^{-1} and a loop diuretic, such as furosemide, enhances free-water excretion and hastens the return to a normal serum [Na^+]. If there are severe neurological symptoms (seizures, obtundation, or coma) 3% NaCl may be infused at 4–6 mL kg^{-1} h^{-1}. Even 29·2% NaCl (50 mL) has been used safely.[23] Serum electrolytes should be carefully monitored.

Chronic, symptomatic hyponatraemia

If hyponatraemia has been present for more than 48 h or the duration is unknown, correction needs to be handled carefully.[24] Whether it is the rate of correction of hyponatraemia or the magnitude that predisposes to osmotic demyelination is unknown but in practice it is difficult to dissociate the two because a rapid correction rate usually means a greater correction over a given period of time. Because cerebral water is increased by only about 10% in severe chronic hyponatraemia the key is to increase the serum [Na^+] promptly by 10% or about 10 mmol/L and then, after that initial correction, not to exceed a correction rate of 1·0–1·5 mmol L^{-1} h^{-1} or 15 mmol/L in 24 h. Monitoring needs to include the rate and electrolyte content of infused fluids and of urine.

For example, in a patient of 50 kg body weight (total body water [TBW] 30 kg], to calculate the nett water loss needed to raise the serum [Na^+] from 110 to 120 mmol/L, multiply current serum [Na^+] by current TBW and equate the product with that of desired serum [Na^+] and new TBW. Here the new TBW is (110×30)÷120 or 27·5 L. Thus the electrolyte-free water loss needed is 2·5 L. Since correction of serum [Na^+] should not exceed 1 mmol/L^{-1} h^{-1} the rate of loss of water is 250 mL/h. To do this, give furosemide, monitor urine output, and replace any Na^+ and K^{+-} and excess free water lost in the urine.

Panel 3: **Management of chronic asymptomatic hyponatraemia**

Treatment	Mechanism	Daily dose	Advantages	Limitations
Fluid restriction	Decreases free water	Variable	Effective and inexpensive	Non-compliance
Pharmacological inhibition of ADH				
Lithium	Inhibits renal response to ADH	900–1200 mg	Unrestricted water intake	Polyuria, narrow therapeutic range, neurotoxicity
Demeclocycline	Inhibits renal response to ADH	1200 mg, followed by 300–900 mg	Effective; unrestricted water intake	Neurotoxicity, polyuria, photosensitivity, nephrotoxicity
V_2-receptor antagonist	Antagonises vasopressin			(Ongoing trials)
Increased solute intake				
Furosemide	Increases free-water clearance	Titrate to optimal dose (+ 2–3 g NaCl)	Effective	Ototoxicity, K^+ depletion
Urea	Osmotic diuresis	30–60 g	Effective; unrestricted water intake	Polyuria, unpalatable, GI symptoms

Panel 4: **Water-deprivation test**

Diagnosis	Urinary osmolality with water deprivation (mosmol/kg H_2O)	Plasma AVP after dehydration (pg/mL)	Increase in urinary osmolality with exogenous AVP
Normal	>800	>2	Little or none
Complete CDI	<300	Undetectable	Substantial
Partial CDI	300–800	<1·5	>10%
NDI	<300–500	>5	Little or none
Primary polydipsia	>500	<5	Little or none

Water intake is restricted until patient loses 3–5% of body weight or until three consecutive hourly urinary osmolalities are within 10% of each other. Care needed lest patient becomes excessively dehydrated. Aqueous arginine-vasopressin (5 units) is given, and urinary osmolality is measured after 60 min. Expected responses are given.
Source: D Lanese, I Teitelbaum, Hypernatremia. In: H R Jacobson, G E Strker, and S Klahr eds., The principles and practice of nephrology 2nd ed. St Louis: Mosby, 1995: 895.

Chronic, asymptomatic hyponatraemia

Here no immediate therapy is required and the underlying disorder can be sought and dealt with (eg, endocrine disorders, drugs, and SIADH). There is no urgency to correct the electrolyte disorder, and this can be tackled in several ways (panel 3).

