HYPONATREMIA

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CLINICAL RECOGNITION

Hyponatraemia is common, being found in some 15–20% of non-selected emergency admissions to hospitals. It is associated with increased mortality, morbidity and increased duration of hospital stay, independent of the cause of admission. Clinical presentation is diverse, ranging from seizure and coma at one extreme to apparent absence of symptoms. This spectrum reflects a number of influences (Figure 1).

- The rate of development of hyponatraemia
- The degree of hyponatraemia
- The neurophysiologic adaptive capacity of the individual
- The influence of co-morbidities

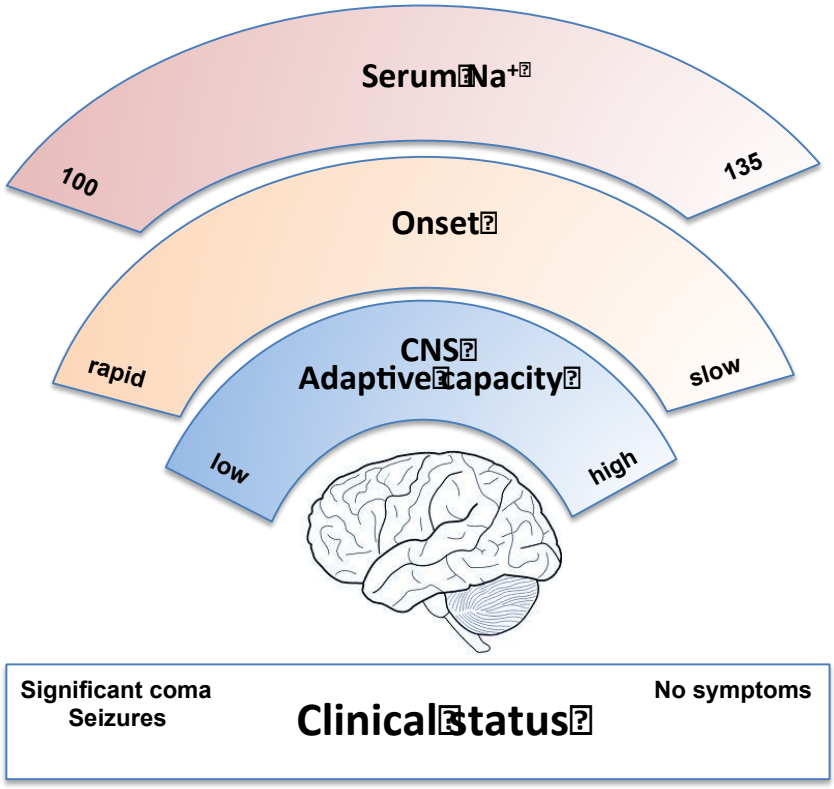

Figure 1. Factors contributing to clinical status in hyponatraemia
Clinical status of the patient reflects the interaction of a number of determinants: the degree of hyponatraemia; rate of change of serum Na^+; and the inherent adaptive capacity of the CNS to osmolar stress.

Management strategy should be stratified and based on an overall assessment of the severity of the clinical presentation.

Plasma sodium concentration reflects the balance between sodium and water content, with each component reflecting the balance of intake and output. This approach can be used to develop a framework for classifying hyponatraemia by aetiology (Table 1).

Table 1. Causes of hyponatremia	
Non-hypotonic hyponatraemia	
Hyperglycaemia Non-physiological osmolyte	
Sodium depletion	
Renal loss	Diuretics
	Salt wasting nephropathy
	Hypoadrenalism
	Central salt wasting
Extra renal loss	Gut loss
Excess water intake	
Dispsogenic DI	
Sodium-free, hypoosmolar irrigant solutions	
Dilute infant feeding formula	
Inappropriate intravenous fluid therapy	
Reduced renal free water clearance	
Hypovolemia	Drugs (e.g. diuretics)
	Renal failure
	Portal hypertension and ascites
	Hypoalbuminemia
	Sepsis and vascular leak syndromes
	Salt wasting
	Fluid sequestration
Other	Cardiac failure
	Nephrotic syndrome
	Hypothyroidism
	Hypoadrenalism
	Syndrome of inappropriate antidiuresis (SIAD)
	Nephrogenic SIAD
	Excess use of AVP analogues (desmopressin [DDAVP], oxytocics)

