

# The diagnosis and management of inpatient hyponatraemia and SIADH

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## ABSTRACT

**Background** Hyponatraemia is a very common medical condition that is associated with multiple poor clinical outcomes and is often managed suboptimally because of inadequate assessment and investigation. Previously published guidelines for its management are often complex and impractical to follow in a hospital environment, where patients may present to divergent specialists, as well as to generalists.

**Design** A group of senior, experienced UK clinicians, met to develop a practical algorithm for the assessment and management of hyponatraemia in a hospital setting. The latest evidence was discussed and reviewed in the light of current clinical practicalities to ensure an up-to-date perspective. An algorithm was largely developed following consensus opinion, followed up with subsequent additions and amendments that were agreed by all authors during several rounds of review.

**Results** We present a practical algorithm which includes a breakdown of the best methods to evaluate volume status, simple assessments for the diagnosis of the various causes and a straightforward approach to treatment to minimise complexity and maximise patient safety.

**Conclusion** The algorithm we have developed reflects the best available evidence and extensive clinical experience and provides practical, useable guidance to improve patient care.

**Keywords** ADH antagonists, Hyponatraemia, SIADH.

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## Introduction

Hyponatraemia is the most commonly seen electrolyte disturbance both in hospital inpatients and in the community [1]. There are numerous recognised causes of hyponatraemia, and extremes of volume status – such as dehydration or fluid overload – are common precipitants. The syndrome of inappropriate antidiuretic hormone secretion (SIADH), the oft-quoted cause of hyponatraemia by medical students, is a diagnosis of exclusion that, by definition, is associated with a normal volume status.

The majority of cases of hyponatraemia are mild, and it is generally thought of as an asymptomatic condition, although

even mild hyponatraemia may have detrimental effects on patients [2,3]. The symptoms of hyponatraemia are nonspecific in the majority, and hyponatraemia is often discovered coincidentally. Rapid changes in sodium levels or acute profound hyponatraemia can be associated with neurological features and are medical emergencies that require urgent intervention and close supervision in a monitored environment.

The two main problems encountered in routine clinical practice relate to the appropriate assessment and initial investigations required to identify the cause of the hyponatraemia in any given patient, and the therapeutic manoeuvres necessary to ameliorate the condition. Several guidelines for

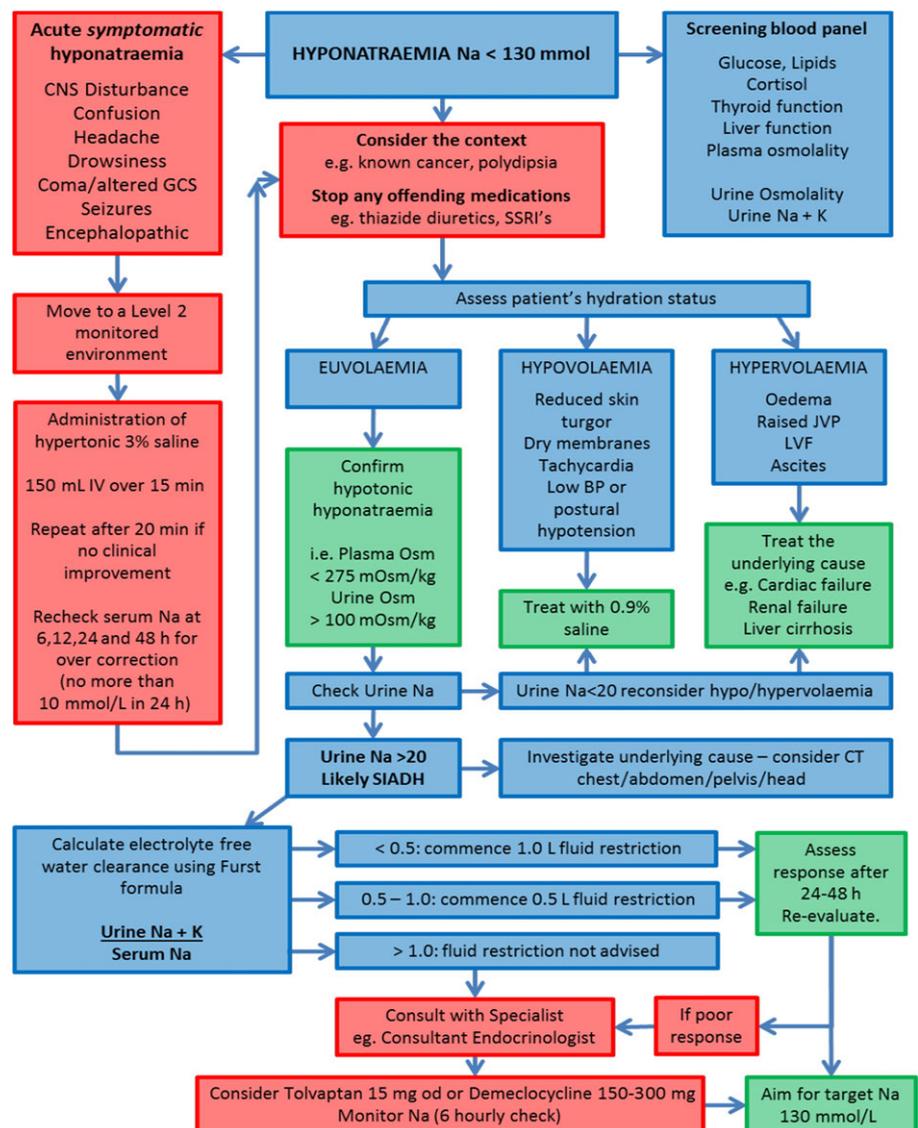
treating hyponatraemia have been proposed [4,5]; however, they often contain algorithms that are complex and impractical for use by nonspecialists. As a group of clinicians from varied specialties, but with a particular interest in hyponatraemia, we have therefore created a simple clinical algorithm that aims to maximise utility and patient safety, whilst being easy to use.