Fluid restriction is the easy and usually successful option if patient complies. It involves calculation of the fluid restriction that will maintain a specific serum [Na^+]. The daily osmolar load divided by the minimal urinary osmolality (a function of the severity of the diluting disorder) determine a patient's maximal urine volume. On a normal North American diet, the daily osmolar load is about 10 mosmol/kg body weight and in a healthy person the minimum urinary osmolality (given no circulating ADH) can be as low as 50 mosmol/kg. Thus, the daily urine volume can be as high as 14 L. If the patient has SIADH and the urinary osmolality cannot be lowered below 500 mosmol/kg, the same osmolar load of 700 mosmol per day allows for only 1·4 L of urine. Thus, if the patient drinks more than 1·4 L per day, the serum [Na^+] will fall.

Lithium was the first drug used to antagonise ADH action in hyponatraemic disorders but it is neurotoxic and its effects are unpredictable so demeclocycline is now the agent of choice.[25] This drug inhibits the formation and action of cAMP in the renal collecting duct. The onset of action is 3–6 days after beginning treatment. The dose needs to be decreased to the lowest level that keeps the serum [Na^+] within the desired range, with unrestricted water intake, and the dose is usually 300–900 mg daily. The drug should be given 1–2 h after meals, and calcium, aluminium, and magnesium containing antacids should be avoided. However, the polyuria tends to make patients non-compliant. Skin photosensitivity may occur, and in children tooth or bone abnormalities may result. Nephrotoxicity also limits its use, especially in patients with underlying liver disease, in whom the hepatic metabolism of demeclocycline may be impaired.

Specific antagonists of ADH action on the collecting duct may soon supplement these agents. OPC-31260 is an orally active non-peptide vasopressin type 2(V_2)-receptor antagonist with encouraging results in animal models of hyponatraemia but this "aquaretic" is not yet clinically available.[26]

Since urine flow can be significantly increased by obligating the excretion of solutes, thereby allowing a greater intake of water, manoeuvres to increase solute excretion have been used. A loop diuretic when combined with high sodium intake (2–3 g additional NaCl) is effective.[27] A single diuretic dose (40 mg furosemide) is usually sufficient. The dose should be doubled if the diuresis induced in the first 8 h is less than 60% of the total daily urine output. Administration of urea, raising the solute load, increases urine flow by causing an osmotic diuresis.[24] This permits a more liberal water intake without worsening the hyponatraemia and without altering urinary concentration. The dose is usually 30–60 g urea daily. The major limitation is gastrointestinal distress and unpalatability.

Hypovolaemic and hypervolaemic hyponatraemia

Symptoms directly relatd to the hyponatraemia are unusual in hypovolaemic hyponatraemia since loss of both sodium and water limits osmotic shifts in the brain. Restoration of ECF volume with crystalloids or colloids will interrupt the non-osmotic release of ADH.

The treatment of hyponatraemia in hypervolaemic states is more difficult because it requires attention to the underlying disorder, be it heart failure or chronic liver disease. In congestive heart failure, besides sodium restriction, water restriction is critical. Refractory patients may be treated with a combination of an angiotensin-converting-enzyme inhibitor and a diuretic. The increase in cardiac output that follows decreases the neurohumoral mediated processes that limit water excretion. Loop diuretics diminish the action of ADH on the collecting tubules, thereby decreasing water reabsorption. Demeclocycline also has a place in patients with chronic congestive heart failure and hyponatraemia.[25] Thiazides should be avoided. They impair urinary dilution and may worsen hyponatraemia. Water and salt restriction are the mainstay of therapy in cirrhotic patients too. Loop diuretics help in excretion of free water, once a negative sodium balance has been achieved. In both disorders V_2 receptor antagonists are under investigation.

Hypernatraemia

The renal-concentrating mechanism is the first defence against water depletion and hyperosmolality. If the urine is inadequately concentrated or if inordinate amounts of hypotonic fluid are lost and/or not replenished, hypernatraemia results (figure 1). Thirst is an important back-up defence. Patients fall into three broad categories, depending on the TBNa^+ (figure 4).