Intravascular volume depletion (hypovolaemia)

Intravascular volume depletion leads to non-osmoregulated vasopressin (AVP) production and reduced free water excretion. AVP production can persist despite ensuing hyponatraemia. Portal hypertension, congestive cardiac failure and hypoalbuminaemia can all reduce effective circulating volume (independent of drug treatment), even in the context of excess total body sodium. Long-term diuretic use is a common cause of hyponatraemia. Because it may develop slowly, patients can be relatively asymptomatic. Those on thiazide diuretics are particularly at risk as these agents produce solute loss without limiting renal concentrating ability.

Excess hypotonic fluid intake

The administration or absorption of hypotonic fluids at a rate that exceeds renal free water excretion will inevitably result in hyponatraemia. This can be seen with oral fluid intake (dipsogenic diabetes insipidus), intravenous fluid therapy and the absorption of hypotonic irrigating fluids following surgery to the lower renal tract or colonoscopy.

Syndrome of inappropriate antidiuresis (SIAD)

In SIAD there is a failure to maximally suppress AVP secretion as plasma osmolality falls below the normal osmotic threshold for AVP release. As patients continue to drink, persistent antidiuresis produces dilutional

hyponatraemia. Diagnosis of SIAD involves the exclusion of volume depletion and other endocrine causes of reduced free water excretion (Table 2).

Table 2. Diagnostic criteria for SIAD
Hyponatraemia
Urine Osmolality >100 mOsm/kg (sub-maximum dilution)
Urine Na+ >20 mmol/L (excluding effective intravascular volume depletion)
Absence of the following: •hypotension and hypovolaemia •non-osmotic stimuli for AVP release •oedema •adrenal failure •hypothyroidism

The majority of patients with SIAD are euvolaemic on clinical examination. Urine sodium concentration is often above 80 mmol/l.

Many drugs cause SIAD. Drug histories are therefore an important part of the clinical assessment of patients presenting with hyponatremia (Table 3).

Table 3. Causes of SIAD	
Drugs	•Antidepressants (Tricyclics, SSRIs) •Dopamine agonists (Metoclopramide, Prochlorperazine, Antipsychotics) •Anticonvulsants (Carbamazepine, Phenytoin, Sodium valproate) •Opiates
CNS Disturbances	•Stroke •Haemorrhage •Infection, •Trauma
Malignancies	•Small cell lung cancer •Pancreatic, duodenal and head/neck cancers
Surgery	•Abdominal, thoracic or pituitary surgery
Pulmonary disease	•Pneumonia •Pneumothorax
Idiopathic	

Central salt wasting

This acquired primary natriuresis is a rare cause of hyponatraemia with hypovolaemia. The underlying mechanism(s) remains unclear, but may involve a number of processes.

•Increased release of natriuretic peptides

•Reduced sympathetic drive

Central salt wasting has ben described following a variety of neurosurgical situations. Diagnosis hinges on the natural history of the process.

•The development of hyponatraemia, preceded by natriuresis and diuresis

•Clinical and biochemical features of hypovolaemia and renal impairment

Central salt wasting is a concern for the neurosurgical patient in whom auto regulation of cerebral blood flow is disturbed such that small reductions in circulating volume can reduce cerebral perfusion. Syndrome of inappropriate antidiuresis (SIAD) can occur in the same group of patients. As management of the two conditions is diametrically opposed, it is important to make the correct diagnosis.

Nephrogenic SIAD

The action of AVP on renal water excretion is mediated by the G-protein-coupled type 2 AVP-receptor (V2-R). Loss-of-function mutations of the V2-R are the cause of X-linked nephrogenic diabetes insipidus. Recent studies have identified the reciprocal phenotype: mutations in the V2-R that are constitutively activating, leading to AVP-independent but V2-R-mediated antidiuresis with persistent hyponatraemia. Patients may present in infancy or may remain undetected until adulthood.

