REVIEW ARTICLE

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Diagnosis and management of hyponatraemia in hospitalised patients

Editor's Choice

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None.

SUMMARY

Hyponatraemia is a commonly encountered electrolyte abnormality in hospitalised patients and is associated with significant morbidity and mortality. The fact that most cases of hyponatraemia are the result of water imbalance rather than sodium imbalance underscores the role of antidiuretic hormone (ADH) in the pathophysiology. Hyponatraemia can be classified according to the measured plasma osmolality as isotonic, hypertonic or hypotonic. Hyponatraemia with a normal plasma osmolality usually indicates pseudohyponatraemia, while hyponatraemia because of a high plasma osmolality is typically caused by hyperglycaemia. After excluding isotonic and hypertonic causes, hypotonic hyponatraemia is further classified according to the volume status of the patient as hypovolaemic, hypervolaemic or euvolaemic. Hypovolaemic hyponatraemia is accompanied by extracellular fluid (ECF) volume deficit, while hypervolaemic hyponatraemia manifests with ECF volume expansion. The syndrome of inappropriate ADH (SIADH) should be suspected in any patient with euvolaemic hyponatraemia with a urine osmolality above 100 mOsm/kg and urine sodium concentration above 40 mEq/l. In the management of any hyponatraemia regardless of the patient's volume status, it is advised to restrict free water and hypotonic fluid intake. Hypertonic saline and vasopressin antagonists can be used to correct symptomatic hyponatraemia. The rate of correction is dependent upon the duration, degree of hyponatraemia and the presence or absence of symptoms. Symptomatic acute hyponatraemia (< 48 h) is a medical emergency requiring rapid correction to prevent the worsening of brain oedema. In asymptomatic patients with chronic hyponatraemia (> 48 h or unknown duration), fluid restriction and close monitoring alone are sufficient, while a slow correction by 0.5 mEq/l/h may be attempted in symptomatic patients. Excessive rapid correction should be avoided in both acute and chronic hyponatraemia, because it can lead to irreversible neurological complications including central osmotic demyelination.

Review Criteria

The relevant manuscripts were identified through a MEDLINE search of the English literature. The key phrase used was hyponatraemia. The literature search was limited to core clinical journals that have accessible full texts. This literature along with the authors' clinical experience was used to construct practical suggestions.

Message for the Clinic

Hyponatraemia is the clinical manifestation of a wide variety of diseases and is an indicator of poor clinical prognosis. As aggressive therapy of hyponatraemia can be harmful, clinicians should be familiar with the diagnosis and management of this disorder. Laboratory assessment should include plasma osmolality, urine osmolality, urine sodium and tests of thyroid and adrenal function. The recently developed vasopressin antagonists represent a novel and an attractive method of management.

Introduction

Hyponatraemia is a commonly encountered electrolyte abnormality in hospitalised patients with a daily incidence and prevalence rates of 0.97% and 2.48% respectively (1). It occurs in one out of 65 US admissions and adds significant costs (2). It is also associated with 60-fold increase in morbidity and mortality compared with patients without documented hyponatraemia (1,2).

Most cases of hyponatraemia are the result of water imbalance rather than sodium imbalance. The aetiology of most cases of hyponatraemia can be deduced from the history, physical examination and basic laboratory tests. As aggressive or inappropriate therapy of hyponatraemia can be more harmful than the condition itself, clinicians should be familiar with the diagnosis and management of various forms of hyponatraemia.

In this communication, the physiology of sodium and fluid balance will be reviewed, the differential diagnosis of hyponatraemia will be discussed and a rational approach to the management will be suggested.

Basic principles of sodium balance

Plasma sodium concentrations normally average 140 mEq/l or 140 mmol/l (3). Sodium is the principal osmole, essential for maintaining extracellular fluid (ECF) volume and for the regulation of blood

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pressure and osmotic equilibrium. Sodium is also the principal determinant of the effective circulating volume (ECV), that is, the arterial blood volume perfusing the tissues.

The ECF sodium is maintained by the action of Na^+/K^+-ATPase. Unlike water that freely crosses cell membranes to maintain isotonicity between the intracellular fluid (ICF) and ECF, sodium cannot freely cross the cell membrane and requires energy dependent pumps to be transported across the cell membranes.

The plasma sodium concentrations are dependent on multiple factors including sodium intake, osmolality and tonicity of plasma, the renin angiotensin system (RAA), total body potassium and water. The following equation defines the relationship between plasma Na^+ concentration and the total body content of sodium, potassium and water (TBW) (4).

$$\text{Plasma } Na^+ = \text{total body } Na^+ + \text{total body } K^+/\text{total body water}$$

The plasma osmolality is primarily determined by the concentration of sodium salts with minor contributions from glucose and blood urea nitrogen (BUN) (5) as shown in the following equation:

$$\text{Plasma osmolality} = (2 \times [Na^+]) + ([\text{glucose}]/18) + (\text{BUN}/2.8)$$

The $[Na^+]$ is multiplied by two to account for the accompanying anions (mostly chloride and bicarbonate) that provide electroneutrality. The corrections in the glucose concentration and BUN are to convert mg/dl into mmol/l. As urea is lipid-soluble and equilibrates across the cell membranes, it is an ineffective osmole and does not contribute to fluid distribution, and therefore it is omitted from calculation of effective plasma osmolality as follows (6):

$$\text{Effective plasma osmolality} = (2 \times [Na^+]) + ([\text{glucose}]/18)$$

Plasma osmolality normally varies between 280 and 290 mOsm/l. A discrepancy between the measured and calculated osmolality is referred to as an osmolal gap (7). Significant osmolal gaps indicate a high concentration of osmotically active molecules in plasma such as ethanol, mannitol, methanol, ethylene glycol or isopropyl alcohol (8).

Average sodium intake in the United States is 4–5 g/day (173–217 mmol/day) (9). Sodium chloride is table salt, which dissolves in water to give sodium and chloride ions. Sodium is 0.39 the weight of sodium chloride. So a gram of table salt or salt tablets contains approximately 400 mg of sodium. One teaspoon of table salt contains about 6 g of NaCl with approximately 2.4 g (104 mmol) sodium. One gram of sodium yields 43 mEq of sodium ions, whereas 1 g of sodium chloride yields 17 mEq of sodium ions.

The total amount of filtered sodium load (25 200 mmol or 583 g/day) is the product of the glomerular filtration rate (GFR) (180 l/day) and plasma sodium concentrations (140 mmol/l). Therefore, to maintain sodium balance with a dietary intake of approximately 200 mmol or 3.2 g/day, a total of 25 000 mmol (i.e. 99.6% of the filtered load) must be reabsorbed (10). About 60–70% of the filtered sodium is reabsorbed in the proximal tubule. An additional 20–30% of filtered sodium is reabsorbed in the ascending limb of the loop of Henle. The majority of the remaining sodium (5–10%) is reabsorbed in the distal tubule and collecting duct, under the direct regulation of aldosterone.

Sudden decreases in blood volume are sensed by mechanoreceptors in the left ventricle, carotid sinus, aortic arch and renal afferent arterioles leading to activation of the RAA system, non-osmotic release of arginine vasopressin and stimulation of thirst (11). Renin is synthesised and secreted by the juxtaglomerular cells of the kidney. Although renin is mostly produced by the kidney, renin isoenzymes have been found in many tissues, including brain, adrenals, vascular beds, uterus and placenta (12,13). Renin cleaves its substrate angiotensinogen to generate the angiotensin I, which is converted to angiotensin II by angiotensin I-converting enzyme. Angiotensin II stimulates aldosterone secretion through the adrenal cortex and also partially suppresses renin secretion by a direct effect on the juxtaglomerular cells (14). Aldosterone increases sodium reabsorption and potassium excretion in the distal tubule and the collecting duct of the nephron. The latter is also the site where ADH controls the rate of water reabsorption (15).

Tonicity refers to the effect of a solution on the cell volume. An isotonic solution has no effect on cell volume, whereas hypotonic and hypertonic solutions increase and decrease cell volume respectively. Infusion of isotonic saline causes volume expansion without changing the plasma osmolality. Consequently, ADH release and thirst are not altered, and the steady state is restored by renal sodium excretion. On the other hand, intake of large quantities of NaCl without water (e.g. consumption of salted pretzels, potato chips or peanuts) results in an elevation in the plasma osmolality and stimulation of thirst and ADH secretion leading to ECV expansion. ECF volume expansion will suppress the RAA system, resulting in increased urinary sodium excretion (16).

Thus, the maintenance of the ECV is dependent on the regulation of sodium balance, while plasma osmolality is largely maintained by the regulation of water balance.

Clinical features of hyponatraemia

The symptoms of hyponatraemia (hyponatraemic encephalopathy) are largely dependent on the rapidity of the development of hyponatraemia. Mild to moderate hyponatraemia (125–135 mEq/l) is usually asymptomatic, unless it develops rapidly. When hyponatraemia develops rapidly and is severe (< 120 mEq/l), initial symptoms of nausea and headache may progress to lethargy, psychosis, seizures, coma, respiratory arrest, brainstem herniation and death. In elderly patients, mild hyponatraemia can be an important cause of frequent falls and attention deficits (17). Rhabdomyolysis is a rare manifestation of significant hyponatraemia and can be recurrent in patients with psychogenic polydipsia (18). Neurological symptoms usually do not occur when serum sodium concentration is above 120–123 mEq/l.