**Methodology**

A group of senior, experienced UK clinicians, many of whom have published in the field of inpatient hyponatraemia and SIADH, met under the direction of Professor Grossman to

develop a practical algorithm for the assessment and management of hyponatraemia. The latest evidence was discussed and reviewed in the light of clinical practicalities to ensure an up-to-date perspective. The algorithm was largely developed during the meeting following consensus opinion, followed up with subsequent additions and amendments that were agreed by all authors during several rounds of review.

Given the dearth of evidence in many aspects of the management of hyponatraemia, we have based the algorithm (Fig. 1) on widely accepted recommendations, expert opinion and published consensus guidelines.



**Figure 1** UK algorithm for management of inpatients with hyponatraemia. CNS, central nervous system; CT, computed tomography; GCS, Glasgow Coma Score; IV, intravenous; JVP, jugular venous pressure; K, potassium; LVF, left ventricular fibrillation; Na, sodium; od, once daily; Osm, osmolality; SSRI, selective serotonin reuptake inhibitor.

**Box 1****Management of acute symptomatic hyponatraemia**

Acute symptomatic hyponatraemia is a medical emergency, and patients should be moved to a Level 2 monitored environment. A consultant endocrinologist or nephrologist should be consulted as soon as possible.

Treatment involves the use of hypertonic saline to gradually correct the hyponatraemia, with the goal of ensuring that the sodium level does not rise by more than 6 mmol/L in the first 6 h or 10 mmol/L in the first 24 h. Rapid overcorrection leads to a risk of osmotic demyelination syndrome.

We suggest starting with 150 mL of 3% saline IV over 15 min. If there is no clinical improvement, repeat the dose after 20 min. Check serum sodium at 6, 12, 24 and 48 h to ensure that overcorrection (serum sodium rise of 10 mmol/L or more in 24 h or less) has not occurred. If the sodium does rise excessively, then intravenous dextrose or desmopressin (e.g. DDAVP) may be required. The serum sodium does not need to be normalised with hypertonic saline; an increase of 4–6 mmol/L often leads to major clinical improvements.

**Making the right diagnosis**

The management of patients with hyponatraemia begins with a good clinical history and examination, an understanding of the *timeline* of the change in serum sodium values and some basic tests to rule out obvious or worrying causes.

**Baseline investigations**

It is important to consider common causes of hyponatraemia, such as hyperglycaemia, as well as pseudo-hyponatraemia, whereby unmeasured factors, such as alcohol or triglycerides, can produce a spuriously low sodium result. A screening investigation panel must therefore be undertaken as soon as the problem is suspected and should include blood glucose, lipid profile, random (ideally at 09:00) cortisol (unless the patient is taking synthetic glucocorticoids), thyroid function tests, liver function tests and plasma osmolality. A urine sample should be taken to check urinary osmolality, sodium and potassium.