DIAGNOSIS and DIFFERENTIAL

History and examination are key to the clinical approach. They provide insights into the aetiology, rate of development, clinical impact and contributing co-morbidities: all factors important in a patient-focused approach to management (Table 4).

Table 4. Focus of history & examination in the patient with hyponatraemia

History	•Fluid loss (e.g. vomiting, diarrhoea) •Causes of SIAD •Symptoms of endocrine dysfunction suggestive of hypoadrenalism or hypopituitarism •Medication/drug use
Examination	•Signs of extracellular volume depletion •Orthostatic or persistent hypotension. •Signs of peripheral oedema, or ascites, heart failure, cirrhosis, or renal failure

Laboratory tests provide important information in the differential diagnosis of hyponatraemia.

Serum osmolality

The serum osmolality (which normally ranges from 275 to 290 mOsmol/kg) is primarily determined by the concentration of serum sodium (and accompanying anions). It is reduced in most cases of hyponatraemia (hypotonic hyponatraemia). In some instances, hyponatraemia is not associated with dilute plasma. This is termed non-hypotonic hyponatraemia (Table 5).

Table 5. Causes of non-hypotonic hyponatraemia

Context	Serum osmolality	Examples
Increase in effective osmolytes raise serum osmolality & can cause hyponatraemia	Isotonic or hypertonic	Glucose, Mannitol & Sorbitol Glycine Hyperosmolar contrast media Maltose
Increase in ineffective osmolytes raise serum osmolality but do not cause hyponatraemia	Isotonic or hypertonic	Urea Alcohols & Ethylene glycol Lactate
Artifact endogenous solutes that can cause pseudohyponatramia	Isotonic	Lipids & protein Immunoglobulin

Urine osmolality

The normal response to hyponatraemia is to suppress AVP secretion,

resulting in the excretion of maximally dilute urine with an osmolality below 100 mOsmol/kg. Values above this level indicate an inability to normally excrete free water, indicating secretion and action of AVP.

Urine sodium concentration

The urine sodium concentration can be used to distinguish between hyponatraemia caused by effective arterial volume depletion (such as in true hypovolaemia, heart failure, and cirrhosis) and that caused by euvolaemic/hypervolaemic hyponatraemia (most often due to SIAD).

The combination of urine osmolality and urine Na^+ concentration can be used to form a utilitarian algorithm for the investigation and differential diagnosis of hyponatraemia (Figure 2).