Distinction between acute and chronic hyponatraemia is clinically important because chronic hyponatraemia is surprisingly well-tolerated, even at very low levels of serum sodium, and overly aggressive treatment may result in serious neurological sequelae. Aggressive initial correction is warranted in patients with acute symptomatic hyponatraemia, which can potentially cause irreversible neurological damage and death (19).

Hyponatraemia is considered acute when it develops within 48 h of prior normal plasma sodium levels. Acute hyponatraemia occurs most often with intake of large volumes of hypotonic fluids (postoperative patients, marathon runners) and also in users of 'ecstasy' (3, 4-methylenedioxymethamphetamine, MDMA). As a result of osmotic effect, water moves intracellularly and results in cerebral oedema. Eventually, the extracellular water is moved into the cerebrospinal fluid, and cerebral oedema gradually resolves by extruding sodium and potassium salts and certain organic solutes called osmolytes.

Hyponatraemia is considered chronic if it develops slowly and persists for greater than 48 h (19). Patients with chronic gradual onset hyponatraemia are typically asymptomatic because of the brain adaptation to changes in osmolality. This adaptation occurs at the expense of loss of intracellular osmolytes, which normally protect the brain from a sudden increase in osmolality of the ECF. In these patients, rapid increase in plasma osmolality results in water moving out of neurons, leading to shrinkage of cerebral tissue (20). This is the possible mechanism of central myelinolysis, which was first described in the pons, but can occur diffusely throughout the brain (21). Neurological deterioration typically develops over several days with fluctuating consciousness, convulsions, hypoventilation and hypotension. Eventually, patients may develop pseudobulbar palsy with difficulty in swallowing, inability to speak and quadriparesis. Recovery from this syndrome is variable, and many neurological complications are permanent. The magnetic resonance imaging (MRI) scans demonstrate the demyelinated lesions 3–4 weeks after the correction of hyponatraemia (22).

Hyponatraemic encephalopathy is more likely to develop in patients who suffer a hypoxic event and have underlying severe liver disease, and in premenopausal women (23). As there is no effective therapy after the development of central demyelination, prevention is of primary importance. Aggressive plasmapheresis performed immediately after diagnosis may have a role in the treatment of central demyelination (24,25).

Classification of hyponatraemic disorders

Hyponatraemia is defined as a plasma sodium concentration less than 135 mEq/l (3). Changes in plasma sodium are typically inversely proportional to the total body water. In most cases, hyponatraemia is the result of retention of more water in relation to sodium and potassium with a possible concurrent abnormality in sodium balance. The appropriate physiological response to hyponatraemia is suppressed ADH release that in turn facilitates the excretion of the excess water to restore the normal sodium and water homeostasis. In the absence of advanced renal disease limiting water excretion or a massive increase in water intake that exceeds water excretory capacity, hyponatraemia is almost always because of an inability to suppress ADH.

To identify the aetiology of hyponatraemia, a systematic algorithm that is based on the measurements of plasma osmolality and an estimation of the volume of the total body water should be followed (Figure 1) (26). It is noteworthy that in any given patient, multiple aetiologies may contribute to the pathogenesis of hyponatraemia. For example, the patient with congestive heart failure (CHF) who has ADH secreting lung cancer and develops severe hyperglycaemia would have at least three independent causes of hyponatraemia. To facilitate the differential diagnosis, the first step in the evaluation of hyponatraemia irrespective of the volume status should start by measuring the

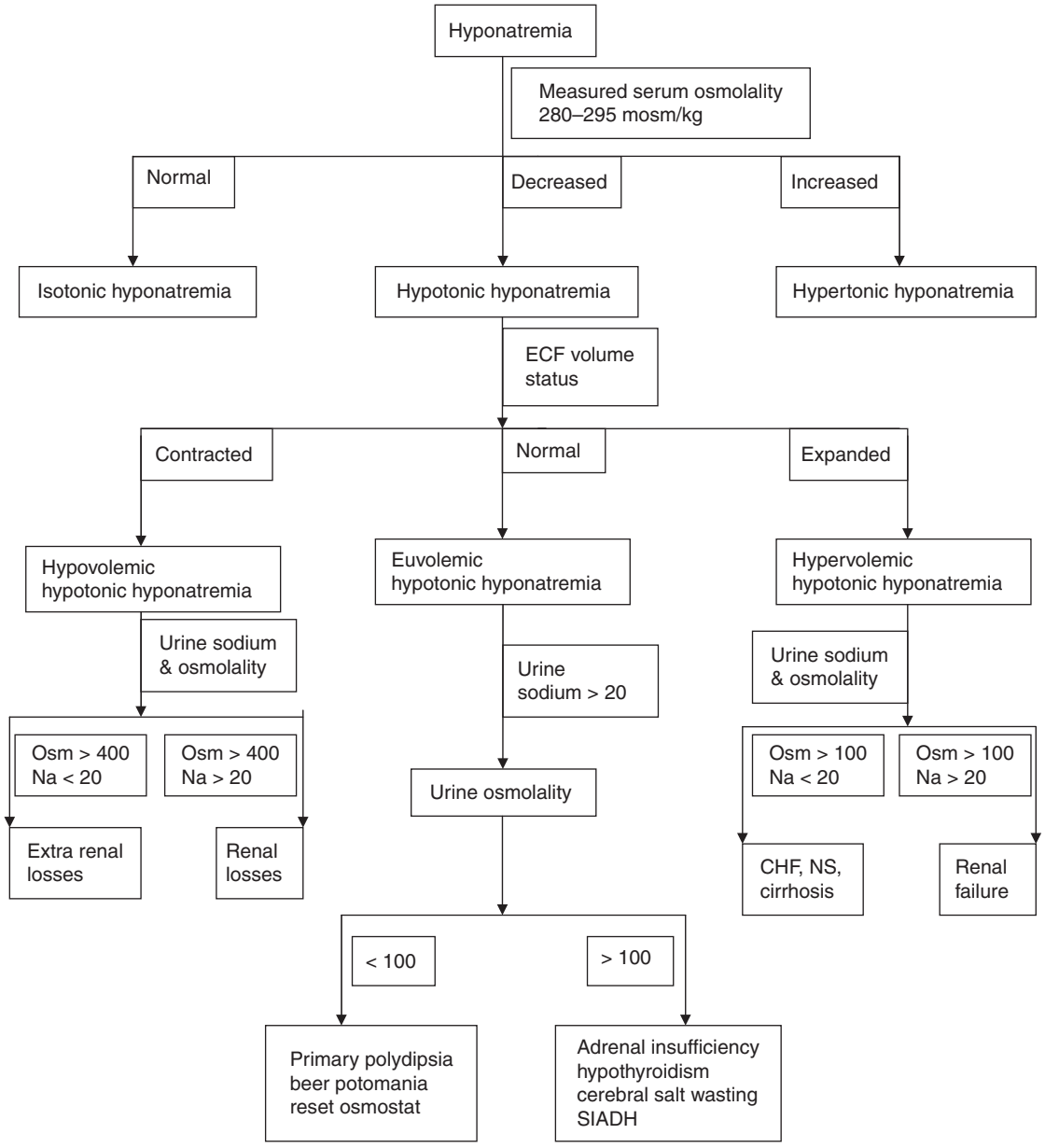

Figure 1 A suggested algorithm for classification of hyponatraemia

plasma osmolality. On the basis of the osmolality, hyponatraemia is classified as isotonic, hypertonic and hypotonic.

Isotonic hyponatraemia

Isotonic hyponatraemia can be produced by the addition of an isosmotic, non-sodium substance to the ECF. It can happen with the use of non-conductive flushing solutions that contain glycine or sorbital during transurethral resection of the prostate (TURP), bladder irrigation and during laparoscopic surgery and hysteroscopy in women (27,28). Variable quantities of these solutions can be absorbed via the prostatic veins. The plasma osmolality changes over time and can be either near normal or low. Glycine initially acts as an ineffective osmole (similar to urea), raising the plasma osmolality without affecting water distribution between the fluid compartments (29). Osmolal gap is also increased because of the excess organic solute. However, when glycine enters the ICF compartment, the free water left behind in the ECF can result in symptomatic dilutional hyponatraemia, that is referred to sometimes as the TURP syndrome (30).

In patients with normal renal function, metabolism and excretion of the excess solute will rapidly correct the hyponatraemia. Hypertonic saline can be given if the plasma osmolality is reduced, but may

not be effective in patients with normal plasma osmolality (31). In symptomatic patients with relatively normal plasma osmolality and in patients with end-stage renal disease, haemodialysis will correct the hyponatraemia and remove glycine and its toxic metabolites (32).

