Guidelines for the management of hyponatraemia in hospitalised patients

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Aims: To provide guidelines for appropriate investigations and treatment of hyponatraemia in hospitalised patients.

<table>
<thead>
<tr>
<th>Normal range</th>
<th>Mild hyponatraemia</th>
<th>Moderate hyponatraemia</th>
<th>Severe hyponatraemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>133-146 mmol/L</td>
<td>127-132 mmol/L</td>
<td>121-126 mmol/L</td>
<td>≤120 mmol/L</td>
</tr>
</tbody>
</table>

Evaluation of hyponatraemia

STEP 1: Rule out artefactual causes

- Is the patient on IV fluids?
- If so, could the sample have been taken “downstream” from the infusion site?
- Could the sample have been taken from the same line?

STEP 2: Clinical history

- Check fluid balance to exclude fluid overload
- Is the patient diabetic? Hyperglycemia may cause dilutional hyponatraemia and increased urinary loss of sodium
- Correct serum sodium for hyperglycemia (rise in plasma glucose >5.5mmol/L) by using equation given in (Appendix 1)
- Consider medications (Table 1). In some cases, stopping the medication or changing to an alternative that does not cause hyponatraemia may be sufficient. Monitor sodium concentrations to assess the effects of this management. It may take several days for the sodium to normalise after withdrawing medications
- Review clinical history for relevant conditions (such as congestive cardiac failure, kidney disease, liver failure, lung pathology)
- Loss of weight /appetite: investigate for malignancy
Table 1: Drugs known to cause hyponatraemia

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Examples known to cause hyponatraemia (other compounds may exist)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretics</td>
<td>Bendroflumethiazide, Metolazone, Indapamide, Chlortalidone</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Furosemide, Bumetanide, Torasemide</td>
</tr>
<tr>
<td>Potassium-sparing diuretics</td>
<td>Amiloride, Spironolactone, Triamterene, Eplerenone</td>
</tr>
<tr>
<td>Combined diuretics</td>
<td>Co-amilofruse, Co-amilozide</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonators</td>
<td>Candesartan</td>
</tr>
<tr>
<td>Tricyclic (&amp; related) antidepressants</td>
<td>Amitriptyline, Clomipramine, Dosulepin, Imipramine, Nortriptyline, Tramipramine, Mianserin, Trazodone</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Citalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline</td>
</tr>
<tr>
<td>MAO inhibitors</td>
<td>Phenelzine, Isocarboxazid, Tranylcypromine, Moclobemide</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, Valproate</td>
</tr>
<tr>
<td>Others</td>
<td>Venlafaxine, Duloxetine, Chlorpropamide, Glimepride, Glipizide</td>
</tr>
</tbody>
</table>

**STEP 3: Clinical examination to assess extracellular volume (Appendix 2)**

- Hypovolaemia: Signs of dehydration, such as hypotension, tachycardia, oliguria, dry oral mucosa, reduced skin turgor, reduced central venous pressure
- Euvolaemia: Normal blood pressure, pulse rate, central venous pressure
- Hypervolaemia: Pedal oedema/ascites

*Clinical findings must be considered when requesting and interpreting the results of laboratory investigations*

**STEP 4: Biochemical investigation**

Samples should be sent to the laboratory for the following investigations as soon as possible, and preferably before starting treatment:

- Paired serum and spot urine for U&E and osmolality
- Plasma glucose

If there is suspicion of adrenal insufficiency or severe hypothyroidism, the following investigations should be performed:

- 9 am serum for cortisol; if equivocal, a short synacthen test may be necessary
- Thyroid function tests

Hyponatraemia may be categorised into three types, depending on the extracellular fluid volume and biochemical investigations.

