The Royal Liverpool and Broadgreen University Hospitals NHS Trust

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.

Normal range	Mild hyponatraemia	Moderate hyponatraemia	Severe hyponatraemia
135-146 mmol/L	130-135 mmol/L	120-129 mmol/L	<120 mmol/L

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

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

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:

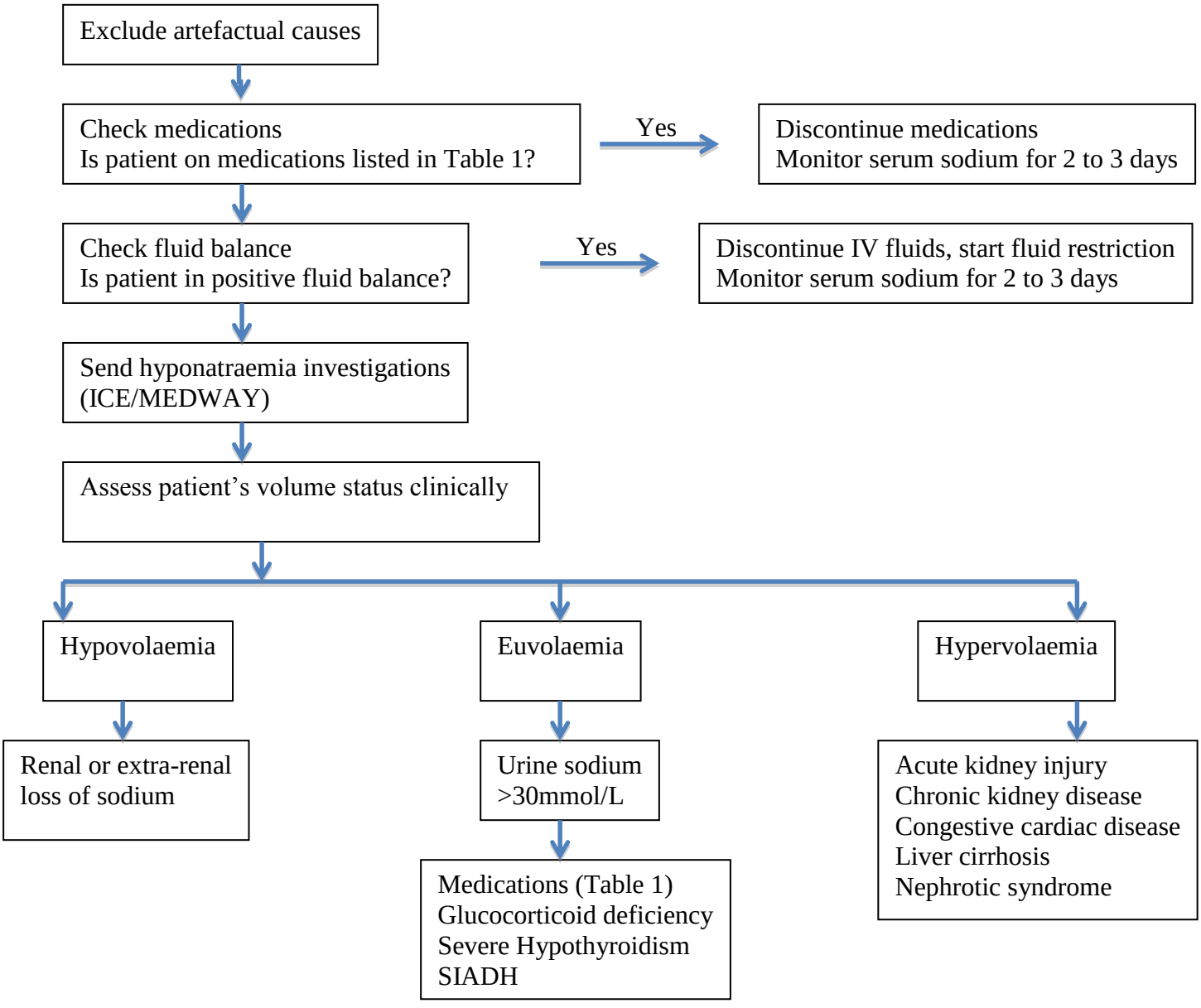
- 9 am serum for cortisol; if equivocal, a short synacthen test may be necessary
- Thyroid function tests

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

When requesting tests through Medway (AUH), request blood biochemistry(U&E, TFT, cortisol, glucose, osmolality) and urine (U&E and osmolality)

Figure 1: Flowchart to aid in diagnosis of underlying causes of hyponatraemia



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 <98mmol/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 Severe Symptomatic Hyponatremia (Serum Na <120mmol/L)

Patient with severe hyponatraemia presenting with symptoms as shown in Table 2

Table 2: Clinical presentation in sever symptomatic Hyponatraemia

Severity	Symptom
Moderately severe	Nausea without vomiting Confusion Headache
Severe	Vomiting Cardiorespiratory distress Abnormal and deep somnolence Seizures Coma (Glasgow Coma Scale ≤ 8)

Management of severe symptomatic hyponatraemia(Table 2)

Patient should be managed in ITU/HDU under close supervision and monitoring

- 90mls of 5% saline IV (through central line) over 20 min
- Continue the same dose every 20min
- Stop the infusion if either happens first
  - serum Na increases by 5 mmol/L
  - clinical improvement in symptoms
- Recheck serum Na after every infusion dose

Clinical Improvement after increase in serum Na by 5 mmol/L (calculation 1)

- Start with normal saline (0.9%) at rate so that serum Na increases by 0.5mmol/L/hour. Overall increase in serum Na should be
  - 10mmol/L during the first 24 hours
  - additional 8mmol/L for every 24 hours or 18mmol/L in 48hours
- Continue till serum Na reaches 130mmol/L