Pseudohyponatraemia is seen when the sodium concentrations are measured by Flame photometry that determines sodium content per litre of plasma. In normal subjects, each litre of plasma contains about 930 ml of water (93%) with fats and proteins accounting for the remaining 70 ml (7%). Thus, a normal plasma sodium concentration of 140 mEq/l represents a concentration in the plasma water of 150 mEq/l as calculated in the following equation (33).

$$140 \text{ mEq/l plasma} \div 0.93 \text{ litre of water plasma per litre of plasma} = 150 \text{ mEq/l plasma water}$$

In patients with marked hyperproteinemia greater than 10 g/dl, the plasma water fraction may fall as low as 720 ml/l (< 80%) (34,35). Plasma osmolality remains isotonic, because lipids and proteins do not substantially affect osmolality measurement (Table 1). In these patients when sodium is measured per litre of plasma, the reported sodium concentration will be artificially reduced as the specimen contains less plasma water (33,36).

This laboratory artefact of pseudohyponatraemia can be eliminated by the direct measurement of serum sodium using ion-selective electrodes (ISE) (37).

Hyperlipidaemia interferes with ISE as well as now rarely used flame photometry measurements. Some interference is seen when triglycerides are > 10 mmol/l, and when triglycerides are > 20 mmol/l a significant interference in the measurement occurs. Laboratories use reagents such as Lipoclear to address this issue, but the results need adjusting for volume changes and errors can occur in these adjustments.

Table 1 The comparative profile of the laboratory features of various conditions of altered plasma tonicity

Condition	Measured plasma Na	Measured plasma osmolality	Effective plasma osmolality
True hypotonicity	Decreased	Decreased	Decreased
Increased non-sodium ECF solutes			
Hyperglycaemia	Decreased	Increased	Increased
Mannitol administration	Decreased	Increased	Increased
Glycine, Sorbital	Decreased	Variable	Normal
Laboratory artefact			
Hyperlipidaemia	Decreased	Normal	Normal
Hyperproteinemia	Decreased	Normal	Normal
Gamma-globulins	Decreased	Normal	Normal

Hypertonic hyponatraemia

Hypertonic hyponatraemia occurs with hyperglycaemia and mannitol administration. Glucose and mannitol osmotically pull intracellular water into the extracellular space, which dilutes all the ECF electrolytes resulting in hyponatraemia.

When evaluating hyponatraemia in the presence of hyperglycaemia, the corrected sodium concentration should be calculated. The sodium concentration falls 1.6 mEq/l for every 100 mg/dl (5.5 mmol/l) rise in glucose when the glucose concentration is between 100 (5.5 mmol/l) and 400 mg/dl (22 mmol/l) (38). If the initial glucose concentration is above 400 mg/dl (> 22 mmol/l), the sodium concentration falls 2.4 mEq/l for every 100 mg/dl (5.5 mmol/l) rise in glucose (38). As this calculation corrects sodium only and no other ECF electrolytes (K^+, Cl^- and $HCO3^-$), anion gap should not be calculated using the corrected sodium value. Hypertonic hyponatraemia is not considered pseudohyponatraemia because it is not an artefact of sodium measurement.

Hypotonic hyponatraemia

As sodium is the predominant extracellular osmole, most cases of hyponatraemia are hypotonic and can be further classified based on the patient's volume status as (i) hyponatraemia with contracted ECF volume (hypovolaemia); (ii) hyponatraemia with expanded ECF volume (hypervolaemia); and (iii) hyponatraemia with normal ECF volume (euvolaemia). For a diagnosis of hypotonic hyponatraemia, the effective osmolality must be < 275 mOsm/kg of water (39).

Hypovolaemic–hypotonic hyponatraemia

Depletional hyponatraemia results from decreased sodium intake or increased losses of sodium, contraction of ECF and appropriate increase in ADH secretion with subsequent free water retention. It is often accompanied by the physical findings of extracellular volume deficit such as flat neck veins, decreased skin turgor, dry mucous membranes, orthostatic hypotension and tachycardia.

Examination of the urinary Na^+ concentration is helpful in assessing whether the losses are renal or extrarenal in origin. A urinary Na^+ concentration of < 20 mEq/l reflects a normal renal response to volume depletion and points to an extrarenal source of Na^+ loss. In patients with hypovolaemic hyponatraemia, urinary Na^+ concentration in excess of

20 mEq/l points to the kidney as the source of the fluid and Na^+ losses (Figure 1).

Hypovolaemic hyponatraemia can be aggravated when fluid losses are replaced with hypotonic fluids. When isotonic saline is used, it eliminates the stimulus for ADH release, thereby allowing the excess water to be excreted. This effect may normalise the plasma sodium concentration rapidly and may be undesirable in patients with chronic hyponatraemia (> 48 h). Administration of desmopressin or hypotonic solutions may be helpful to slow the rate of sodium correction in these patients (40).

Although there are many causes of hypovolaemic–hypotonic hyponatraemia, the two common aetiologies are diuretic induced and cerebral salt wasting (CSW) (Table 2).

Diuretics are commonly used in the management of hypertension and CHF. A subset of diuretics, especially thiazide containing preparations such as the amiloride/hydrochlorthiazide combination pills, causes significant hyponatraemia (41,42). A similar risk is associated with the use of some antibiotics that contribute to the high incidence of hyponatraemia in intensive care units (43).

Hyponatraemia is a potentially fatal complication of thiazide therapy, even when low doses (12.5–25 mg/day) are used. It is usually evident within 14 days of onset of therapy, but can occur up to 2 years later (44). It appears to be more common in women and elderly patients with low body weight with an underlying tendency of increased water intake (45). While the initial volume depletion induced by thiazides can stimulate the release of ADH, susceptible patients appear to have a reduced innate ability to excrete water load (46). These patients may not have clinical features of volume depletion described above and can be also classified as euvolaemic hypotonic hyponatraemia (45). Cerebral oedema is extremely rare even when plasma sodium concentration is 115 mEq/l (45). In many of these patients, hyponatraemia is reproducible with a thiazide rechallenge (47).

Table 2 Causes of depletional hyponatraemia

GI losses	Vomiting
	Diarrhoea
	Fistulas
	gastrointestinal suction or drainage tubes
Third spacing of fluids	Burns
	Peritonitis
	Bowel obstruction
	Pancreatitis
Renal losses	Adrenal insufficiency
	Proximal renal tubular acidosis – sodium losses induced by bicarbonaturia
	Salt-wasting nephropathy (interstitial nephropathy, medullary cystic disease, polycystic kidney disease)
	Presence of an osmotically active non-reabsorbable solute in the urine (glycosuria, ketonuria, mannitol, urea) causes renal excretion of sodium
	Severe vomiting with the metabolic alkalosis and bicarbonaturia – sodium accompanies bicarbonate in the urine to maintain electroneutrality.
	Cerebral salt wasting
	Diuretic use
Sweat losses	Marathon runners

The use of high doses of loop diuretics may result in hypovolaemic hyponatraemia by inducing overt volume depletion. Loop diuretics because of their effect on urine concentrating ability typically do not cause severe hyponatraemia. By preventing active sodium reabsorption in the loop of Henle, loop diuretics make the medullary interstitium hypotonic and typically lead to excretion of urine with a concentration of about 0.45% saline (75 mEq/l) (48).

Diuretic induced K^+ depletion can also lead to hyponatraemia, independent of the effects of Na^+ depletion (49). Hypokalaemia impairs the urinary concentrating ability and can lead to nocturia, polyuria and polydipsia (50).

In most cases, diuretic induced hyponatraemia will resolve by discontinuing the diuretic. Once the patient becomes euvolaemic, ADH release will be appropriately suppressed and rapid excretion of the excess water occurs. If patient is symptomatic, hypertonic saline can be slowly infused for gradual sodium correction.

Another important cause of hypotonic–hypovolaemic hyponatraemia is CSW. It is a rare syndrome described primarily in patients with intracranial disease such as infections, cerebrovascular accidents, tumours and neurosurgery that may lead to renal salt wasting and volume contraction in some patients. The mechanisms implicated in impaired renal tubular sodium reabsorption include decreased sympathetic tone that normally promotes sodium, uric acid and water reabsorption in the proximal tubule (51), increased production of brain natriuretic peptide (BNP) that inhibits renin release and decreases sodium reabsorption in proximal and distal tubules (52). The typical onset of hyponatraemia because of CSW is within 10 days following the neurological insult and is rarely seen after 30 days (53).

As SIADH is the most common cause of hyponatraemia in patients with intracranial disease, it should be carefully differentiated from CSW (Table 3). Treatment of CSW should be attempted

Table 3 Comparative profile of the syndrome of inappropriate ADH secretion (SIADH) and cerebral salt wasting (CSW)

Clinical features	SIADH	CSW
Plasma sodium	Low	Low
ECF volume	Normal or slightly increased	Decreased
Total body water volume	Increased	Increased
Blood pressure	Normal	May be low
Postural hypotension	Absent	Present
Antidiuretic hormone	Increased	Increased
Urine osmolality	Inappropriately high	Appropriately high
Urine osmolality after volume expansion	Relatively fixed	Decrease to < 100 mOsm/kg
Urinary sodium excretion	Increased > 40 mEq/l because of volume expansion	Increased > 40 mEq/l because of salt wasting
Plasma uric acid level	Low due to volume expansion	Low due to urinary losses
Fractional excretion of urate	Normal after correction of Plasma sodium	Elevated after correction of plasma sodium
Brain natriuretic peptide	Normal	Normal to high
Effect of isotonic saline	May worsen hyponatraemia	Improves hyponatraemia
Treatment	Free water restriction, hypertonic saline infusion, ADH antagonists, loop diuretics, high solute intake, Demeclocycline	Salt loading volume replacement, fludrocortisone acetate

with isotonic saline. Volume repletion will suppress the release of ADH resulting in the excretion of the excess water and correction of the hyponatraemia. Salt tablets and fludrocortisone can be also be used to treat CSW (54). As CSW is usually transient, long-term therapy is not necessary (55).