*When requesting tests through ICE (RLBUHT), click on the “Hyponatraemia investigations” link for a list of tests that should be requested to investigate a patient with hyponatraemia*
Figure 1: Flowchart to aid in diagnosis of underlying causes of hyponatraemia

1. Exclude artefactual causes
2. Check medications
   - Is patient on medications listed in Table 1?
   - Yes → Discontinue medications
     - Monitor serum sodium for 2 to 3 days
   - No → Check fluid balance
3. Check fluid balance
   - Is patient in positive fluid balance?
   - Yes → Discontinue IV fluids, start fluid restriction
     - Monitor serum sodium for 2 to 3 days
   - No → Send hyponatraemia investigations
     - See link on ICE under U&E
4. Assess patient’s volume status clinically
5. Hypovolaemia → Renal or extra-renal loss of sodium
6. Euvolaemia → Urine sodium >30mmol/L
   - Medications (Table 1)
     - Glucocorticoid deficiency
     - Severe Hypothyroidism
     - SIADH
   - Hypervolaemia → Acute kidney injury
   - Chronic kidney disease
   - Congestive cardiac disease
   - Liver cirrhosis
   - Nephrotic syndrome
Management of hyponatraemia

Treatment depends on the patient’s

- Estimated volume status
- Serum sodium concentration
- Chronicity
- Rate of fall of the serum sodium concentration

Hypovolaemic hyponatraemia

- Rehydrate with sodium chloride 0.9% infusion or balanced crystalloid solution (Hartmann)
- Volume and rate of fluid to be administered in severe chronic hyponatraemia can be calculated by equation 1 (see below)
- Hartmann (balanced crystalloid solution) should be preferred over normal saline provided patient does not have hyperkalaemia, alkalosis (raised bicarbonate) and hypercalcaemia
- Normal saline should be given where there is upper gastrointestinal loss (loss of hydrochloride) or serum chloride <90mmol/L
- Check U&E after infusion and prescribe further fluids based upon the result

Hypervolaemic hyponatraemia

- Fluid and salt restriction
- Consider diuretics
- Treat the underlying cause

Euvolaemic hyponatraemia

- If possible treat the cause (e.g. chest infection, malignancy or hormonal insufficiency)
- If treating SIADH (Appendix 3) - Commence fluid restriction (500-750 ml/day)
- Maintain accurate fluid balance chart
- Measure weight of the patient daily
  If serum Na not corrected despite adherence to appropriate fluid restriction, consider Tolvaptan
  (only after discussion with Endocrinology consultant)

Management of acute severe symptomatic hyponatraemia (serum sodium ≤120mmol/L)
(Appendix 4)

- Acute (<48 hours) severe symptomatic hyponatremia can cause substantial morbidity and mortality
- When hyponatremia develops quickly over several hours, the ability of the brain to adapt is exceeded, and cerebral edema may result. Thus, patients with acute (<48 hours) hyponatremia may present with alarming neurological findings, and they sometimes die of brain herniation
- Patient presenting with confusion, seizures, coma, Glasgow coma score <11, headache should be assessed clinically to determine whether these symptoms are due to acute severe symptomatic hyponatremia or induced by other conditions. If these symptoms are suggestive of symptomatic hyponatremia, please seek Consultant advice URGENTLY
Infusion of IV 3% hypertonic saline 100mls bolus infused over 10 min (x3 as needed) may be required for life-threatening acute severe symptomatic hyponatraemia (This should be administered only after approval from Consultant and with high dependency support)

A small, quick increase in the serum Na (4-6 mmol/L) is effective in treating acute hyponatremia because reducing brain swelling even slightly will substantially decrease intracerebral pressure.

**Rate of correction of chronic severe hyponatraemia (serum sodium ≤120mmol/L)(Appendix 4)**

- Remember that rapid correction of chronic hyponatraemia can cause potentially fatal brain stem demyelination ("central pontine myelinolysis) or osmotic demyelination syndrome (ODS) as it impairs brain's ability to re capture lost organic osmolytes.
- It is highly unlikely to occur in patients who have been hyponatraemic for <24 hours or in patients whose serum Na is >120 mmol/L

**The rate of serum sodium correction should be no more than 0.5 mmol/L/hr (10-12 mmol/L/24hr).**

**The following formula can be used to calculate sodium replacement using 0.9% saline (Equation 1)**

- In order to achieve a 0.5 mmol/h increase in serum sodium, use this formula to calculate the amount of intravenous sodium needed per hour (mmol/h):
  - Amount of sodium replacement (mmol/h) = 0.6 x wt (kg) x 0.5 (desired correction rate mmol/h),
  - When using 0.9% saline (Normal Saline)(1000ml contains 154 mmol sodium) the rate of infusion required to achieve a 0.5 mmol/h improvement in serum sodium is given by:

\[
\text{Amount of sodium replacement (mmol/h) } \times (1000/154) = \text{ml/hr of 0.9% saline required.}
\]