**Consider the context**

Known conditions may inform the diagnosis. Taking a good history will reveal the likelihood, for example, of primary polydipsia or recent medication changes that may have an influence on serum sodium levels. Other medical conditions, such as an underlying malignancy and its treatment, may provide a clear explanation for the revealed electrolyte imbal-

ance – certain types of lung cancer are well recognised to precipitate SIADH. Such knowledge, along with appropriate initial investigations and clinical judgement, may thereby allow one to circumvent the full algorithm and proceed rapidly with the right therapy. These principles should be considered at all points of the algorithm.

**Assessment of volume status**

Diagnosis and management of hyponatraemia depends on assessment of whether the patient is hypovolaemic, hypervolaemic or euvolaemic. However, this is frequently difficult and often suboptimal, even when performed by experienced clinicians [6]. If the volume status is unclear, an infusion of normal saline (e.g. 1 L over 12 h) as a therapeutic trial will often reveal the true situation. Hypovolaemic patients will respond well (typically serum sodium will rise > 5 mmol/L), whereas patients with SIADH will often not improve and may experience a worsening of hyponatraemia. It is imperative that serum sodium is rechecked 6 h after the infusion is started.

**Acute severe hyponatraemia**

If the patient has significant neurological symptoms (see Fig. 1 'acute symptomatic hyponatraemia' for examples), this is a medical emergency and should be treated immediately, without waiting for the diagnosis of the cause of hyponatraemia. See Box 1 for the management of acute severe hyponatraemia.

**Treatment of hyponatraemia**

**Rates of correction.** The treatment of this condition needs to take into account the duration of the hyponatraemia and the degree of symptoms relating to it. The acute treatment of symptomatic hypotonic hyponatraemia requires an understanding of its targets and risks, as well as continuous monitoring of the patient's clinical status and relevant serum biochemical values.

Patients who have hyponatraemia for more than 48 h are at risk of neurological sequelae if the correction of serum sodium occurs too rapidly [7] due to the development of osmotic demyelination (central pontine demyelination). A safe limit for the treatment of hyponatraemia is a rise of no more than 10 mmol/L in the first 24 h and 8 mmol/L in the subsequent 24 h (18 mmol/L in 48 h).

Certain medical disorders are known to place patients at an increased risk of complications from rapid correction of serum sodium concentration. Individuals most at risk for developing osmotic demyelination syndrome are elderly patients, children under 16 years of age, malnourished patients, patients with alcoholism, patients with central nervous system disease or hypoxaemia and patients in the post-operative setting. A

tighter safety limit for correction of 8 mmol/L in 24 h and 14 mmol/L in 48 h should be considered in such patients.

Large-volume polyuria in this context is an ominous sign. For these patients, early identification of risk factors, close monitoring of serum sodium correction and the use of 5% dextrose with or without desmopressin to prevent or reverse overcorrection are important components of treatment [8].

**Stop any offending medications.** Where practical, discontinue the use of medications that may be causing or exacerbating hyponatraemia (Table 1). The most common are thiazide diuretics, selective serotonin reuptake inhibitors, proton pump inhibitors, angiotensin-converting enzyme inhibitors and loop diuretics.

**Treatment of hypovolaemic patients.** Hypovolaemic hyponatraemia is common and is usually caused by sodium loss through the gastrointestinal or renal tract. Characteristic symptoms are reduced skin turgor, dry mucous membranes, tachycardia, low blood pressure or postural hypotension. Patients should be treated with 0.9% saline.

**Treatment of hypervolaemic patients.** Hypervolaemic hyponatraemia may be caused by cardiac failure, renal failure or liver cirrhosis. Characteristic symptoms are oedema, raised

**Table 1** Causes of drug-induced hyponatraemia [23]

Anticancer agents	Vinca alkaloids (vincristine, vinblastine) Platinum compounds (cisplatin, carboplatin) Alkylating agents (intravenous cyclophosphamide, melphalan and ifosfamide)
Antidepressants	Tricyclic antidepressants Selective serotonin reuptake inhibitors Monoamine oxidase inhibitors
Anti-epileptic drugs	Carbamazepine Oxcarbazepine Sodium valproate
Antihypertensive agents	Angiotensin-converting enzyme inhibitors Amlodipine
Antipsychotic drugs	Phenothiazines Butyrophenones
Diuretics	Thiazides Indapamide Amiloride Loop diuretics
Proton pump inhibitors	Omeprazole

jugular venous pressure, left ventricular failure and/or ascites. Management should focus on treating the underlying cause to improve hyponatraemia. In these circumstances, loop diuretics will produce a diuresis that exceeds the increased 24-h urine sodium losses they produce and so can be used safely.

