MedicineToday 2014; 15(3): 49-54

PEER REVIEWED FEATURE
2 CPD POINTS

CLINICAL INVESTIGATIONS FROM THE RACP

Hyponatraemia
More salt or less water?

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Key points

- Acute hyponatraemia is a medical emergency that can cause permanent brain damage, coma and death.
- Chronic hyponatraemia is common and can cause forgetfulness, ataxia, asterixis and drowsiness but is usually asymptomatic.
- History and examination can help determine the patient's volume status and guide initial treatment.
- In all cases, an underlying cause should be sought and if possible corrected.
- Water-overloaded (hypervolaemic) and euvolaemic patients need fluid restriction, and dry (hypovolaemic) patients need intravenous saline to correct hyponatraemia.
- Measurement of serum and urine osmolality and calculation of the osmolar gap can clarify some cases.
- In most patients, hyponatraemia is multifactorial and resolves after assessment of volume status, medication review and treatment of the underlying condition.

In this series, we present authoritative advice on the investigation of a common clinical problem, especially commissioned for family doctors and written by members of the Royal Australasian College of Physicians.

Hyponatraemia is the most common electrolyte disorder. It occurs in many settings, including in patients taking antidepressants or diuretics, up to 30% of nursing home patients and 15 to 20% of hospitalised patients (with 3 to 5% found to have serum sodium levels less than 130 mmol/L; normal range, 135 to 145 mmol/L). It can also occur after strenuous exercise; for example, a study of athletes who finished the 2002 Boston marathon found that 13% had a serum sodium concentration less than 135 mmol/L.[1]

Acute symptomatic hyponatraemia is a medical emergency that can lead to permanent brain damage, coma and death. In contrast, a gradual fall in sodium levels may cause symptoms such as forgetfulness, ataxia and drowsiness but in most patients is completely asymptomatic. In patients undergoing surgery, preoperative hyponatraemia is associated with a 44% risk-adjusted increase in 30-day perioperative mortality, although this may reflect the underlying condition rather than hyponatraemia per se.[2]

A systematic approach to diagnosis and treatment of hyponatraemia depends on an understanding of the chemistry and physiology of salt and water regulation.

SALT AND WATER REGULATION

Chemically, the osmotic force of a fluid is referred to as its tonicity. It can be expressed as osmolarity (the number of osmotically active particles per litre of water) or osmolality (the number of particles per kilogram of water, equivalent to 1 litre

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1. A WOMAN WITH INCIDENTAL HYPONATRAEMIA FOUND ON ROUTINE TESTS

A 75-year-old woman has stress incontinence incompletely controlled by oxybutynin 10 mg and drinks frequent cups of tea to relieve her dry mouth. Routine testing shows that her serum sodium level is 128 mmol/L, with otherwise normal results on blood tests and physical examination.

Possible causes

The anticholinergic action of oxybutynin reduces bladder contractility but also may cause dry mouth. Increased fluid intake increases urine output and the risk of stress incontinence. Increased fluid intake may also cause dilutional hyponatraemia in the elderly, with age-related nephrosclerosis reducing the capacity for free water clearance.

Investigations

This patient has euvolaemic hyponatraemia and is expected to be hypotonic. As a potential cause of her hyponatraemia is clinically apparent and there is no suspicion of acute poisoning, it is not necessary to assess osmolality and osmolar gap. However, expected values are:

- serum osmolality, 255 mmol/kg
- urine osmolality, 150 mmol/kg
- calculated serum osmolality (see Box 3) 2 x 128 + 3 + 5 = 264 mmol/kg
- osmolar gap, 264 – 255 = 9 mmol/kg (i.e. normal).

Suggested management

A reduced oxybutynin dose may improve the patient's dry mouth, permitting gentle fluid restriction without worsening the stress incontinence.

Clinical course

The patient is first provided with incontinence pads, pelvic-floor training and lip balm to be applied when thirsty. Her oxybutynin dose is reduced to 5 mg and then 2.5 mg, with no incontinence episodes. Her dry mouth improves and serum sodium levels gradually return to normal over eight weeks.

2. A MAN WITH INCIDENTAL HYPONATRAEMIA FOUND ON PREOPERATIVE SCREENING

A 70-year-old man is scheduled for hip replacement surgery. Preoperative measurement of his electrolytes shows a serum sodium level of 130 mmol/L, but results are otherwise normal. He has hypertension controlled by a perindopril–thiazide diuretic combination, ongoing chronic hip pain despite paracetamol and tramadol, and reactive depression treated with sertraline. He feels otherwise well and is euvolaemic.