Hypernatraemia with low TBNa^+

These patients sustain losses of both sodium and water, but with a relatively greater loss of water. They manifest signs of hypovolaemia such as orthostatic hypotension, tachycardia, flat neck veins, poor skin turgor, dry mucous membranes, and sometimes altered mental status. The causes reflect primarily hypotonic water losses from the kidneys and/or the gastrointestinal tract. In the latter case the urinary [Na^+] will be low.

Hypernatraemia with increased TBNa⁺

This is the least common form. It results from hypertonic solutions such as 3% NaCl, intra-amniotic instillation for therapeutic abortion, and the administration $NaHCO_3$ for treatment of metabolic acidosis, hyperkalaemia, and cardiorespiratory arrest. It may also happen accidentally in dialysis against a high-sodium dialysate or from the consumption of salt tablets.

Hypernatraemia with normal TBNa⁺

Most patients with hypernatraemia secondary to water loss appear euvolaemic with normal TBNa⁺ because loss of water without sodium does not lead to overt volume contraction. Water loss per se need not culminate in hypernatraemia unless it is unaccompanied by water intake. Since such hypodipsia is uncommon, hypernatraemia usually supervenes only in those who have no access to water or who have a neurological deficit that does not allow them to see it (eg, the very young and very old). Extrarenal water loss occurs from the skin and respiratory tract in febrile or other hypermetabolic states. Urine osmolality is very high, reflecting an intact osmoreceptor-ADH-renal response. Thus the defence against hyperosmolality requires both stimulation of thirst and the ability to respond by drinking water. The urine [Na^+] varies with the intake.

The renal losses of water that lead to euvolaemic hypernatraemia are a consequence of either a defect in vasopressin production and/or release (central diabetes insipidus) or failure of the collecting duct to respond to the hormone (nephrogenic). Central and nephrogenic diabetes insipidus, which are part of euvolaemic hypernatraemia, nevertheless deserve separate consideration.

Diabetes insipidus

Central diabetes insipidus

In both central (CDI) and nephrogenic (NDI) diabetes insipidus the patient presents with polyuria and polydipsia. The two entities can be differentiated by measurement of vasopressin and the response to water deprivation followed by vasopressin (panel 4). Separation of primary polydipsia (compulsive water drinking) from CDI is on clinical features. CDI usually has an abrupt onset whereas the compulsive water drinker tends to give a vague history of onset. Patients with CDI have a constant need for water intake while water intake and urine output vary widely in compusive water drinkers. Nocturia, common in CDI, is unusual in compulsive water drinking. Also, patients with CDI prefer cold water. A plasma osmolality of above 295 mosmol/kg suggests CDI; below 270 mosmol/kg suggests compulsive water drinking.

About 50% of cases of CDI are idiopathic; the rest are caused by tumours (metastatic from breast, craniopharyngioma, pinealoma), trauma, cysts, histiocytosis, granuloma (tuberculosis, sarcoid), aneurysms, meningitis, encephalitis, Guillain-Barré syndrome. An inherited autosomal dominant form caused by point mutations in the vasopressin gene has been described,[28] as has a rare autosomal recessive form associated with diabetes mellitus, optic atrophy, and deafness (Wolfram syndrome) linked to a defect in chromosome 4 and involving abnormalities in mitochondrial DNA.[29]

Panel 5: **Treatment of CDI**

CDI	Drug	Dose
Complete	DDAVP	10–20 µg intranasally every 12–24 h
Partial	Vasopressin tannate	2–5 U intramuscularly every 24–48 h
	Aqueous vasopressin	5–10 U every 4–6 h
	Chlorpropamide	250–500 mg daily
	Clofibrate	500 mg three or four times daily
	Carbamazepine	400–600 mg daily

CDI may be treated with hormone replacement or drugs (panel 5). In acute settings, where renal water losses are extensive, aqueous vasopressin has a short duration of action that allows for careful monitoring and avoids complications such as water intoxication. This agent should be used with caution in patients with coronary artery and peripheral vascular disease because it may cause vascular spasm and prolonged constriction. In chronic CDI desmopressin acetate is the agent of choice. It has a long half-life, does not have significant vasoconstrictive effects, can be administered intranasally every 12–24 h, is usually tolerated well, is safe in pregnancy, and is not degraded by circulating vasopressinase. In partial diabetes insipidus, drugs that potentiate the release of ADH may be used (panel 5) but they need to be combined with hormonal therapy, decreased solute intake, or a diuretic.