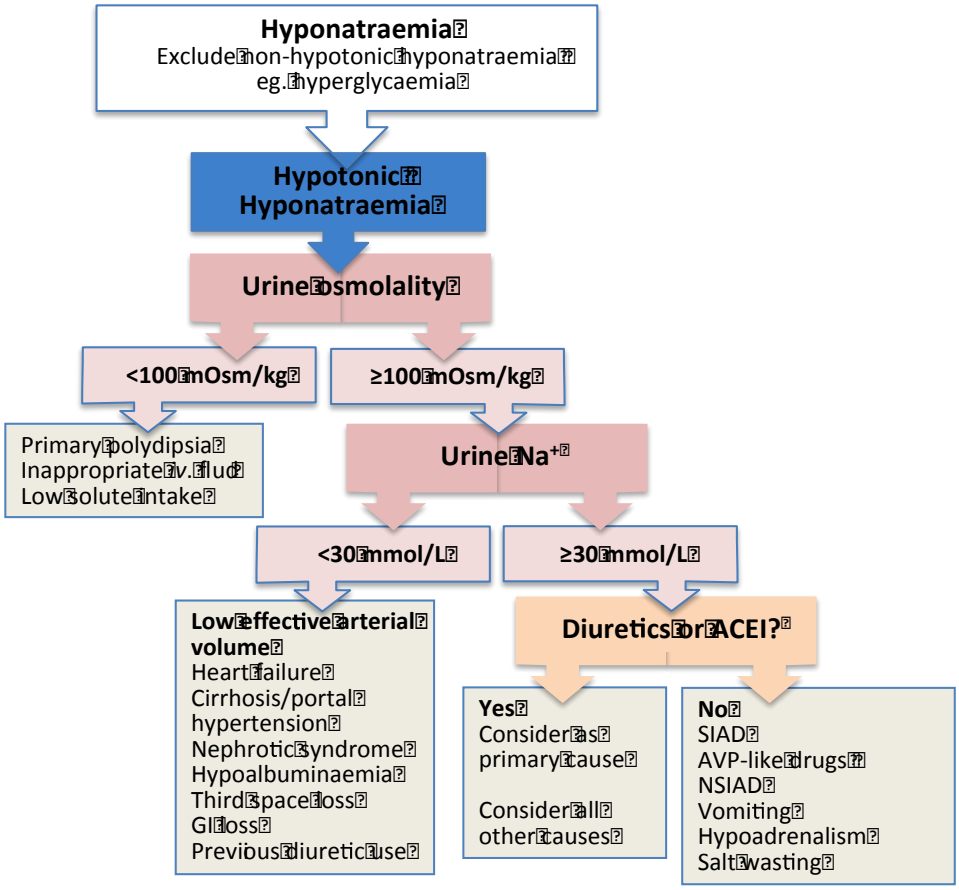

Figure 2. Diagnostic algorithm for patients presenting with hyponatraemia

TREATMENT

While hyponatraemia can be life threatening, chronic hyponatraemia can be tolerated very well even when profound. This diversity poses a management challenge: clinicians must balance the efficacy of any intervention with that of the potential adverse impact of both the intervention and persisting hyponatraemia. Rapid correction of hyponatraemia can trigger central nervous system osmotic demyelination and should therefore only be used in those patients with the highest risk of morbidity and mortality from on-going hyponatraemia. Importantly, the aim of management should not be to normalise plasma sodium. Rather, it should be achieving a plasma sodium level that reverses or reduces morbidity at such a rate that minimises risk of osmotic demyelination. This requires a stratified approach based on clinical presentation: balancing a number of clinical drivers to optimise outcome (Figure 3).

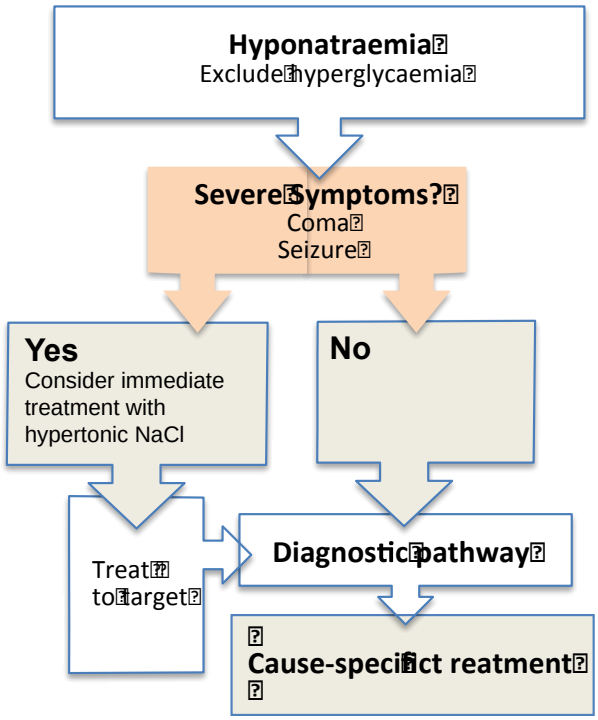

Figure 3. Management algorithm for the treatment of hyponatraemia

General and supportive measures

The appropriate clinical environment for the management of hyponatraemia is the one that matches the clinical needs of the patient. Management of hyponatraemia in a patient with significant neurological morbidity, in whom plasma sodium is being raised over hours, requires close clinical and biochemical observation. This is best achieved in a high-dependency setting. Cerebral oedema and coma associated with hyponatraemia may need supportive management with assisted ventilation.