**Example: for an 80 kg patient:**
- 0.6 x 80 x 0.5 = 24 mmol/hr sodium required
- \((1000/154) \times 24= 156\text{ml/hr of 0.9% saline}\)

Check serum sodium every 4 hours and continue the infusion until:
- serum sodium > 120 mmol/L
- serum sodium rises faster than 0.5 mmol/h or 2mmol/4 hours
- serum sodium rises by more than 6 mmol/L in 12 hours or 12 mmol/L in 24 hours

Please contact the Duty Biochemist in Clinical Biochemistry or On call Endocrinology SpR (through the switch board) for advice on management of hyponatraemia.
APPENDICES

Appendix 1
Equation for correction of serum sodium for hyperglycaemia

Corrected serum Sodium (mmol/L) =

Measured serum sodium + 2.4 X \[
\frac{[\text{Serum Glucose (mmol/L)} - 5.5\text{mmol/L}]}{5.5\text{mmol/L}}
\]

Adapted from Hillier et al (1999)

Appendix 2 Classification of Hyponatraemia

Hypovolaemic hyponatraemia

- Whole body sodium and water depletion, with renal or extra-renal sodium loss
- Extra-renal loss of sodium stimulates the renin-angiotensin-aldosterone axis, reducing the excretion of sodium in the urine (urine Na ≤30 mmol/L)
- In cases of renal loss (including diuretics), there is increased excretion of sodium (urine Na >30 mmol/L)
- Clinically these patients present with signs and symptoms of dehydration

Hypervolaemic hyponatraemia

- An excess of sodium and a greater excess of water
- Accumulation of interstitial fluid reduces the effective circulating volume, which stimulates aldosterone and ADH secretion, increasing the reabsorption of sodium and water from the kidney
- Clinically may present with detectable oedema or ascites due to reduced oncotic pressure, which causes a shift of fluid into the interstitial space

Euvolaemic hyponatraemia

- Normal whole body sodium with water excess
- The cause of apparently euvolaemic hyponatraemia is often not immediately apparent
- In hospitalised patients, a common cause of euvolaemic hyponatraemia is inappropriate intravenous fluids
- Other causes of euvolaemic hyponatraemia must be ruled out before the diagnosis of SIADH is made (see Appendix 2). SIADH should be differentiated from cerebral salt wasting syndrome (see Appendix 2)
### Appendix 3  Criteria for the diagnosis of SIADH

**Criteria for the diagnosis of SIADH**

- Serum osmolality <275mosm/kg
- Urine osmolality >100mosm/kg
- Urine sodium >30mmol/L
- Absence of adrenal, thyroid, pituitary or renal insufficiency
- Clinically euvolemic

Adapted from Schwartz et al (1957)

### Appendix 4  Management of severe hyponatraemia

**(serum sodium ≤120mmol/L)**

<table>
<thead>
<tr>
<th>Acute severe symptomatic hyponatraemia</th>
<th>Chronic severe hyponatraemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration:</strong> &lt;48 hours</td>
<td>Duration: ≥48 hours</td>
</tr>
<tr>
<td>Morbidity: Brain herniation</td>
<td>Morbidity: Osmotic demyelination syndrome</td>
</tr>
<tr>
<td>Neurological symptoms are present: Seizures, confusion, headache, low GCS, coma</td>
<td>Neurological symptoms are absent</td>
</tr>
<tr>
<td>Commonly seen in post-operative patients, patients with self-induced water intoxication associated with endurance exercise, psychiatric diseases (eg, acute psychosis, schizophrenia), use of drugs such as “ecstasy” (methyleneoxy-N-methamphetamine or MDMA)</td>
<td>Can be seen with any type of hyponatraemia:</td>
</tr>
<tr>
<td>o Urgent correction by 4-6 mmol/L to prevent brain herniation and neurological damage from cerebral ischemia</td>
<td>o Rate of correction should be between 10-12mmol per 24 hours</td>
</tr>
<tr>
<td>o Sever symptoms: 100 mL of 3% saline infused intravenously over 10 minutes X 3 as needed</td>
<td>o In high risk patients should be 8mmol per 24 hours</td>
</tr>
<tr>
<td>o Mild to moderate symptoms with a low risk of herniation: 3% saline infused at 0.5-2 mL/kg/h</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Verbalis J (2013) et al
References