Possible causes

Any or all of this man's medications can cause hyponatraemia: thiazide diuretics predominantly through sodium loss, and tramadol and sertraline through water retention. The main cause may be identified by reviewing previous electrolyte measurements in relation to the timing of his commencing each medication. Hip pain itself can exacerbate water retention through stimulating excess ADH production (syndrome of inappropriate ADH).

Investigations

This patient most probably has mild hypotonic hyponatraemia. Serum blood sugar and urea levels are expected to be normal, with a low total serum osmolality of about 270 mmol/kg. As a potential cause of the hyponatraemia is apparent, with no suspicion of acute poisoning, calculation of osmolality and osmolar gap is unnecessary. Spot urine osmolality will be affected by thiazide therapy, which impairs the ability to appropriately concentrate or dilute the urine.

Suggested management

If the patient's pain is currently tolerable then more severe postoperative pain could easily worsen the pre-existing hyponatraemia, so the surgery should be deferred until his electrolyte levels are investigated and improved. Options include swapping the thiazide diuretic to a low-dose calcium channel blocker to maintain blood pressure control, withdrawal of sertraline and/or more potent analgesia.

Clinical course

The surgery is deferred. The patient is switched from perindopril–thiazide to perindopril–amlodipine, and sertraline is tapered and then ceased. His body weight falls 3 kg, and his serum sodium level normalises within a fortnight. Subsequent hip surgery is uncomplicated.

for plasma and urine). Once albumin and other proteins are removed from plasma, then 97% of serum osmolarity (and osmolality) is determined by the sodium concentration.

Homeostasis, or maintenance of a stable volume and sodium–water balance, requires intact monitoring and correction systems; problems at any level can contribute to hyponatraemia.

Volume status is monitored by carotid baroreceptors, atrial stretch receptors and the juxtaglomerular apparatus, which send a tightly co-ordinated series of messages via the sympathetic nervous system, atrial natriuretic peptide, the renin–angiotensin axis and prostaglandin–bradykinin systems. Renal sodium retention increases rapidly in response to potential volume depletion, with 70% achieved in the loop of Henle and 15% in the distal convoluted ducts, but is less responsive to volume overload. Hence, it is easier to develop hyponatraemia than hypernatraemia.

Serum osmolarity is monitored through the cerebral ventral hypothalamic nuclei. An increase in serum osmolarity generates the sensation of thirst and release of antidiuretic hormone (ADH, also known as vasopressin) from the posterior pituitary gland, which acts via pure water channels (aquaporin) in the renal collecting ducts to retain water. Vasopressin receptors are also found in the central nervous system, so that excessive ADH release causes both renal and cerebral water retention.

Thermal monitoring generates sweating; sodium concentrations of sweat are

relatively fixed, but volumes can be increased to up to 1 L/hour during vigorous exercise. Thus the replacement of sweat losses with large volumes of pure water during endurance events such as marathons can induce hyponatraemia.

SYMPTOMS OF HYPONATRAEMIA

The speed of onset of hyponatraemia determines the symptoms. A relative excess of water causes swelling of all cells but symptoms are primarily neurological, caused by intracranial pressure due to cerebral swelling within the fixed confines of the skull. More subtle changes within brain cells are also possible.

Acute symptomatic hyponatraemia is a medical emergency. A sudden decrease in sodium levels from normal to less than 120 mmol/L in one to two days can cause coning of the brainstem through the foramen magnum, with abrupt onset of third nerve palsies, followed by coma and death. Patients may have focal neurological signs that mimic cerebral ischaemia. At a microscopic level, acute hyponatraemia can lead to central pontine myelinolysis and a long-term 'locked-in' syndrome with mute quadriparesis. Similarly, too rapid correction (e.g. a rise in serum sodium level of more than 8 mmol/L in less than 24 hours) can cause the same pathology.

In contrast, a gradual fall in sodium levels is usually asymptomatic, but some patients can develop mild nonspecific symptoms (e.g. dizziness, fatigue, anorexia, memory loss, unsteadiness, cramps) with no or only subtle signs (e.g. ataxia, asterixis or flapping tremor, and drowsiness).

