Guidelines for the management of hyponatraemia

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DISCLAIMER: These guidelines were produced in good faith by the author(s) in conjunction with the paediatric nephrology team at the University Hospital of Wales, Cardiff reviewing available evidence/opinion. They were designed for use by paediatric nephrologists at the University Hospital of Wales, Cardiff for children under their care. They are neither policies nor protocols but are intended to serve only as guidelines. They are not intended to replace clinical judgment or dictate care of individual patients. Responsibility and decision-making (including checking drug doses) for a specific patient lie with the physician and staff caring for that particular patient.

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Summary
These guidelines are aimed at providing the doctors presented with a child with hyponatraemia with information to help identify the underlying problem and to guide treatment.

Introduction
Hyponatremia, defined as serum $[\text{Na}^+]$ sodium < 135 mmol/l, reflects deficiency of sodium relative to water. Serum $[\text{Na}^+]$ is the main determinant of plasma osmolality and hence hyponatraemia reflects hypo-osmolality. This will result in water movement into cells including brain cells, accounting for the symptoms of hyponatraemia.

Serum osmolality (calculated) = 2 × (serum $[\text{Na}^+]$) + serum [urea] + serum [glucose]

Effective circulating volume refers to that part of the extracellular fluid (ECF) that is in the vascular space and available to perfuse tissues.

Volume depletion refers to a decrease in ECF volume from any cause, most often due to sodium and water loss.

Serum $[\text{Na}^+]$ and plasma osmolality are monitored by a very sensitive osmoreceptor in the hypothalamus that regulates the secretion of the antidiuretic hormone, arginine vasopressin (AVP). AVP facilitates urinary concentration increasing the transcription and insertion of water channels (Aquaporin-2) into the apical membrane of the distal convoluted tubule and collecting duct epithelial cells and water excretion is enhanced in its absence.

Serum $[\text{Na}^+]$ is determined mainly by total body water but also by total body sodium and renal excretion of sodium is regulated by effective plasma volume (not by plasma osmolality). Water retention (due to a defect in excretion) leading to an excess of water in relation to solute is the common denominator in almost all patients with hyponatraemia. Virtually all (except those with renal failure & primary polydipsia) will have an excess of antidiuretic hormone (ADH), most often due to effective circulating volume depletion or rarely due to SIADH.

Causes
Mechanisms for hyponatremia:
1. Loss of sodium in excess of water
2. Gain of water in excess of sodium

Hypovolaemic - ECF volume contraction (Total body water ↓, total body sodium ↓)
Renal (Urine $[\text{Na}^+]$ > 20 mmol/l) -
- Mineralocorticoid deficiency/resistance
- Diuretics
- Polyuric acute renal failure
- Salt wasting renal disease
- Renal tubular acidosis
- Metabolic alkalosis
- Syndromes - Bartter’s / Gitelman’s
Gastrointestinal (Urine $[Na^+] < 20$ mmol/l) -
- Diarrheal dehydration
- GI suction/fistula/stoma
- Laxative abuse
- Transcutaneous - Cystic fibrosis, heat exhaustion
- Third space loss
- Burns, major surgery
- Septic shock, trauma
- Intestinal obstruction

**Euvolaemic - Normal ECF volume** (Total body water $\uparrow$, total body sodium $\leftrightarrow$)
- Glucocorticoid deficiency
- Hypothyroidism

**Hypervolaemic - ECF volume expansion** (Total body water $\uparrow\uparrow$, Effective circulating volume $\uparrow$, total body sodium $\uparrow$)
- Acute renal failure (e.g. PIGN)
- Chronic renal failure
- Cirrhosis / Congestive cardiac failure
- Nephrotic syndrome
- Capillary / vascular leak syndrome
- Psychogenic polydipsia / compulsive drinking

**Mild hypervolaemia**
- Antidiuretic drugs
- Reduced renal water excretion
- Inappropriate secretion of ADH (SIADH)

**Factitious** – hyperglycaemia / mannitol / sorbitol

**History**
1. Symptoms suggestive of underlying disorder
2. Symptoms of hyponatraemia

Symptoms of hyponatraemia primarily reflect neurological dysfunction (due to brain cell swelling) induced by hypo-osmolality, the severity of which depends on the speed and degree of the reduction in the serum $[Na^+]$. The symptoms include anorexia, nausea, vomiting, malaise, lethargy, confusion, agitation, headache, seizure, coma and decreased reflexes. Hyponatraemia can also cause hypothermia, muscle cramps and weakness.

Assessment of urine output, fluid balance and weight changes is essential.

**Physical examination**
In addition to basic parameters (e.g. Wt, BP), it should include clues of the underlying cause and assessment of ECF volume status.
Investigations
In addition to the appropriate tests to confirm the underlying disorder, the following investigations are essential:

Blood
- Osmolality
- Sodium, potassium, chloride, bicarbonate
- Urea, creatinine, glucose
- Blood gas if bicarbonate abnormal

Urine
- Osmolality
- Sodium, potassium, chloride
- Urea, creatinine
- Calculate fractional excretion of sodium and fractional excretion of water

Calculation of fractional excretions of water (FEH₂O) and sodium (FENa)
FEH₂O = serum [creatinine] / urine [creatinine]
FENa = (urine [Na⁺] / serum [Na⁺]) x (serum [creatinine] / urine [creatinine])
Convert serum [creatinine] to mmol/l

FE values are often expressed as % (multiply result by 100)

The FEH₂O is the fraction of the glomerular filtrate volume (GFR) that appears as urine.
The FENa is the fraction of the sodium filtered by the glomeruli which appears in the urine.
The FE values in health vary because people’s water and salt intakes vary; there are therefore no normal ranges. However, under stress they respond predictably, so can be used to understand the pathophysiology. Even mild dehydration causes a release of ADH and renin, and thus avid tubular reabsorption of water and salt leading to a fall in FEH₂O and FENa. Children with healthy kidney tubules can lower both FE values to <1%, and often much lower.