Hypervolaemic–hypotonic hyponatraemia

Hypervolaemic–hypotonic hyponatraemia results from water retention in excess of sodium retention in the face of elevated total body sodium content. The most common causes are cardiac disease, cirrhosis, renal failure and nephrotic syndrome. With the exception of renal failure, these states are characterised by avid Na^+ retention (urinary Na^+ concentration < 10 mEq/l) that may be obscured by the concomitant use of diuretics (Figure 1).

The decreased ECV in CHF despite increased ECF volume leads to activation of the RAA and sympathetic nervous systems along with ADH release to promote sodium and water retention (56). The retained solute and volume extravasate from the intravascular space to ECF causing dilutional hyponatraemia. Persistent hyponatraemia is associated with an adverse short-term and long-term prognosis in patients with acute myocardial infarction and heart failure (57–59). Restricting water intake combined with angiotensin converting enzyme (ACE) inhibitors and loop diuretic is the mainstay of therapy in hyponatraemic patients with cardiac dysfunction (60). Vasopressin receptor antagonists such as conivaptan and tolvaptan produce a selective water diuresis without affecting sodium excretion and may have a role in the management of hyponatraemia associated with heart failure (61,62).

In cirrhosis, ECV is decreased because of splanchnic vasodilatation induced possibly by nitric oxide (63). This leads to activation of RAA system and ADH release, and the latter is roughly proportional to the severity of the cirrhosis (64). Hyponatraemia (< 130 mEq/l) is a powerful predictor of prognosis and death, in patients with cirrhosis waiting for the liver transplantation (65,66). As symptomatic hyponatraemia is unusual in cirrhosis, the mainstay of therapy is restricting water and salt intake combined with diuretics. Vasopressin receptor antagonists may also have a role in the management of hyponatraemia associated with cirrhosis (67).

Nephrotic syndrome typically results in sodium retention induced by the renal disease and decreased ECV caused by the low plasma oncotic pressure. The incidence of hyponatraemia in the nephrotic syndrome is lower compared with both CHF and cirrhosis.

Sodium and water balance are usually maintained in patients with chronic renal failure, until the GFR falls below 10–15 ml/min. Patients with advanced renal failure have impaired free water clearance, and the minimum urine osmolality is 200–250 mOsm/kg despite the appropriate suppression of ADH (68).

Hypervolaemic hyponatraemia occurs when the water intake exceeds the ability to excrete equivalent volumes. When hyponatraemia develops in patients with renal failure, the plasma osmolality may be normal or high because of the retention of urea (ineffective osmole), but their corrected or effective plasma osmolality will remain normal and is calculated as follows (69):

$$\text{Corrected plasma osmolality} = \text{Plasma osmolality} - (\text{BUN} \div 2.8)$$

Hyponatraemia of chronic renal failure generally responds to the combination of dietary sodium and water restriction combined with diuretic therapy.

Euvolaemic hypotonic hyponatraemia

Euvolaemic hypotonic hyponatraemia has a broad differential diagnosis including hypothyroidism, adrenal insufficiency, medications, exercise-induced and the syndrome of inappropriate ADH (SIADH). These processes are mediated directly or indirectly through ADH. The exceptions to the latter are primary polydipsia, beer potomania and reset osmostat. All of the above conditions typically have normal urinary sodium excretion, and the urine osmolality is elevated only in conditions associated with excess ADH release (Figure 1).

Hypothyroidism has been shown to be associated with decreased GFR and renal plasma flow. Elevated ADH levels are seen with severe hypothyroidism, and ADH levels are corrected by thyroxine replacement. ADH excess combined with diminished distal fluid delivery mediates the impaired water excretion in this disorder (70).

Glucocorticoids have an important role in the normal water excretion, and glucocorticoid deficiency is associated with elevated ADH levels (71). These elevated ADH levels are corrected with physiological doses of glucocorticoids. Prolonged glucocorticoid deficiency (14–17 days) can also cause alterations in renal haemodynamics by an ADH-independent effect that impairs water excretion (72).

Exercise-associated hyponatraemia (EAH) seen after endurance exercise (e.g. triathlon events and marathons) is caused by a combination of excessive hypotonic fluid intake and continued ADH secretion (73). Non-osmotic mechanisms of ADH secretion in endurance athletes include hypovolaemia because of sweat losses, intense exercise pain and emotion (74). The clinical manifestations of acute hyponatraemia because of EAH vary from dizziness, nausea and vomiting to seizures, coma and death (75). Hyponatraemic patients with mild to moderate symptoms should be treated with fluid restriction and observed until the onset of a spontaneous diuresis. Patients with severe neurological symptoms should be treated with hypertonic saline till the resolution of neurological symptoms. This condition is best prevented by educating the endurance athletes to drink according to thirst during the race, and to understand that consumption of sports drinks does not provide much protection (76).

Euvolumic hyponatraemia is also a feature of primary polydipsia. Many patients with chronic psychiatric diseases notably schizophrenia demonstrate water consumption in excess of 10 to 15 l a day. This excess water is readily excreted as dilute urine (osmolality approximately 50 mOsm/kg) as a result of suppression of the ADH (77). Euvolaemia is also maintained through renal excretion of sodium (urine sodium > 20 mEq/l). A central defect in thirst regulation possibly plays an important role in the pathogenesis of polydipsia (78). These patients are at increased risk of developing hyponatraemia when they are acutely psychotic and also when treated with certain antipsychotic medications that increase thirst through anticholinergic side effects (79). Psychotic exacerbations appear to be associated with increased vasopressin levels in schizophrenic patients with hyponatraemia (80). Limiting the use of drugs that cause dry mouth and restricting fluid intake may be helpful in the long-term management (81).

The hyponatraemia of beer potomania occurs in patients who consume large amounts of beer with very low solute intake (82). A similar hyponatraemia has been described in malnourished patients who consume low-protein, high-water diets, where the carbohydrate load will suppress endogenous protein breakdown and urea excretion (83,84).

Patients with reset osmostat regulate plasma sodium and plasma osmolality around a lower set point. As osmoreceptor function is normal around the new baseline, they can concentrate or dilute the urine in response to dehydration and water loading. Patients typically present with a stable mild to moderate hyponatraemia (between 125 and 135 mEq/l). The diagnosis can be confirmed clinically by observing the response to a water load, where patients with reset osmostat typically excrete > 80% of ingested water within few hours.

Downward resetting of the osmostat is a normal consequence of pregnancy, which results in a decreased plasma osmolality of approximately 10 mmol/kg and an increase in plasma volume. The shift in osmotic threshold appears in the first trimester and persists throughout pregnancy, returning to normal by 2 weeks after delivery (85). Reset osmostat has been also described in patients with quadriplegia, psychosis, tuberculosis, chronic malnutrition, cachexia,

hypothalamic tumours and hypothalamic injury from trauma or surgery (86–88). As attempting to raise the serum sodium concentration is likely to be ineffective, treatment should be primarily directed at the underlying disease.

Hyponatraemia is also found in up to 50% of hospitalised and 20% of ambulatory patients with human immunodeficiency virus (HIV) infection (89). The aetiology is multifactorial and includes SIADH secondary to drugs, encephalopathy or secondary infections such as cytomegalo virus, hepatitis C or toxoplasmosis, depletion because of chronic diarrhoea, renal tubular toxicity associated with therapy and adrenal insufficiency (90).

Hyponatraemia of unknown aetiology should prompt a work up for neuroendocrine amine precursor uptake and decarboxylating (APUD) tumours as well as oat cell, breast and ovarian tumours that are often difficult to detect.

One of the aetiologies of euvolaemic hypotonic hyponatraemia that is commonly diagnosed in hospitalised patients is the SIADH.

SIADH

The SIADH is associated with increased morbidity and mortality of hospitalised patients and is a measure of the severity of the underlying illness (91). Under normal circumstances, hypovolaemia and hyperosmolality 'appropriately' stimulate ADH secretion. ADH release is considered 'inappropriate' without these physiological cues. High levels of vasopressin are secreted intermittently at an abnormally low threshold or continuously despite low osmolality. The presence of hyponatraemia with a urine osmolality higher than maximal dilution confirms the diagnosis (Figure 1). Drug-related and other major causes of SIADH are listed in Tables 4 and 5 respectively (92). Nausea and pain are potent stimulators of ADH release and commonly lead to SIADH in hospitalised postoperative patients.

In many patients, the initiating event of SIADH is ingestion of water that is not excreted because of the elevated vasopressin. Although water is retained in hyponatraemia, approximately 60% of the excess fluid goes into the cells. This leads to the expansion of extracellular and intracellular volume with an associated natriuresis of isotonic urine in an effort to bring the ECF volume back to normal.