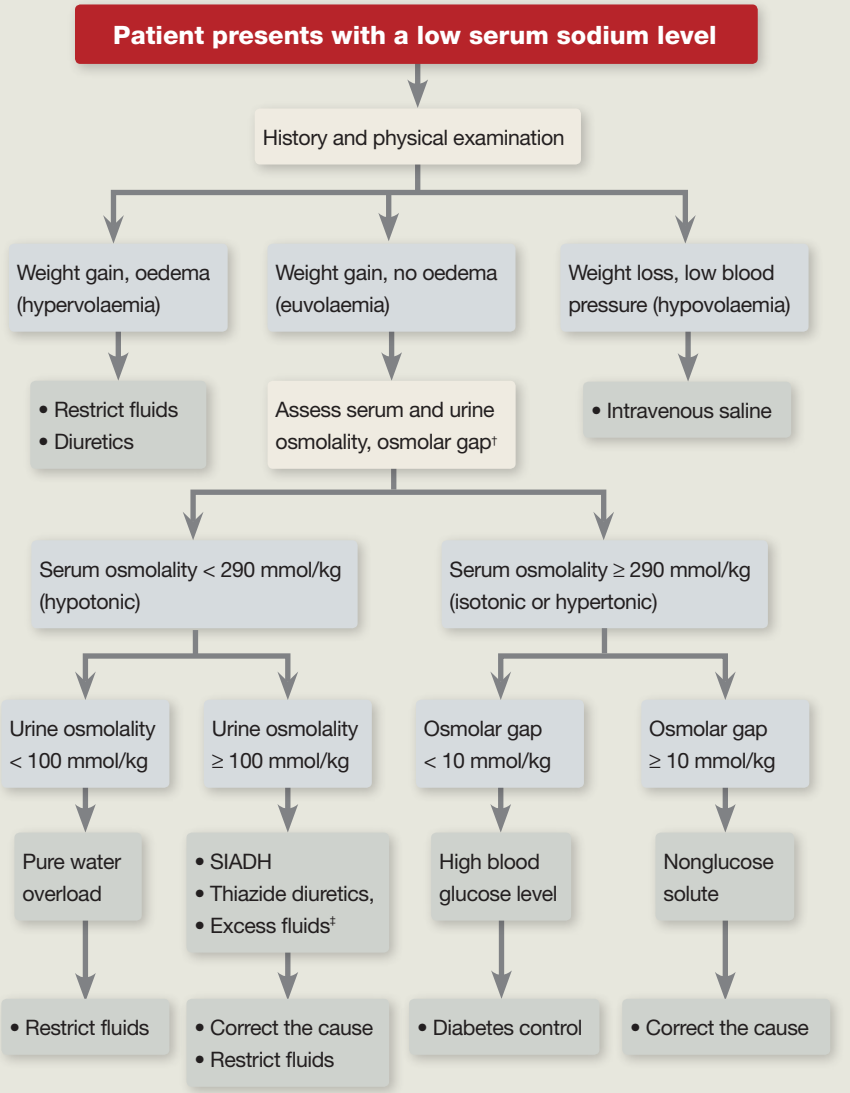
CLINICAL APPROACH TO HYPONATRAEMIA

In general practice, patients with hyponatraemia may present with symptoms but more commonly hyponatraemia is found during routine tests or preoperative screening (see the cases in Boxes 1 and 2). Patient assessment aims to classify the hyponatraemia and identify the cause as a basis for treatment. Hyponatraemia can be classified as:

- acute or chronic
- symptomatic or asymptomatic
- hypervolaemic ('wet'), euvolaemic or hypovolaemic ('dry') – by assessing volume status
- hypertonic, isotonic or hypotonic – by measuring serum osmolality.

An approach to investigation and treatment of a patient with hyponatraemia is summarised in the flowchart.

A SIMPLIFIED MANAGEMENT ALGORITHM FOR PATIENTS WITH HYPONATRAEMIA*



ABBREVIATION: SIADH = syndrome of inappropriate antidiuretic hormone secretion.
* In all cases search for an underlying cause and if possible correct it.
† Assessment of osmolality and osmolar gap is not necessary in all patients if a potential cause of hyponatraemia is clinically apparent and acute poisoning is not suspected.
‡ Other causes include antidepressants, narcotics, tramadol, hypothyroidism and uncontrolled pain.

History and examination

A targeted history and bedside examination can suggest potential causes of hyponatraemia and classify patients by volume status, which can then guide initial treatment as follows (also see the Table).