Urine osmolality
Indicates whether water excretion is normal or impaired. The majority of patients with hyponatraemia will have a value just above 100 mOsm/kg, but it may still be hypop-osmotic to plasma and inappropriately high.
Syndrome of inappropriate ADH secretion (SIADH)
This rare but frequently over diagnosed condition is characterized by non-physiologic release of ADH (not inhibited by either low serum osmolality or expanded intravascular volume) and by the unusual finding of impaired water excretion at a time when sodium excretion is normal. Persistent ADH release leads to water retention resulting in dilution (hyponatremia and hypoosmolality) and expansion of body fluids. The kidneys increase sodium excretion (hence no oedema) in an effort to correct the volume status, leading to a mild decrease in total body sodium.

Causes of SIADH
CNS disorders
- Infections
- Malignancy
- Trauma
- Hypoxic damage
- Cerebral malformations
- Vascular accidents
- Guillain-Barre syndrome
Post-surgery
- Abdominal
- Cardiothoracic
- Neurosurgery
- Anaesthetic or premedication
Pulmonary
- Infections
- Malignancy
- Cystic fibrosis
- Mechanical ventilation
Drugs
- Cyclophosphamide
- Carbamazepine
- Vincristine
- Vinblastine,
- Others
Others
- Leukaemia
- Lymphoma,
- Porphyria
- HIV infection
- Ectopic production of ADH

Diagnostic criteria
The term SIADH is a diagnosis of exclusion and is frequently misused in clinical practice, since many patients thought to have SIADH have an alternative explanation for hyponatraemia. Frequently the secretion of ADH is appropriate rather than inappropriate and unrecognised hypovolaemia is present.
Presence of….
1. Hyponatremia & hypoosmolality
2. Urine osmolality is inappropriately high, commonly >100 (usually > plasma osmolality)
3. Decrease in haematocrit, plasma albumin, urea & creatinine due to increased ECF volume
4. Urine sodium >20 (usually >40 mmol/l) and shows normal response to sodium restriction

Absence of….
1. Dehydration/volume depletion or ingestion of diuretics
2. Renal, hepatic or cardiac failure/dysfunction
3. Pituitary or thyroid dysfunction
4. Other known stimuli for ADH secretion - pain, nausea, drugs or thermal injury

Management of hyponatraemia (see algorithm)
1. Identify and treat the underlying cause
2. If hyponatraemia has developed acutely (over 12-24 hours) and the patient has severe neurological symptoms, urgent correction is needed (until symptoms are controlled) - by infusing 4-6 ml/kg of 3% sodium chloride, which will increase serum [Na⁺] by 3-5 mmol/l. Maximum infusion rate is 4 ml/kg/h (which raises serum [Na⁺] by 3 mmol/l/h). Further correction can be done slowly.
3. Those with chronic hyponatraemia tend to be the least symptomatic and are at higher risk of severe side effects (e.g. central pontine myelinolysis) if serum [Na⁺] is corrected too rapidly.
4. If there is ECF volume depletion infusing a fluid isotonic to the patient is ideal in order to avoid too rapid a rise in serum [Na⁺] if using 0.9% NaCl.
5. Hyponatraemia should be corrected slowly (rate of correction of serum [Na⁺] should be < 0.3 mmol/l/h or < 8 mmol/l/day). Regular measurement of serum [Na⁺] is essential.
6. The focus of treatment depends on the clinical setting:
   a. Create a negative balance for electrolyte free water (EFW)
   b. Create a positive balance for Na⁺
   c. Replace any deficit of K⁺

Sodium deficit = 0.6 × Wt (in Kg) × (desired serum [Na⁺] - current serum [Na⁺])
Management of Hyponatremia

Hyponatremia (HN)

Severe (<125)?

Yes

Severe neurological symptoms?

Yes

Likely to be of acute onset (12-24 hours)

Urgent correction
4-6mL/kg of 3% NaCl till symptoms improve

No

Likely to be chronic
Urgent correction not needed

What is ECF volume status?

Hypovolemic

- Fluid resuscitation if in shock
  - Then replace water & sodium losses (deficit + maintenance = ongoing) orally or intravenously

Euvolemic

- Treat thyroid/adrenal deficiency
  - SIADH: Water restriction
  - (25-50% of maintenance)
  - 3% sodium chloride IV
  - Loop diuretics
demeclocycline

Hyypervolemic

- Treat underlying cause
  - Restrict salt & water
  - Diuresis, 70% Albumin
  - ACE inhibitors
  - Capillary leak syndrome
  - Low dose mannitol
  - Hemofiltration