**Diagnosis of euvoalaemic patients.** If a patient is euvoalaemic, it is important to confirm that the patient has hypotonic hyponatraemia. Check plasma osmolality and urine osmolality. If plasma osmolality is > 275 mOsm/kg, consider causes of hypertonic hyponatraemia, such as hyperglycaemia or mannitol infusions.

If urinary osmolality is < 100 mOsm/kg, consider primary polydipsia or 'beer drinker's potomania' (low-solute diet associated with reduced capacity to excrete free water).

If plasma osmolality is < 275 mOsm/kg, and urine osmolality is > 100 mOsm/kg, check urinary sodium concentration. SIADH is the likely diagnosis if urinary sodium is > 20 mmol/L. If urinary sodium is < 20 mmol/L, reconsider the volume status of the patient, as this usually reflects intravascular volume depletion.

**Treatment of patients with SIADH.** SIADH is characterised by the presence of hypotonic hyponatraemia in a context of inadequately diluted urine given the hypo-osmolality in plasma, in the absence of a low effective circulating volume (either with hypovolaemia or hypervolaemia) [5]. In most, if not all, cases, the most common cause of hyponatraemia is the nonosmotic release of arginine vasopressin (AVP) [9].

Exclude the following conditions for definitive diagnosis: renal failure, adrenal insufficiency, severe hypothyroidism, as well as nonosmotic physiological stimuli of AVP secretion (e.g. volume depletion, pain, stress and nausea [10]). Causes of SIADH are multiple and varied and range from medication side effects to underlying malignancy. If there is no clear cause following initial investigations, or if there is a repeat admission with hyponatraemia, consider systematic radiological investigations, such as computed tomography of the chest/abdomen/pelvis and magnetic resonance imaging of the head.

Fluid restriction is the mainstay of treatment for SIADH; however, the degree of restriction necessary will vary, depending on the patient's ability to excrete electrolyte-free water.

Once SIADH has been definitively diagnosed, use the Furst formula (Box 2) to estimate electrolyte-free water clearance through the urine/plasma electrolyte ratio (U/P). If U/P is 0.5–1.0, then commence fluid restriction of 500 mL/day. If U/P is < 0.5, then commence fluid restriction of 1000 mL/day. If U/P > 1.0, then there is no excretion of electrolyte-free water and fluid restriction is unlikely to be beneficial.

## Box 2

**The Furst formula**

Dilute urine may be considered to have an isotonic portion and an electrolyte-free water portion. The proportions of electrolyte-free water and isotonic urine can be measured by the ratio of effective solutes (principally sodium and potassium, with associated anions) between the plasma and the urine [21].

Restriction of water intake to less than the amount of electrolyte-free water excreted will cause plasma tonicity, and hence serum sodium, to rise. The amount of electrolyte-free water that can be cleared from the kidneys will therefore affect the patient's response to fluid restriction. A clinically useful equation simplified by Furst *et al.* for estimating free-water clearance is the urine/plasma electrolyte ratio measured in a urine sample [22]:

$$\text{U/P electrolyte ratio} = \frac{\text{Urine sodium concentration (mmol/L)} + \text{urine potassium concentration (mmol/L)}}{\text{Serum sodium concentration (mmol/L)}}$$

The principle of fluid restriction for the management of SIADH should be clearly understood and followed. The degree of fluid restriction can be difficult to calculate, initiate and maintain for patients in hospital and is also an added burden to the patients themselves as well as the nursing staff. When the urine to plasma electrolyte ratio is  $> 1.0$ , almost no amount of water restriction will result in a rise in serum sodium because free water is being retained, a process that will promote hyponatraemia.

**Undertaking effective fluid restriction.** Important features in the practice of fluid restriction include the use of fluid balance sheets, bedside notices and removal of excess bedside fluids. Paramedical staff, such as volunteers with tea rounds, must be made aware of the importance of the practice. Daily assessment of urea and electrolytes and clinical review must be made on all patients who are fluid restricted.

**Specialist review.** Patients in whom fluid restriction is not advised, or patients who have a poor response to fluid restriction after 24–48 h, should be reviewed by a consultant with experience of treating hyponatraemia – such as a consultant endocrinologist – who may consider use of pharmacological treatments, such as tolvaptan or demeclocycline. However, the latter treatment may cause problems with subsequent chemotherapy, for example candidiasis or impairment of renal function.