Sometimes it is difficult to differentiate SIADH from mild to moderate depletional hyponatraemia caused by renal losses (e.g. diuretic use) (93). The response of urinary and plasma sodium concentration to an infusion of 1–2 l of 0.9% saline may help in the differential diagnosis. In the patient with SIADH who is at equilibrium, the administered saline will be excreted and therefore there will be an increase in urinary sodium, while plasma sodium concentration will either not change or decrease slightly. If the patient has depletional hyponatraemia from renal losses, sodium from the administered saline will be retained and the excess water is excreted. There will be a decrease in urinary sodium, while the plasma sodium concentration will rise (94).

Laboratory and clinical features of SIADH include the following: (1) euvolaemic hyponatraemia; (2) decreased measured plasma osmolality (<275 mOsm/kg); (3) urine osmolality > 100 mOsm/kg; (4) urine sodium usually > 40 mEq/l; (5) normal acid–base and potassium balance; (6) BUN < 10 mg/dl (3.57 mmol/l); (7) hypouricemia < 4 mg/dl (238 μmol/l); (8) normal thyroid and adrenal function and (9) absence of advanced cardiac, renal, or liver disease. There is an over-reliance in clinical practice on plasma: urine osmolality ratios that can be misleading and absolute values of plasma and urine osmolality are far better indicators of the diagnosis (41). In clinical practice, ADH levels are not required to be measured in patients with suspected SIADH. However, in some clinical centres where ADH assays are readily available, the measurements may be helpful.

It is a common misconception to expect urine osmolality to be higher than that of serum osmolality in patients with SIADH. The latter is more often seen in patients with depletional hyponatraemia. In euvolaemic patients with SIADH, urine osmolality above 100 mOsm/kg is inappropriately high and is an indirect measure of persistent ADH secretion (95). Patients with SIADH may have a low urine sodium concentration if they are also volume depleted or if their sodium intake is extremely low. In such patients, the diagnosis of SIADH is confirmed by 0.9% saline loading as describe above (i.e. the urine sodium rises, but the urine osmolality remains high).

The low BUN and plasma uric acid concentrations in patients with SIADH are partly dilutional, but also result from increased urea and uric acid clearances in response to the ECF volume expansion (96).

Management of SIADH and other hyponatraemic disorders

Management of the SIADH should begin with water restriction and treatment of the underlying aetiology, such as stopping inciting medications, treatment of nausea, pain, infections and chemotherapy for cancer. In all patients with hyponatraemia, free water intake from all sources should be restricted to less than 1–1.5 l/day. The negative water balance caused

Table 4 Drug-induced hyponatraemia

Anti-psychotics	**Anti-depressants**	**Anti-convulsants**	**Analgesics & Recreational drugs**
Phenothiazines	SSRI's	Carbamazepine,	Morphine (high
Haloperidol	TCA's	Oxcarbazepine,	doses), Tramadol, MDMA
	MAOI's	Sodium	(Ecstasy), NSAID's, Colchicine,
	Bupropion	valproate	Venlafaxine, Cymbalta
			(duloxetine)
Cardiac drugs	**Anti-diabetics**	**Anti-neoplastic agents**	**Antibiotics**
Thiazides, clonidine,	Chlorpropamide,	Cyclophosphamide	Azithromycin Trimethoprim-
ACE inhibitors,	Tolbutamide,	Vincristine	sulfamethoxazole,
Aldosterone antagonists,	Glipizide	Vinblastine Cisplatin,	ciprofloxacin, cefoperazone/
Amiloride,	**Lipid lowering agents**	Hydroxyurea,	sulbactam, rifabutin
Loop diuretics,	Clofibrate	Melphalan	**Gastrointestinal drugs**
Methyldopa, Amlodipine,		**Immunosuppressive drugs**	Somatostatin analogs,
Amiodarone, lorcainide,		Tacrolimus, Methotrexate,	Omeprazole
Propafenone, Theophylline,		interferon	**Others**
Terlipressin, Unfractionated		α and γ, levamisole,	Bromocriptine
heparin (aldosterone antagonist)		Monoclonal	
		antibodies	

SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; MAOI, monoaminooxidase inhibitor; MDMA, methylenedioxy-methamphetamine; NSAID, non-steroidal anti-inflammatory drugs; ACE, angiotensin converting enzyme.

Table 5 Non-drug induced causes of the syndrome of inappropriate ADH secretion (SIADH)

Non-osmotic stimuli	CNS lesions	Malignancies	Increased intrathoracic pressure
Nausea	Tumours (neuroblastoma)	Lymphoma, leukaemia, and Hodgkin disease	Mediastinal tumours (thymoma, sarcoma)
Pain	CVA	Carcinoma of the uterus	positive pressure ventilation
Stress	Meningitis	Ureteral, prostate, bladder carcinoma	Infections (pneumonia, TB, aspergillosis, lung abscess)
HIV	Encephalitis	Carcinoma of duodenum and pancreas	Bronchogenic carcinoma, mesothelioma
Acute psychosis	Abscess	Ectopic production of vasopressin by tumours (small cell lung ca, carcinoids	Bronchiectasis
Surgery	Guillain–Barré syndrome	Cancers of the head and neck and nasopharynx	Empyema
Pregnancy (physiological)	Hydrocephalus	Renal cell carcinoma	Chronic obstructive pulmonary disease
Hypokalaemia	Pituitary stalk lesion	Osteosarcoma	Pneumothorax
CHF exacerbation	Delirium tremens		
	Demyelinating disease		
	Acute porphyria		

CVA, cerebrovascular accident; HIV, human immunodeficiency virus; TB, tuberculosis; CHF, congestive heart failure.

by water restriction will gradually increase the serum sodium concentration. In patients with mild symptoms, the rate of urinary solute excretion, the main determinant of the urine output, can be increased by a high salt, high protein diet or supplementation with urea (30–60 g/dl) or salt tablets (200 mEq/day) (97). However, salt therapy is generally contraindicated in patients with hypertension and oedema, as it leads to exacerbation of both conditions.

Symptomatic or severe hyponatraemia generally requires hospitalisation for observation, careful monitoring of fluid balance and body weight and frequent

measurements of plasma sodium concentrations. Giving hypotonic fluids in the setting of elevated ADH levels can produce severe and life-threatening hyponatraemia. Electrolyte concentrations and osmolalities of commonly used intravenous fluids are listed in Table 6 (3).

In view of the devastating neurological consequences of acute symptomatic hyponatraemia, the plasma sodium level could be raised rapidly by 1–2 mEq/l/h (no more than 8–10 mEq/l/24 h) till the cessation of neurological symptoms (98–100). In general, a rate of 1 mEq/l/h is safe and usually sufficient for amelioration of symptoms. Then the correction rate is reduced to 0.5 mEq/l/h till the plasma sodium has reached a level of 120–125 mEq/l.

The major therapeutic intervention for the management of hyponatraemia has been the intravenous saline infusion to increase the rate of urine solute excretion, which is accompanied by excess free water excretion. Various available salt infusions are 0.9% saline, 3% hypertonic saline or 5% hypertonic saline (Table 6). However, it is noteworthy that normal saline for a patient with severe hyponatraemia is considered hypertonic (101). To increase the plasma sodium concentration, the osmolality of the infused saline solution must exceed the urine osmolality. Thus, the use of 0.9% saline (308 mOsm/l) alone may make the hyponatraemia worse, depending on the patient's serum and urine osmolality. The 0.9% saline may be attempted in selected patients with urine osmolality of < 500 mOsm/kg water (102). The 3% hypertonic saline (1026 mOsm/l) infusion is the best way to raise the sodium concentration to treat acute, symptomatic hyponatraemia. In rare patients with urine osmolality above that of 3% saline because of severe SIADH, 5% hypertonic saline (1710 mOsm/l) could be administered. Even though hypertonic saline infusion draws water from ICF and expands ECF volume (Table 6), when it is excreted in the urine, it not only removes the water drawn from ICF but also takes extra amount of ECF water as well.

In patients prone to develop volume overload, hypertonic saline infusion is frequently combined with furosemide (e.g. 20 mg given intravenously) to prevent rapid expansion of ECF volume (3). But, it should be realised that loop diuretic may enhance the rate of sodium correction by hypertonic saline, by inhibiting ADH effect in the collecting tubule.