- Hypervolaemia (characterised by weight gain with oedema). Body sodium and water content are both increased, with water gain greatest. Common causes include chronic cardiac failure, chronic kidney disease, nephrotic syndrome, liver failure and inappropriate fluid intake (e.g. intravenous therapy with excess dextrose solution compared with saline). Treatment comprises diuretics and fluid restriction.

TABLE. CAUSES AND TREATMENT OF HYPONATRAEMIA ACCORDING TO VOLUME STATUS

Volume status	Causes (water intake > sodium intake)	Causes (water excretion < sodium excretion)	Treatment (in addition to correcting the cause)
Hypervolaemic ('wet')	• IV dextrose excess vs saline	• Chronic cardiac failure • Chronic kidney disease • Hepatic cirrhosis • Nephrosis	Fluid restriction ± diuretics
Euvolaemic	• Psychogenic polydipsia • IV dextrose (no saline)	• SIADH • Thiazide diuretics • Hypothyroidism	Fluid restriction
Hypovolaemic ('dry')	• Water rehydration after strenuous exercise	• Vomiting • Diarrhoea • Loop diuretics • Adrenal insufficiency	Intravenous saline

ABBREVIATIONS: IV = intravenous; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

- Euvolaemia (characterised by weight gain without oedema). Total body water is increased, while total body sodium content remains normal. Common causes include the syndrome of inappropriate ADH secretion (SIADH), treatment with thiazide diuretics (discussed below) and excessive fluid intake (e.g. intravenous therapy with dextrose alone, psychogenic polydipsia). Rarely, severe hypothyroidism can present in this way. Treatment involves fluid restriction.
- Hypovolaemia (characterised by weight loss with postural hypotension). Water and sodium are both lost from the body, but sodium loss is greater. Common causes include strenuous exercise, prolonged vomiting or diarrhoea, diuretics and mineralocorticoid deficiency (e.g. Addison's disease, steroid withdrawal). Treatment is with intravenous saline.

Investigations

Assessing serum and urine osmolality and osmolar gap (see below) can clarify some cases of hyponatraemia. However, if a potential cause of hyponatraemia is clinically apparent and there is no suspicion of acute poisoning then these investigations are not necessary in all patients with hyponatraemia. Investigation is indicated for patients with hyponatraemia who present in an acutely confused state and for asymptomatic patients with chronic hyponatraemia whose serum sodium level fails to improve with simple measures.

Syndrome of inappropriate antidiuretic hormone secretion

Excessive secretion of ADH occurs in many circumstances, including cancer, head injury, severe pain and use of drugs such as narcotics, anticonvulsants and antidepressants (including tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin and noradrenaline reuptake inhibitors). SIADH leads to pure water retention with no abnormality in sodium metabolism. Patients appear euvolaemic with a serum sodium level less than 135 mmol/L and serum osmolality less than 270 mmol/kg but urine osmolality greater than 100 mmol/kg (instead of less than 50 mmol/kg as expected with pure water overload). Serum urea and uric acid levels will be relatively low from dilution.

The formal diagnosis of pure SIADH requires intact kidney, adrenal and thyroid function with no interfering medications (including diuretics) or fluid resuscitation. In practice, SIADH is often probable rather than proven, because of multiple comorbidities (see Box 2).

Thiazide diuretics

Thiazide diuretics are frequently associated with hyponatraemia. The mechanism appears multifactorial, with a combination of impaired free water clearance, relative excess urinary sodium losses and thirst disorder all combining to produce euvolaemic hyponatraemia, especially in the elderly.

Exclude an artefactual low serum sodium level

Calculation of the osmolar gap can help identify an artefactual low serum sodium level caused by the presence of an osmotically active solute other than sodium in the serum. This investigation is particularly useful in acute symptomatic hyponatraemia, especially when acute poisoning is a possibility.

In the common examples of hyponatraemia listed in the Table, total serum osmolality falls in parallel with the serum sodium level, with no extra substances that can act as hyperosmolar agents in their own right. In these cases, the measured serum osmolality (which assesses solute concentration) will be close to the calculated serum osmolality (which is calculated from serum sodium, glucose and urea levels). The 'osmolar gap' between the two values is less than 10 mmol/kg (see Box 3).