**Treatment with tolvaptan.** By binding to and blocking the V2 receptor, vaptan drugs can be used to correct hyponatraemia in SIADH. This is an attractive therapeutic avenue because it tackles the cause of the underlying fluid retention [11].

The SALT-1 and SALT-2 trials have shown that serum sodium can be safely improved in patients with hyponatraemia through removal of excess free water, producing additional

benefits in patients' quality of life, as measured by 12-item Short Form General Health Survey scores [11]. The prompt correction of hyponatraemia in patients with SIADH may be associated with a reduction in hospital stay [12].

Before initiating tolvaptan, it is essential to remove any fluid restriction and ensure that patients can drink in response to thirst, as correction of hyponatraemia can occur too rapidly if they are combined. Tolvaptan should be initiated at a dose of 15 mg, orally, once daily, and serum sodium should be monitored 6 h after starting treatment to exclude overly rapid correction [13]. Clinical experience is limited and its use should be restricted to consultant endocrinologists, oncologists, nephrologists or other appropriate specialists with significant experience of using this medication. We suggest that it should be prescribed as single doses and not as a repeated prescription: in many cases, just two or possibly three doses are required.

**Treatment with demeclocycline.** In the United Kingdom, demeclocycline is licensed to treat hyponatraemia associated with SIADH secondary to malignant disease, where fluid restriction is ineffective, and the patient does not have liver cirrhosis [13]. Demeclocycline should be started at a dose of 150 mg three times daily, assessed after 3 days and increased if necessary. However, the patient's response to demeclocycline can be unpredictable, and it has a slow onset of action [5]. The evidence base is sparse, and the frequency of its known hepatotoxic and nephrotoxic side effects [14–17] is unclear.

### Considerations regarding hyponatraemia and SIADH management

There remains controversy in the literature regarding the importance of prompt intervention in the setting of hyponatraemia and its implications for morbidity and inpatient hospital length of stay. Critics suggest that there is a lack of

evidence regarding the link between hyponatraemia and worsening patient outcomes, and indeed the majority of the work that has been carried out in this regard has been through retrospective studies rather than looking at prospective work with interventions to correct hyponatraemia [18]. Hyponatraemia is certainly associated with a number of disease states and may be a poor prognostic marker, but is not a discrete disease state in itself. It is usually a consequence of an inability of the kidneys to excrete a free water load, but given the complex aetiology of many medical conditions and their comorbidities, it can be difficult to ascertain to what degree the hyponatraemia is independently contributing to morbidity and mortality.

Whether hyponatraemia in a patient with cancer is merely a marker of poor prognosis or whether its presence may alter the patient's quality of life has not been definitively answered, but there is increasing evidence that hyponatraemia can no longer be considered just a biochemical 'bystander' in the ill patient [19]. A systematic diagnostic approach is necessary to determine the specific aetiology of a patient's hyponatraemia. Therapy must then be dictated not only by recognised reversible causes, such as advanced hypothyroidism, adrenal insufficiency, diuretics or other medicines, but also by whether the hyponatraemia occurs acutely or chronically and the degree of symptoms related to it [5].

Critically, most evidence suggests that overenthusiastic treatment of SIADH is considerably more dangerous than treatment that is slow or relatively ineffective. It is vital that all doctors should be aware of the need for a slow pace of normalisation of serum sodium except in the most extreme circumstances: *primum non nocere*.

## Summary

Hyponatraemia is under-recognised, incorrectly investigated and suboptimally managed, leading to poor patient outcomes. There is a well-recognised association with inpatient morbidity and mortality. Frequently, insufficient diagnostic assessment and investigations take place, and this can affect both patient management and outcomes [20]. Failure to treat hyponatraemia correctly may impede both patient outcomes and other factors, such as hospital length of stay. With regard to medical treatments, AVP antagonists offer a novel therapeutic approach. Currently, clinical experience is limited with these agents and randomised controlled trials to compare vaptans with the current standard of care are needed to demonstrate a clear benefit to patients with SIADH-related hyponatraemia to add to the evidence already available. We feel that the algorithm we have developed (Fig. 1) reflects the best available evidence and extensive clinical experience and provides practical, useable guidance to improve patient care.

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## Author contributions

All authors contributed equally to the development and design of the algorithm. Dr Grant and Professor Grossman were lead authors in drafting the submitted manuscript, to which all authors contributed.

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