To avoid overcorrection, it is advised to calculate the sodium required to increase plasma sodium to a safe level of 120 mEq/l rather than to a normal level of 140 mEq/l. Thus, in an 80 kg man with symptomatic acute hyponatraemia of 110 mEq/l, the following equations are used to estimate the amount of sodium needed to be replaced (Table 7):

$$\begin{aligned}\text{Na deficit (mEq)} &= (\text{TBW}) \times (\text{desired } Na^+ \\ &\quad - \text{actual } Na^+) = (\text{Body Weight} \\ &\quad \times 0.6 = 48\text{L}) \times (120 - 110 = 10) \\ &\quad = 480\end{aligned}$$

To achieve target Na^+ concentration of 120 mEq/l over 10 h, sodium should be replaced at a rate of 48 mEq/h (i.e. 480/10 = 48). If 0.9% saline is used, the hourly infusion rate would be 311 ml (calculated as 48 mEq/0.154 mEq (normal saline) = 311 ml), while using 3% saline that contains 0.513 mEq/ml of sodium, the required hourly fluid supplementation rate is 93 ml/h. If urine osmolality is 680 mOsm/l in this hypothetical patient, using 1 l of 0.9% saline (308 mOsm/l) may worsen hyponatraemia, because all of the NaCl infused will be excreted in only 453 ml of water leading to retention of 547 ml out of 1000 ml

Table 6 Electrolyte concentrations and osmolalities of commonly used intravenous fluids (IVF)

1 l infusate*	Na^+ (mEq/l)	Cl^- (mEq/l)	H_2O (ml)	Change in ICF (ml)	Change in ECF (ml)		Osmolality (mOsm/kg)
					Total	Intravascular	
0.9% saline 1 l	154	154	0	0†	1000†	250 ml†	308
3% saline 1 l‡	513	513	0	Decreased due to osmotic shift	1000 + water drawn from ICF	Increased	1026
5% saline 1 l‡	855	855	0	Decreased due to osmotic shift	1000 + water drawn from ICF	Increased	1710
Ringer's lactate 1 litre	130	109	0	100	900	225	273
0.45% saline 1 l	77	77	500	335	665	166	154
D5W	0	0	1000	667	333	83	253

ICF, Intracellular fluid; ECF, extracellular fluid; TBW, Total body water. *Assumes: ICF = 2/3rd TBW; ECF = 1/3rd TBW; Intravascular (plasma) volume = 1/4th ECF. †Only in patient with normal plasma osmolality. Hypertonic for a patient with hyponatraemia. ‡Changes in ECF and ICF volume are dependent on patient's degree of hyponatraemia.

Table 7 A clinical example of an 80 kg man with SIADH, plasma Na^+ 110 mEq/l, urine osmolality 680 mOsm/l and is restricted to 1 l of water intake. The expected net loss of free water in response to various amounts of saline administration is shown

	NaCl, (mOsm)	H_2O (ml)
Isotonic saline		
In (1000 ml 0.9% saline + 1000 ml consumed water)	308 (1 l)	1000
Out (1000 ml 0.9% saline + 308/680 mOsm/kg = 453 ml water)	308 (1 l)	453
Net	0	+547
Hypertonic saline		
In (1000 ml 3% saline + 1000 ml consumed water)	1026 (1 l)	1000
Out (1000 ml 0.9% saline + 1026/680 mOsm/kg = 1500 ml water)	1026 (1 l)	1500
Net	0	−500
Hypertonic saline + loop diuretic (Urine osmolality may be decreased to 450 mOsm by furosemide)		
In (1000 ml 3% saline + 1000 ml consumed water)	1026 (1 l)	1000
Out (1000 ml 0.9% saline + 1026/450 mOsm/kg = ∼ 2280 ml water)	1026 (1 l)	2280
Net	0	−1280

fluid given to the patient. As the isotonic saline is hypertonic for a patient with hyponatraemia, plasma sodium may initially increase, but retention of more than half of administered water will eventually result in worsening of hyponatraemia (Table 7). If 1 l of hypertonic saline is given to this patient, all the total NaCl given is excreted in a larger volume of 1500 ml with a net loss of 500 ml of water. If the patient also receives loop diuretic such as furosemide that may lower the ADH urinary concentrating capacity to 450 mOsm/kg, the net water loss will increase to 1280 ml. These calculations are illustrated in Table 7.

Alternatively, one can directly calculate the degree to which 1 l of a saline infusate would initially raise the plasma sodium concentration (3). The increase in plasma Na^+ concentration ($P[Na^+]$) can be calculated with the following equation:

$$\text{Estimated increase in } P[Na^+] = (\text{Infusate } [Na^+] - P[Na^+]) \div (\text{TBW})$$

For the patient described in the example given above, the infusion of 1 litre of 3% saline will increase the serum sodium concentration by $[(513 - 110)/(48)] = \sim 8.4$ mEq/l.

It is important to appreciate that potassium is as osmotically active as sodium and any concurrent administration of potassium must be taken into account when calculating the expected increase in plasma sodium concentration ($P[Na^+]$) as follows (3):

$$\text{Increase in } P[Na^+] = (\text{Infusate } [Na^+] + (\text{Infusate } [K^+] - P[Na^+])) \div (\text{TBW})$$

As such computed estimates are not capable to precisely predict the magnitude of change, the sodium concentration should be monitored as frequently as every 1–2 h (100). It is also noteworthy that normal (0.9%) saline is usually sufficient for the management of most cases of hyponatraemia, and the risk of cerebral symptoms with hypertonic saline is significant unless close monitoring is performed (103,104) .

A recent alternative to saline administration in the management of hyponatraemia is the use of ADH receptor antagonists. The most specific treatment for SIADH is to block the V2 receptors in the kidney that mediate the diuretic effect of ADH. Vasopressin antagonists are currently indicated for the treatment of euvolaemic and hypervolaemic hyponatraemia, and these agents are usually preferred if SIADH or ADH is the cause (104). For hospitalised patients, conivaptan is given as an intravenous loading dose of 20 mg delivered over 30 min, then as 20 mg continuously over 24 h. Subsequent infusions may be administered every 1–3 days at 20–40 mg/day by continuous infusion (105). Rapid correction of hyponatraemia has been reported in patients receiving conivaptan (106). Therefore, frequent checks of plasma sodium are needed. Each vial (20 mg/4 ml) of conivaptan typically costs approximately $500 and when used over 3 days at the recommended doses, the total cost of such infusion could reach $3000.00.

More recently, an orally active vasopressin receptor antagonist tolvaptan became available. The efficacy of oral tolvaptan in ambulatory patients with SIADH, heart failure and cirrhosis has been recently demonstrated (62). V2-receptor antagonists are not suitable for certain causes of hyponatraemia, such as CSW syndrome, psychogenic polydipsia and potomania.

While SIADH is frequently a transient phenomenon, a chronic phase can occur in patients with ectopic ADH producing tumours and in patients where antipsychotic drugs cannot be discontinued. If water restriction and salt tablet therapy are ineffective in these patients, the following drug therapy to antagonise the effect of ADH could be attempted: (i) administration of loop diuretic along with salt tablets; (ii) demeclocycline; (iii) lithium carbonate; and (iv) orally active vasopressin antagonists such as tolvaptan.

Administration of loop diuretic (20 mg furosemide orally twice a day) along with salt tablets will not only antagonise the effect of ADH but also prevents the oedema formation by the latter (107).

Demeclocycline (300–600 mg orally twice a day) inhibits the effect of ADH in the collecting tubule. Its onset of action may require 1 week, and urinary concentrating ability may be permanently impaired, resulting in nephrogenic diabetes insipidus and even hypernatraemia. Demeclocycline is nephrotoxic in patients with cirrhosis and is contraindicated in children because of interference with bone development and teeth discoloration (108).

Lithium carbonate (300 mg orally twice a day) also inhibits the effect of ADH. It is less effective than demeclocycline and when used chronically, it may induce interstitial nephritis and renal failure. Therefore, lithium should be considered for use only in patients in whom demeclocycline is contraindicated, such as children and patients with liver disease (109).

Conclusions

Hyponatraemia is the clinical manifestation of a wide variety of diseases, and therefore the treatment will depend on identifying the underlying mechanism. Mild chronic hyponatraemia in geriatric patients frequently causes falls and attention deficits. Persistent hyponatraemia is a marker of underlying serious illness and is also an indicator of poor prognosis. Awareness of effects of various commonly used medications on plasma sodium concentration is helpful in the clinical management.

As aggressive or inappropriate therapy of hyponatraemia can be more harmful than the condition itself, clinicians should be familiar with the diagnosis and management of various forms of hyponatraemia. The aetiology of most cases of hyponatraemia can be deduced from the history, physical examination and basic laboratory tests. Evaluation starts by obtaining a thorough history of new medications, changes in fluid intake and fluid output along with a focused physical examination of the patient's volume status. Laboratory assessment should include plasma osmolality, urine osmolality and urine sodium. Additional tests of thyroid and adrenal function may also be necessary.

Plasma osmolality should be carried out to exclude hyperosmolar causes (hyperglycaemia or mannitol) and pseudohyponatraemia. Based on the patient's volume status, depletional vs. dilutional causes of hyponatraemia should be evaluated. When sodium losses are extrarenal, urine sodium levels are usually low (< 20 mEq/l), whereas with renal causes of sodium loss, urine sodium levels are high (> 20 mEq/l). Dilutional causes of hyponatraemia are usually associated with increased ECF volume from CHF, cirrhosis and renal failure. A normal volume status in the context of hyponatraemia should prompt an evaluation for a SIADH. As most hyponatraemia is caused by the non-osmotic release of vasopressin, the recently developed vasopressin antagonists represent a novel and an attractive method of management.

References

1 Anderson RJ, Chung HM, Kluge R, Schrier RW. Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. *Ann Intern Med* 1985; **102**: 164–8.

2 Callahan MA, Do HT, Caplan DW, Yoon-Flannery K. Economic impact of hyponatremia in hospitalized patients: a retrospective cohort study. *Postgrad Med* 2009; **121**: 186–91.