Occasionally, however, the serum sodium level is low but the measured serum osmolality remains normal (isotonic hyponatraemia) or high (hypertonic hyponatraemia), suggesting the low sodium level is an artefact. In practice, the most common cause of isotonic hyponatraemia is diabetes with kidney impairment, where insulin deficiency

3. CALCULATING THE OSMOLAR GAP

Step 1. Measure serum osmolality

Normal measured serum osmolality
= 290 mmol/kg
(normal range, 285–295 mmol/kg)

Step 2. Calculate serum osmolality

Calculated serum osmolality
= 2 x (serum sodium [mmol/L]) +
(serum glucose [mmol/L]) +
(serum urea [mmol/L])

Normal calculated serum osmolality
= 2 x 140 + 5 + 5 mmol/kg
= 290 mmol/kg

Step 3. Calculate osmolar gap

Osmolar gap = measured – calculated serum osmolality

Normal osmolar gap
= 290 – 290 mmol/kg = 0 mmol/kg
(normal range, < 10 mmol/kg)

4. A WOMAN WITH ISOTONIC HYPONATRAEMIA

A 55-year-old woman with obesity, type 2 diabetes and stable stage 3 chronic kidney disease is admitted to hospital with a three-week history of polyuria, polydipsia and worsening blood sugar control. Her blood sugar level has risen from 10 to 25 mmol/L, serum sodium level has fallen from 140 to 130 mmol/L and serum creatinine has remained stable at 150 mmol/L. She is thirsty but euvolaemic. Her medications include irbesartan, amlodipine and gliclazide.

Possible causes

The acute fall in serum sodium level coincides with the acute rise in blood glucose level, so this is most likely isotonic hyponatraemia caused by a shift of intracellular water into the extracellular space in response to the rising blood glucose levels – especially if her body weight has remained stable. If her water intake has exceeded her water loss through polyuria, there may be an element of dilutional (hypotonic) hyponatraemia as well, especially if her body weight has increased. Uncontrolled diabetes can be catabolic, however, so interpretation of body weight may be complicated by muscle loss.

Suggested investigations and management

Measuring her serum osmolality will determine whether the patient's serum is hypotonic or isotonic. If isotonic (normal serum osmolality of about 290 mmol/kg), then replacement of gliclazide with insulin should improve her blood sugar levels; if her serum sodium level normalises, then no further management is required. If she is hypotonic and her serum sodium level remains low despite correction of hyperglycaemia, then she will need fluid restriction as well.

Clinical course

The patient's serum osmolality is 295 mmol/kg. She is switched from gliclazide to an insulin infusion. Her blood sugar falls to less than 10 mmol/L and her serum sodium level returns to 140 mmol/L with no change in her body weight.

or resistance prevents the free movement of glucose into cells (thus causing a compensatory shift of water out of cells) and kidney impairment prevents adequate compensatory polyuria. As glucose is included in the equation to calculate serum osmolality, hyperglycaemic hyponatraemia has no osmolar gap (see the case in Box 4).

Rarely, an additional interfering osmotically active substance is present. This will create an osmolar gap between the measured and calculated osmolality. Examples of osmotically active substances include:

- nonglucose sugars such as mannitol (used in management of acute cerebral oedema)
- alcohols in poisonings (e.g. ethanol, methanol, ethylene glycol)
- lipids in severe hypertriglyceridaemia
- proteins in Waldenstrom's macroglobulinaemia.

TREATMENT OF HYPONATRAEMIA

The treatment of patients with hyponatraemia depends on the cause and speed of onset of the hyponatraemia and the patient's volume status and symptoms. Asymptomatic patients with stable mild hyponatraemia (130 to 135 mmol/L) who do not wish to restrict fluid intake do not necessarily require treatment. Patients who have symptoms or a sodium level between 120 and 130 mmol/L should be referred to a nephrologist or general physician with an interest in nephrology. Those with an acute onset of symptoms or a serum sodium level less than 120 mmol/L require urgent hospital treatment (see the case in Box 5).

Treat the cause and adjust fluids and diuretics

In most patients with hyponatraemia, withdrawal of the cause plus simple fluid and diuretic adjustment will correct the abnormalities. For patients with euvolaemic or hypervolaemic hyponatraemia, strict fluid restriction to 500 to 750 mL fluid daily (intravenous and oral) should be maintained until the serum sodium level has risen to more than 130 to 135 mmol/L.