Patients with significant coma or seizures

Treatment with hypertonic sodium chloride addresses the reduction of plasma sodium concentration simply and directly. Moreover, the ensuing natriuresis increases obligate renal water loss. An infusion of 3% sodium chloride at 1-2 ml/kg/ hour, or the use 100-150ml boluses of 3% sodium chloride are acceptable approaches. The increase in plasma sodium should be limited to of no more than 10 mmol/L in the first 24 hours. Given the risk of over-correction, a pragmatic strategy is to aim for a rise of 6-8 mmol/L in first 24 hours. A relatively rapid rise in plasma sodium of 2–4 mmol/L over the initial 2–4 hours appears safe in this setting and may aid in reducing intra-cerebral pressure in the acute setting. After the first 24 hours, the rate of rise of sodium should be limited to no more than 8 mmol/L per day.

Avoidance of over-correction is critical. If over-correction does occur, it is important to seek expert advice and consider actively controlling the rate of rise of plasma sodium with hypotonic fluid. Hypertonic fluid should be stopped when the defined clinical target (such as cessation of seizures) or a sodium concentration of 130 mmol/L is reached, whichever is first. If hypertonic sodium chloride cannot be given safely, it should not be given.

Patients with mild or less severe symptoms and signs

The clinician has time to make a diagnosis, identify and address contributing factors if possible and introduce a focussed intervention based on aetiology. Importantly, the limits on rate of rise of sodium remain the same. The majority of patients will have circulating volume depletion or SIAD. Where these are due to drug treatments, the

removal of the causal agent may be sufficient to normalise sodium. There will be some cases where the causal agent cannot be removed or where there is an alternative diagnosis. Plasma sodium may rise faster than 2 mmol/l/hour during 'auto correction' of hyponatraemia when an underlying cause has simply been removed, for example a correction of glucocorticoid insufficiency or withdrawal of excess desmopressin. Osmotic demyelination can still occur in these circumstances.

Fluid challenge in hypovolaemic hyponatraemia

Mild to moderate hypovolaemia can be difficult to diagnose clinically and low urine sodium excretion (<20 mmol/L) may be unreliable as a diagnostic test in the face of diuretic use or renin-angiotensin system blockade. If volume depletion is suspected, a moderate intravenous fluid challenge with 0.5–1 L N-saline over 2–4 hours may be both diagnostic and therapeutic.

Fluid restriction in SIAD

Fluid restriction of 0.5–1 L/day is a reasonable initial intervention when excess plasma water is suspected and when the clinical condition is not critical. In patients with primary polydipsia, reduction in fluid intake remains the most reasonable approach. All fluids need to be included in the restriction. As SIAD is associated with negative sodium balance, sodium intake needs to be maintained. Several days of restriction may be required before sodium levels rise and a negative fluid balance needs to be confirmed through appropriate monitoring.

Management of persistent hyponatraemia

Hyponatraemia may persist or recur after initial intervention. It is important that the differential diagnosis is reviewed and the basis for intervention reconsidered.

•In SIAD, fluid restriction may be only partly effective or may prove non-sustainable

•Chronic liver or cardiac dysfunction may persist

•Drug therapy exacerbating hyponatraemia may need to continue

Clinical decisions on further management have to balance the merits of incremental intervention with those of tolerating mild, persisting hyponatraemia. Treatment aimwd at simply raising serum Na^+ may be of limited benefit.

Demeclocycline

Demeclocycline has been used in SIAD. It produces a form of nephrogenic diabetes insipidus and so increases renal water loss, even in the presence of high concentrations of AVP. Treatment is 600–1,200 mg/day in divided doses. There is a lag time of some 3–4 days in onset of action. Dose adjustment needs to take this into account. Photosensitive skin reactions and renal impairment are significant adverse effects and limit clinical utility.

Urea

Urea can be used to treat persisting hyponatraemia of SIAD. Active orally at doses of 30 g/day, urea increases renal free water excretion and decreases urinary sodium.

Vasopressin receptor antagonists

Vasopressin receptor antagonists (Vaptans) are a rational approach to the management of SIAD. They are classified as either selective (V2-R specific) or non-selective (V2- and V1a antagonism). Both increase renal water excretion without a significant impact on renal electrolyte loss (aquaretic action). To avoid precipitating a rapid rise in plasma Na^+, fluid restriction should be relaxed if these drugs are introduced. They should not be used in profound hyponatraemia or in patients with severe symptoms. Their role in management of SIAD remains to be clarified.

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