3 Adrogue HJ, Madias NE. Hyponatremia. *N Engl J Med* 2000; **342**: 1581–9.

4 Sterns R. Sodium and water balance disorders. *Neph SAP* 2006; **5**: 35–50.

5 Rose BD, Post TW. *Clinical Physiology of Acid-Base and Electrolyte Disorders*, 5th edn. New York: McGraw-Hill, 2001: 607–8.

6 Rose BD, Post TW. *Clinical Physiology of Acid-Base and Electrolyte Disorders*, 5th edn. New York: McGraw-Hill, 2001: 247–8.

7 Hoffman RS, Smilkstein MJ, Howland MA, Goldfrank LR. Osmole gaps revisited: normal values and limitations. *J Toxicol Clin Toxicol* 1993; **31**: 81–93.

8 Purssell RA, Lynd LD, Koga Y. The use of the osmole gap as a screening test for the presence of exogenous substances. *Toxicol Rev* 2004; **23**: 189–202.

9 Adrogue HJ, Madias NE. Sodium and potassium in the pathogenesis of hypertension. *N Engl J Med* 2007; **356**: 1966–78.

10 Greger R. Physiology of renal sodium transport. *Am J Med Sci* 2000; **319**: 51–62.

11 Skott O, Jensen BL. Cellular and intrarenal control of renin secretion. *Clin Sci (Lond)* 1993; **84**: 1–10.

12 Peach M. Renin-angiotensin system: biochemistry and mechanisms of action. *Physiol Rev* 1977; **57**: 313–70.

13 Millar J, Leckie B, Semple P. Different responses of active and inactive plasma renin to various stimuli. *Clin Sci Mol Med* 1978; **55**: 155s–7s.

14 Reid I. The renin-angiotensin system and body function. *Arch Intern Med* 1985; **145**: 1475–9.

15 Agre P. Aquaporin water channels in kidney. *J Am Soc Nephrol* 2000; **11**: 764–77.

16 Sagnella GA, Markandu ND, Buckley MG. Hormonal responses to gradual changes in dietary sodium intake in humans. *Am J Physiol* 1989; **256**: R1171–5.

17 Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med* 2006; **119**: e1–8.

18 Cronin RE. Psychogenic polydipsia with hyponatremia: report of eleven cases. *Am J Kidney Dis* 1987; **9**: 410–6.

19 Fraser CL, Arieff AI. Epidemiology, pathophysiology, and management of hyponatremic encephalopathy. *Am J Med* 1997; **102**: 67–77.

20 Lien YH, Shapiro UI, Chan L. Study of brain electrolytes and organic osmolytes during correction of chronic hyponatremia. Implication for the pathogenesis of central pontine myelinolysis. *J Clin Invest* 1991; **88**: 303–9.

21 Oya S, Tsutsumi K, Ueki K, Kirino T. Reinduction of hyponatremia to treat central pontine myelinolysis. *Neurology* 2001; **57**: 1931–2.

22 Sterns RH, Cappuccio JD, Silver SM, Cohen EP. Neurologic sequelae after treatment of severe hyponatremia, a multicenter perspective. *J Am Soc Nephrol* 1994; **4**: 1522–30.
23 Arieff AI. Influence of hypoxia and sex on hyponatremic encephalopathy. *Am J Med* 2006; **119**(Suppl. 1): S59–64.
24 Bibl D, Lampl C, Gabriel C. Treatment of central pontine myelinolysis with therapeutic plasmapheresis. *Lancet* 1999; **353**: 1155.
25 Grimaldi D, Cavalleri F, Vallone S. Plasmapheresis improves the outcome of central pontine myelinolysis. *J Neurol* 2005; **252**: 734.
26 Narins RG. Diagnostic strategies in disorders of fluid, electrolyte and acid-base homeostasis. *Am J Med* 1982; **72**: 496–520.
27 Issa MM, Young MR, Bullock AR. Dilutional hyponatremia of TURP syndrome: a historical event in the 21st century. *Urology* 2004; **64**: 298–301.
28 Gonzalez R, Brensilver JM, Rovinsky JJ. Posthysteroscopic hyponatremia. *Am J Kidney Dis* 1994; **23**: 735–8.
29 Bernstein GT, Loughlin KR, Gittes RF. The physiologic basis of the TUR syndrome. *J Surg Res* 1989; **46**: 135–41.
30 Jensen V. The TURP syndrome. *Can J Anaesth* 1991; **38**: 90–7.
31 Agarwal R, Emmett M. The post-transurethral resection of prostate syndrome: therapeutic proposals. *Am J Kidney Dis* 1994; **24**: 108–11.
32 Campbell HT, Fincher ME, Sklar AH. Severe hyponatremia without severe hypoosmolality following transurethral resection of the prostate (TURP) in end-stage renal disease. *Am J Kidney Dis* 1988; **12**: 152–5.
33 Rose BD, Post TW. *Clinical Physiology of Acid-Base and Electrolyte Disorders*, 5th edn. New York: McGraw-Hill, 2001: 712–3.
34 Turchin A, Seifter JL, Seely EW. Clinical problem-solving. Mind the gap. *N Engl J Med* 2003; **349**: 1465–9.
35 Steinberger BA, Ford SM, Coleman TA. Intravenous immunoglobulin therapy results in post-infusional hyperproteinemia, increased plasma viscosity, and pseudohyponatremia. *Am J Hematol* 2003; **73**: 97–100.
36 Weisberg LS. Pseudohyponatremia: a reappraisal. *Am J Med* 1989; **86**: 315–8.
37 Maas AHJ, Siggaard-Andersen O, Weisberg HF, Zijlstra WG. Ion-selective electrodes for sodium and potassium: a new problem of what is measured and what should be reported. *Clin Chem* 1985; **31**: 482–5.
38 Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. *Am J Med* 1999; **106**: 399–403.
39 Ellison DH. Clinical practice. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007; **356**: 2064–72.
40 Perianayagam A, Sterns RH, Silver SM. DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. *Clin J Am Soc Nephrol* 2008; **3**: 331–6.
41 Wierzbicki AS, Ball SG, Singh NK. Profound hyponatraemia following an idiosyncratic reaction to diuretics. *Int J Clin Pract* 1998; **52**: 278–9.
42 Fadel S, Karmali R, Cogan E. Safety of furosemide administration in an elderly woman recovered from thiazide-induced hyponatremia. *Eur J Intern Med* 2009; **20**: 30–4.
43 Zietse R, Zoutendijk R, Hoorn EJ. Fluid, electrolyte and acid-base disorders associated with antibiotic therapy. *Nat Rev Nephrol* 2009; **5**: 193–202.
44 Chow KM, Kwan BC, Szeto CC. Clinical studies of thiazide-induced hyponatremia. *J Natl Med Assoc* 2004; **96**: 1305–8.
45 Sonnenblick M, Friedlander Y, Rosin AJ. Diuretic induced severe hyponatremia. Review and analysis of 129 reported patients. *Chest* 1993; **103**: 601–6.
46 Clark BA, Shannon RP, Rosa RM, Epstein FH. Increased susceptibility to thiazide-induced hyponatremia in the elderly. *J Am Soc Nephrol* 1994; **5**: 1106–11.
47 Friedman E, Shadel M, Halkin H, Farfel Z. Thiazide-induced hyponatremia. Reproducibility by single dose challenge and an analysis of pathogenesis. *Ann Intern Med* 1989; **110**: 24–30.
48 Szatalowicz VL, Miller PD, Lacher JW. Comparative effect of diuretics on renal water excretion in hyponatremic oedematous disorders. *Clin Sci* 1982; **62**: 235–8.
49 Fichman MP, Vorherr H, Kleeman CR, Tefler N. Diuretic induced hyponatremia. *Ann Intern Med* 1971; **75**: 853–63.
50 Marples D, Frokiaer J, Dorup J. Hypokalemia-induced downregulation of aquaporin-2 water channel expression in rat kidney medulla and cortex. *J Clin Invest* 1996; **97**: 1960–8.
51 Palmer BF. Hyponatremia in patients with central nervous system disease: SIADH versus CSW. *Trends Endocrinol Metab* 2003; **14**: 182–7.
52 Berendes E, Walter M, Cullen P. Secretion of brain natriuretic peptide in patients with aneurysmal subarachnoid hemorrhage. *Lancet* 1997; **349**: 245–9.
53 Zogheri A. Hyponatremia and pituitary adenoma: think twice about the etiopathogenesis. *J Endocrinol Invest* 2006; **29**: 750–3.
54 Taplin CE, Cowell CT, Silink M, Ambler GR. Fludrocortisone therapy in cerebral salt wasting. *Pediatrics* 2006; **118**: e1904–8.
55 Al-Mufti H, Arieff AI. Hyponatremia due to cerebral salt-wasting syndrome. Combined cerebral and distal tubular lesion. *Am J Med* 1984; **77**: 740–6.
56 Benedict CR, Johnstone DE, Weiner DH, for the SOLVD Investigators. Relation of neurohumoral activation to clinical variables and degree of ventricular dysfunction: a report from the registry of Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol* 1994; **23**: 1410–20.
57 Gheorghiade M, Abraham WT, Albert NM. Relationship between admission plasma sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. *Eur Heart J* 2007; **28**: 980–8.
58 Goldberg A, Hammerman H, Petcherski S. Hyponatremia and long-term mortality in survivors of acute ST-elevation myocardial infarction. *Arch Intern Med* 2006; **166**: 781–6.
59 Lee WH, Packer M. Prognostic importance of plasma sodium concentration and its modification by converting-enzyme inhibition in patients with severe congestive heart failure. *Circulation* 1986; **73**: 257–67.
60 Dzau VJ, Hollenberg NK. Renal response to captopril in severe heart failure: role of furosemide in natriuresis and reversal of hyponatremia. *Ann Intern Med* 1984; **100**: 777–82.
61 Udelson JE, Smith WB, Hendrix GH. Acute hemodynamic effects of conivaptan, a dual V1A and V2 vasopressin receptor antagonist in patients with advanced heart failure. *Circulation* 2001; **104**: 2417–23.
62 Schrier RW, Gross P, Gheorghiade M. Tolvaptan, a selective oral vasopressin V2-receptor antagonist for hyponatremia. *N Engl J Med* 2006; **355**: 2099–112.
63 Vallance P, Moncada S. Hyperdynamic circulation in cirrhosis: a role for nitric oxide? *Lancet* 1991; **337**: 776–8.
64 Ginès P, Guevara M. Hyponatremia in cirrhosis: pathogenesis, clinical significance, and management. *Hepatology* 2008; **48**: 1002–10.
65 Papadakis MA, Fraser CL, Arieff AI. Hyponatraemia in patients with cirrhosis. *Q J Med* 1990; **76**: 675–88.
66 Heuman DM, Abou-Assi SG, Habib A. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. *Hepatology* 2004; **40**: 802–10.
67 Gerbes AL, Gulberg V, Gines P. Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: a randomized double-blind multicenter trial. *Gastroenterology* 2003; **124**: 933–9.
68 Tannen RL, Regal EM, Dunn MJ, Schrier RW. Vasopressin-resistant hyposthenuria in advanced chronic renal failure. *N Engl J Med* 1969; **280**: 1135–41.
69 Milionis HJ, Liamis GL, Elisaf MS. The hyponatremic patient: a systematic approach to laboratory diagnosis. *CMAJ* 2002; **166**: 1056–62.
70 Hanna F, Scanlon M. Hyponatremia, hypothyroidism and role of arginine vasopressin. *Lancet* 1997; **350**: 755–6.
71 Oelkers W. Hyponatremia and inappropriate secretion of vasopressin in patients with hypopituitarism. *N Engl J Med* 1989; **321**: 492–6.