No clinical Improvement after increase in serum Na by 5 mmol/L (calculation 2)

- Continue with 5% saline with rate of increase in serum Na 1mmol/L/hour
- Stop the infusion if either happens first:
  - improvement in clinical symptoms
  - total increase in serum Na by 10mmol/L
  - Serum Na reaches 130mmol/L
- Keep checking serum sodium every 4 hourly

***if symptoms do not improve by increasing the serum Na by 10mmol/L or serum Na reaches 130mmol/L ; investigate for any other cause responsible for symptoms other than hyponatremia**

Management of moderately symptomatic hyponatraemia(Table 2)

Patient can be managed on ward as follows

• 250mls of 1.8% saline IV (through peripheral line) over 20 min

• Continue the same dose every 20min

• Stop the infusion if either happens first

- serum Na increases by 5 mmol/L
- clinical improvement in symptoms

• Recheck serum Na after every infusion dose

Clinical Improvement after increase in serum Na by5 mmol/L (calculation1)

• Start with normal saline (0.9%) at a rate 0.5 mmol/L/hour so that increase in serum Na

- 10mmol/L during the first 24 hours
- additional 8mmol/L for every 24 hours or 18mmol/L in 48hours

• Continue till serum Na reaches 130mmol/L

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) =

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

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 euvolaemic

Adapted from Schwartz et al(1957)

Appendix 4

Management of severe hyponatraemia

(serum sodium <120mmol/L)

Definition

- Acute hyponatremia is defined as hyponatremia (serum Na < 135mmol/L) presenting within 48 hours
- Symptomatic hyponatremia is defined as any biochemical degree of hyponatremia presenting with moderately to severe neurological symptoms
- Symptomatic hyponatremia is usually associated with acute severe hyponatremia at serum Na < 120mmol/L

Pathogenesis of Symptomatic hyponatremia

- When hyponatremia develops within few hours(<48hours), ability of brain cells to adapt is exceeded and results in cerebral oedema(low osmolality)
- It is usually seen in post operative conditions associated with excess fluid retention
- It is a life threatening condition as it can result in severe brain damage or death of the patient
- After 48 hours (chronic hyponatremia) brain cells adapt by extruding sodium, potassium, chloride and osmolytes and return to their normal size (normal osmolality). Therefore patients with chronic hyponatremia are asymptomatic

Clinical presentation of symptomatic hyponatremia

- The symptoms of acute severe hyponatremia is due to cerebral oedema leading to brain herniation which is life threatening
- A small increase in serum Na rapidly by 5mmol/L is effective as it increases the osmolality, reduces brain swelling and intracerebral pressure
    - Infusion of hypertonic saline increases the serum Na rapidly and is effective in patients with symptomatic hyponatremia

Na content :

- 0.9% saline = 154mmol/1000mls
- 1.8% saline= 308mmol/1000mls
- 5% saline= 856mmol/1000mls

Total body water:

- Non-elderly men: 0.6
- Non-elderly women: 0.5
- Elderly men: 0.5
- Elderly women: 0.45

Calculations (Adrogue-Madias, NEJM 2000;342:1581-1589)

To achieve serum Na at 0.5mmol/L/hour with normal saline (Calculation 1)
The following formula can be used to calculate Na replacement using 0.9% saline

- In order to achieve a 0.5 mmol/h increase in serum Na, use this formula to calculate the amount of intravenous sodium needed per hour (mmol/h):
  - Amount of sodium replacement (mmol/h) = 0.6(total body water in non-elderly man) x weight (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:

Amount of sodium replacement (mmol/h) X (1000/154) = ml/hr of 0.9% saline required

For Example: for an 80 kg patient

- 0.6 x 80 x 0.5 = 24 mmol/hr sodium required
- 24 X(1000/154) = 156ml/hr of 0.9%saline

To achieve serum Na at 1mmol/L/hour with hypertonic saline (Calculation 2)
The following formula can be used to calculate sodium replacement using 1.8% or 5% saline

- In order to achieve a 1 mmol/h increase in serum Na, use this formula to calculate the amount of intravenous Na needed per hour (mmol/h):
  - Amount of sodium replacement (mmol/h) = 0.6(total body water in non-elderly man) x weight (kg) x 1 (desired correction rate mmol/h)
  - When using 1.8% saline(1000ml contains 308 mmol Na) the rate of infusion required to achieve a 1 mmol/h improvement in serum Na is given by:

Amount of sodium replacement (mmol/h) X (1000/308) = ml/hr of 1.8% saline required

For Example: for an 80 kg patient:

- 0.6 x 80 x 1 = 48mmol/hr sodium required
- 48 X(1000/308) = 155ml/hr of 1.8%saline

Acute severe symptomatic hyponatraemia	**Chronic severe hyponatraemia**
Duration: <48hours	Duration: ≥48 hours
Morbidity: Brain herniation	Morbidity: Osmotic demyelination syndrome
Neurological symptoms are present: Seizures, confusion, headache, low GCS, coma	Neurological symptoms are absent
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" (methylenedioxy-N-methamphet- amine or MDMA)	Can be seen with any type of hyponatraemia: • Hypovolaemic • Euvolaemic • Hypervolaemic
○ Urgent correction by 4-6 mmol/L to prevent brain herniation and neurological damage from cerebral ischemia ○ Sever symptoms: 100 mL of 3% saline infused intravenously over 10 minutes X 3 as needed ○ Mild to moderate symptoms with a low risk of herniation: 3% saline infused at 0.5-2 mL/kg/h	○ Rate of correction should be between 10-12mmol per 24 hours ○ In high risk patients should be 8mmol per 24 hours

Adapted from Verbalis J (2013)et al

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