Congenital NDI

One form of congenital NDI clinically expresses itself fully only in males and subclinically in females, suggesting X-linked dominant inheritance with variable penetrance in the female.[30] The V_2 receptor is encoded on the X chromosome. 87 putative disease-causing mutations in the *AVPR2* gene in 106 presumably unrelated families with X-linked have now been reported.[30] The autosomal recessive form of NDI is caused by mutation in *AQP2*.[31]

The diagnosis of congenital NDI is usually made when an infant presents with hypoosmolar urine in the face of severe dehydration, hypernatraemia, vomiting, and fever. Unlike some females, with variable penetrance, male patients do not concentrate their urine despite severe dehydration and ADH administration. These patients usually have impaired growth and mental retardation. Hydronephrosis is not unusual.

Neither pharmacological nor hormonal manoeuvres are effective. Since the excretion of solute requires further water losses, rehydration therapy should include hypotonic (2·5%) rather than isotonic (5%) glucose. The solute intake should be kept low (low-sodium diet). Thiazide diuretics decrease urine output by extracellular volume contraction, thereby enhancing proximal tubular

Panel 6: **Groups at increased risk of severe hypernatraemia**

Elderly patients or infants
Inpatients receiving
- Hypertonic infusions
- Tube feedings
- Osmotic diuretics
- Lactulose
- Mechanical ventilation

Altered mental status
Uncontrolled diabetes mellitus
Underlying polyuric disorders

sodium and water reabsorption; and the addition of amiloride to hydrochlorothiazide has been found to be useful too.

Nonsteroidal antiinflammatory agents such as tolmentin, are well tolerated. A change in urine osmolality from 50 to 200 mosmol/kg water is very important because it translates into a substantial reduction in urine output, from 10–12 down to 3–4 L daily.

Acquired NDI

The acquired form of NDI is more common and it is rarely as severe as congenital NDI. In most patients, the ability to elaborate a maximally concentrated urine is impaired, but urinary concentration mechanisms are partly preserved and daily urinary volumes are less than 3 L, in contrast to congenital NDI or CDI or compulsive water drinking. The causes are renal disease, electrolyte disorders, and drugs.

Most patients with advancing chronic renal failure have a defect in urinary concentrating ability, and advanced chronic renal insufficiency of any cause can lead to resistance to ADH associated with hypotonic urine.[32] The mechanism for the concentrating defect is multifactorial. Disruption of the inner medullary structures or local alterations in medullary blood flow, as is seen in tubulointerstitial diseases, sickle-cell disease, and analgesic nephropathy, may be causative; impairment in thick-ascending-limb transport of NaCl may also have a role; and in a rat model ADH resistance has been associated selective down-regulation of the V_2-receptor in the inner medullary tubular membranes.[33] In caring for patients with chronic renal failure, it is important to recognise that some fluid intake is necessary, in most patients who still make urine, to achieve daily osmolar clearance.

Hypokalaemia causes an abnormality in urinary concentration by stimulating water intake and lowering interstitial tonicity, which relates to a decrease in thick-ascending-limb NaCl reabsorption. Hypokalaemia also affects intracellular cAMP accumulation and decreases ADH sensitive *AQP2* activity.[34] Hypokalaemia (eg, from diarrhoea, chronic diuretic use, or primary aldosteronism) may also be associated with a usually reversible defect in urinary concentration. Hypercalcaemia results in an abnormality in urinary concentration.

Ethanol and phenytoin have a central effect on ADH release while the concentrating defect in patients taking amphotericin and foscarnet may be related to these drugs' renal toxicity Demeclocycline reduces adenylate cyclase activity in the renal medulla, decreasing ADH activity on the collecting system and so elaborating a dilute urine. Up to 50% of patients on the drug lithium develop NDI, probably via down-regulation of *AQP2*.[35] The concentrating defect may persist even when lithium is discontinued.