72 Olchovsky D, Ezra D, Vered I. Symptomatic hyponatremia as a presenting sign of hypothalamic-pituitary disease: s syndrome of inappropriate secretion of antidiuretic hormone (SIADH)—like glucocorticosteroid responsive condition. *J Endocrinol Invest* 2005; **28**: 151–6.
73 Noakes TD, Sharwood K, Speedy D. Three independent biological mechanisms cause exercise-associated hyponatremia: evidence from 2,135 weighed competitive athletic performances. *Proc Natl Acad Sci USA* 2005; **102**: 18550–5.
74 Freund BJ, Shizuru EM, Hashiro GM, Claybaugh JR. Hormonal, electrolyte, and renal responses to exercise are intensity dependent. *J Appl Physiol* 1991; **70**: 900–6.
75 Davis DP, Videen JS, Marino A. Exercise-associated hyponatremia in marathon runners: a two-year experience. *J Emerg Med* 2001; **21**: 47–57.
76 Hew-Butler T, Ayus JC, Kipps C. Statement of the Second International Exercise-Associated Hyponatremia Consensus Development Conference, New Zealand, 2007. *Clin J Sport Med* 2008; **18**: 111–21.
77 Barlow ED, De Wardener HE. Compulsive water drinking. *Q J Med* 1959; **28**: 235–58.
78 Thompson CJ, Edwards CR, Baylis PH. Osmotic and non-osmotic regulation of thirst and vasopressin secretion in patients with compulsive water drinking. *Clin Endocrinol (Oxf)* 1991; **35**: 221–8.
79 Riggs AT, Dysken MW, Kim SW, Opsahl JA. A review of disorders of water homeostasis in psychiatric patients. *Psychosomatics* 1991; **32**: 133–48.
80 Kawai N, Atsuomi B, Toshihito S, Hiroyasu S. Roles of arginine vasopressin and atrial natriuretic peptide in polydipsia-hyponatremia of schizophrenic patients. *Psychiatry Res* 2001; **101**: 37–45.
81 Hariprasad MK, Eisinger RP, Nadler IM. Hyponatremia in psychogenic polydipsia. *Arch Intern Med* 1980; **140**: 1639–42.
82 Hilden T, Svendsen TL. Electrolyte disturbances in beer drinkers. *Lancet* 1975; **2**: 245–6.
83 Thaler SM, Teitelbaum I, Berl T. ''Beer potomania'' in non-beer drinkers: effect of low dietary solute intake. *Am J Kidney Dis* 1998; **31**: 1028–31.
84 Fox BD. Crash diet potomania. *Lancet* 2002; **359**: 942.
85 Lindheimer M, Davison J. Osmoregulation, the secretion of arginine vasopressin and its metabolism during pregnancy. *Eur J Endocrinol* 1995; **132**: 133–43.
86 Robertson GL, Aycinena P, Zerbe RL. Neurogenic disorders of osmoregulation. *Am J Med* 1982; **72**: 339–53.
87 Kahn T. Reset osmostat and salt and water retention in the course of severe hyponatremia. *Medicine* 2003; **82**: 170–6.
88 Hill AR, Uribarri J, Mann J, Berl T. Altered water metabolism in tuberculosis. Role of vasopressin. *Am J Med* 1990; **88**: 357–64.
89 Tang WW, Kaptein EM, Feinstein EI, Massry SG. Hyponatremia in hospitalized patients with the acquired immunodeficiency syndrome (AIDS) and the AIDS-related complex. *Am J Med* 1993; **94**: 169–74.
90 Vitting KE, Gardenswartz MH, Zabetakis PM. Frequency of hyponatremia and nonosmolar vasopressin release in the acquired immune deficiency syndrome. *JAMA* 1990; **263**: 973–8.
91 Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med* 2006; **119**(Suppl. 1): S30–5.
92 Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. *Am J Kidney Dis* 2008; **52**: 144–53.
93 Chung H-M, Kluge R, Schrier RW, Anderson RJ. Clinical assessment of extracellular fluid volume in hyponatremia. *Am J Med* 1987; **83**: 905–8.
94 Strange K. Regulation of solute and water balance and cell volume in the central nervous system. *J Am Soc Nephrol* 1992; **3**: 12–27.
95 Saeed BO, Beaumont D, Handley GH, Weaver JU. Severe hyponatraemia: investigation and management in a district general hospital. *J Clin Pathol* 2002; **55**: 893–6.
96 Beck LH. Hypouricemia in the syndrome of inappropriate secretion of antidiuretic hormone. *N Engl J Med* 1979; **301**: 528–30.
97 Decaux G, Brimioulle S, Genette F, Mockel J. Treatment of the syndrome of inappropriate secretion of antidiuretic hormone by urea. *Am J Med* 1980; **69**: 99–106.
98 Lauriat SM, Berl T. The hyponatremic patient: practical focus on therapy. *J Am Soc Nephrol* 1997; **8**: 1599–607.
99 Palmer BF, Gates JR, Lader M. Causes and management of hyponatremia. *Ann Pharmacother* 2003; **37**: 1694–702.
100 Sterns RH. The treatment of hyponatremia: first, do no harm. *Am J Med* 1990; **88**: 557–60.
101 Rose BD. New approach to disturbances in the plasma sodium concentration. *Am J Med* 1986; **81**: 1033–40.
102 Musch W, Decaux G. Treating the syndrome of inappropriate ADH secretion with isotonic saline. *QJM* 1998; **91**: 749–53.
103 Chubb SP. Hyponatremia treatment guidelines 2007: expert panel recommendations. *Clin Biochem Rev* 2009; **30**: 35–8.
104 Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: expert panel recommendations. *Am J Med* 2007; **120**(11 Suppl 1): S1–21.
105 Zeltser D, Rosansky S, van Rensburg H. Assessment of the efficacy and safety of conivaptan in euvolemic and hypervolemic hyponatremia. *Am J Nephrol* 2007; **27**: 447–57.
106 Ghali JK, Koren MJ, Taylor JR. Efficacy and safety of oral conivaptan: a V1A/V2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. *J Clin Endocrinol Metab* 2006; **91**: 2145–52.
107 Decaux G, Waterlot Y, Genette F, Mockel J. Treatment of the syndrome of inappropriate secretion of antidiuretic hormone with furosemide. *N Engl J Med* 1981; **304**: 329–34.
108 Forrest JN Jr, Cox M, Hong C. Superiority of demeclocycline over lithium in the treatment of chronic syndrome of inappropriate secretion of antidiuretic hormone. *N Engl J Med* 1978; **298**: 173–7.
109 Hensen J, Haenelt M, Gross P. Lithium induced polyuria and renal vasopressin receptor density. *Nephrol Dial Transplant* 1996; **11**: 622–7.

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