Hypertonic saline

Additional measures come with greater expense or risks. Accelerating recovery through the use of hypertonic (3%) saline may prevent central pontine myelinolysis by limiting the duration of exposure to sudden hyponatraemia, but paradoxically may precipitate the same condition through too rapid correction. For most clinical situations, the risk of hypertonic saline outweighs the potential benefits. A useful rule of thumb is to let the rate of recovery match the rate of onset.

Other treatments

Oral urea can force a pure water diuresis but is difficult to access and often poorly tolerated because of nausea. Demeclocycline 300 to 600 mg twice a day inhibits the kidney's response to ADH, but may take one to two weeks to be effective.

ADH antagonists specific for the renal vasopressin (V2) receptor ('vaptans') have been licensed recently in Europe and the USA for treatment of hyponatraemia. They include tolvaptan, satavaptan and lixivaptan. However, as their benefits are

5. A MAN WITH ACUTE SYMPTOMATIC HYPONATRAEMIA

A 27-year-old man with schizophrenia is admitted to hospital with confusion, three weeks after discontinuing his medications and becoming increasingly agitated. He is compulsively drinking water despite denying thirst, and is clinically euvolaemic.

Investigations

The patient's serum sodium level is 115 mmol/L (having been normal two weeks earlier), with serum osmolality of 240 mmol/kg and a low spot urine osmolality of 50 mmol/kg.

Possible cause

This is most likely acute water overload caused by psychogenic polydipsia, with the patient's intake overwhelming the appropriate compensatory water diuresis. If his spot urine osmolality is greater than 100 mmol/kg then there might be an additional element of SIADH, raising the possibility of an acute intracranial condition as an alternative or additional cause of confusion.

Suggested management

Enforced strict fluid restriction to less than 500 mL/day should be followed by rapid metabolic improvement, aided by recommencement of his antipsychotic medication. This is a medical emergency, given the risk of permanent neurological sequelae. The patient will require immediate investigation to exclude other possible diagnoses, with intensive monitoring of serum sodium level and urine output. If his condition deteriorates then a cautious trial of saline with frusemide may be necessary to arrest any further fall in serum sodium level.

Clinical course

The patient is managed in the intensive care unit, with strict restriction of fluids to 500 mL per day and use of sedatives as well as his usual antipsychotics. He has a prolonged large diuresis, with an 8 kg fall in body weight, and his serum sodium level rises steadily over three days to 130 mmol/L. His fluid restriction is liberalised to 750 mL and then 1000 mL as his serum sodium level normalises over another two days.

marginal and variable (no better than oral urea) and they are expensive and have occasionally been associated with acute fatal hepatic injury (although a causal role is considered unlikely), their place remains uncertain.[3,4] Treatment of chronic SIADH is often unsatisfactory as long-term fluid restriction can be difficult to maintain.

MONITORING RECOVERY

It is crucial to monitor total body water as well as serum sodium level. The simplest and most accurate way of monitoring shifts in total body water is by daily weighing. For acute symptomatic hyponatraemia, mental state can be monitored with the Glasgow Coma Score, orientation to time, place and person, and severity of asterixis (number of beats per 5 seconds).

For patients complaining of thirst despite water overload, fluid restriction should be maintained and alternative causes of dry mouth (e.g. anticholinergics, mouth breathing, Sjögren's syndrome) excluded. Useful symptomatic management can include lip balm, encouraging saliva flow with lemon lozenges, and cooling the face with atomiser water sprays.

Overcorrection to a serum sodium level greater than 145 mmol/L will cause thirst and increasing drowsiness, so monitoring should continue until serum sodium level has stabilised on a tolerable fluid regimen.

CONCLUSION

Water-overloaded (hypervolaemic) and euvolaemic patients need fluid restriction, and dry (hypovolaemic) patients need intravenous saline to correct hyponatraemia. Daily measurement of body weight is the most objective way of assessing changes in total body fluid volume. Close monitoring of serum electrolyte levels is required until the patient is stabilised. Mental state should also be monitored in acute emergency situations.

Most clinical situations of hyponatraemia are multifactorial and resolve after volume status assessment, medication review and treatment of the underlying condition. Assessing the difference between calculated and measured serum osmolality and checking urine osmolality can clarify some cases, but results may be uninterpretable because of comorbidities or medications. MT

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COMPETING INTERESTS: Dr Thomas is an investigator in a multicentre trial of tolvaptan in polycystic kidney disease sponsored by the Otsuka Pharmaceutical Company.