Patients with sickle cell disease or trait often have a urinary concentrating defect. The "sickled" red blood cells occlude the vasa recta and cause papillary damage, and the resultant medullary ischaemia impairs NaCl transport in the ascending limb. In long-standing sickle-cell disease medullary infarcts occur, and the concentrating defects become irreversible. Extensive water intake also impairs maximal urinary concentration because of a decrease in medullary interstitial tonicity. A much reduced intake of NaCl and protein does this too since sodium and urea (product of protein metabolism) account for most of the interstitial tonicity.[36] Gestational diabetes insipidus is typically vasopressin unresponsive. The cause here is a rise in circulating vasopressinase, which is produced by the placenta.[37] Desmopressin acetate is usually effective in decreasing urine flow because it is not degraded by this enzyme.

Panel 7: **Management options for patients with hypernatraemia***

Hypovolaemic hypernatraemia

Correction of volume deficit

- Isotonic saline until hypovolaemia improves
- Treat causes of volume losses (insulin, relief of obstruction, removal of osmotic diuretics)

Correction of water deficit

- Calculate deficit
- 0·45% saline, 5% dextrose, or oral water replacing deficit and ongoing losses

Euvolaemic hypernatraemia

Correction of water deficit

- Calculate deficit
- 0·45% saline, 5% dextrose or oral water to replace the deficit and ongoing losses
- In CDI with severe losses, aqueous vasopressin
- Monitor serum [Na^+] to avoid water intoxication

Long-term therapy

- CDI (see panel 5)
- NDI

Correctiion of [$K]^+$ and [$Ca]^{2+}$

Removal of offending drugs

Low-sodium diet

Thiazide diuretics

Amiloride (for lithium-induced NDI)

Hypervolaeic hypernatraemia

Removal of sodium

- Discontinue offending agents
- Furosemide
- Haemodialysis as needed for renal failure

*Modified with permission from Halterman R, Berl T. Therapy of dysnatremic disorders. In: Brady H; Wilcox C, eds. Theapy in nephrology and hypertension.. Philadelphia: Saunders (in press).

Signs and symptoms of hypernatraemia

Hypernatramia (panel 6) is far less common than hyponatraemia. It always reflects a hyperosmolar state so CNS symptoms are prominent. The signs and symptoms are: altered mental status, lethargy, irritability, restlessness, seizures (usually seen in children), muscle twitching, hyperreflexia, and spasticity; fever; nausea or vomiting; laboured respiration; and intense thirst. Morbidity and mortality of patients with acute hypernatraemia are high in children and two-thirds of survivors have neurological sequelae.[38] In contrast, mortality in chronic hypernatraemia is 10%. In adults, a serum [Na^+] above 160 mmol/L is associated with a 75% mortality, while in chronic hypernatraemia mortality is

about 60%. Hypernatraemia, in adults, occurs in the setting of serious disease, so the high mortality figures may reflect the underlying disease rather than the hypernatraemia per se.

Management of hypernatraemia

The primary goal in the management of hypernatraemia is restoration of serum tonicity (panel 7). The treatment regimen depends upon the volume status. The following guidelines should be helpful.

Hypovolaemic hypernatraemia

Here there is a low $TBNa^+$ and orthostatic hypertension, and isotonic saline should be given until systemic haemodynamics are stabilised. Thereafter, fluid management generally involves 0·45% NaCl or 5% dextrose solution to correct the water deficit.

Hypervolaemic hypernatraemia

The goal for these patients is to remove the excess Na^+ which is achieved with diuretics along with 5% dextrose. If there is renal impairment, dialysis may be needed.

Euvolaemic hypernatraemia

In this group of patients water losses far exceed solute losses, and the mainstay of therapy is 5% dextrose. To correct the hypernatraemia appropriately the TBW deficit must be estimated. This is calculated on the basis of the serum [Na^+] and on the assumption that 60% of the body weight is water.

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