Guy's and St Thomas' NHS Foundation Trust

Clinical Guideline

The management of hyponatraemia in inpatient adult patients

Document Detail	
Document Type	Guidelines
Document name	The management of hyponatraemia in inpatient adult patients
Document location	GTi Clinical Guidance Database
Version	1.0
Effective from	*04 October 2018*
Review date	*04 October 2021*
Owner	Medical Specialties
Author	Dr Paul Carroll, Consultant Endocrinologist Dr Stephen Thomas, Consultant Diabetes and Endocrinology Dr Imran Malik, Locum Consultant Diabetes and Endocrinology Roqsana Ara, Clinical Pharmacist Diabetes and Endocrinology Fraser Hanks, Clinical Pharmacist Intensive Care Department Dr Katherine Henderson, Consultant Emergency Department Dr Aarthi Surendran, Specialty Registrar, Diabetes and Endocrinology Dr David Game, Consultant Nephrologist, Renal Department
Approved by, date	Drug and Therapeutics Committee, *October 2018*
Superseded documents	
Related documents	
Keywords	Hyponatraemia, hypo-osmolar, hyponatraemia, serum sodium, extracellular fluid, hypovolaemia, hypervolaemia, euvolaemia, osmolality
Relevant external law, regulation, standards	

Change History		
Date	Change details, since approval	Approved by

USING THE GUIDANCE

This guideline covers the investigation and management of acute and chronic hyponatraemia in adult patients, but does not cover the diagnosis or treatment of the underlying conditions.
This guideline does not cover hyponatraemia in children.
The following steps must be followed for the safe use of this guidance.
Step 1: Classify hyponatraemia based on the duration, biochemical severity and symptoms.
Step 2: Use the diagnosis algorithm to establish the cause.
Step 3: Use treatment algorithm to manage, based on symptoms, time of onset and fluid status.
Step 4: Always remember to limit the rise of serum sodium to a maximum of 10 mmol/L in the first 24h (regardless of baseline sodium) and 8 mmol/L every 24h thereafter. If necessary, see section on '*Managing overly rapid correction of hyponatraemia'*.

Introduction:

Hyponatraemia (serum Na^+ < 135 mmol/l) is a clinical feature in 15-20% of emergency admissions to hospital. It is associated with increased mortality, morbidity and length of hospital stay in patients presenting with a range of conditions. Hyponatraemia is therefore, both common and important.

Pathophysiology:

Hyponatraemia is largely influenced by fluid balance and vasopressin, also known as anti-diuretic hormone (ADH). Although, its pathophysiology is complex, the following are often contributing factors:

- Excessive fluid intake - e.g. polydipsia, excessive IV dextrose
- Fluid loss - e.g. diarrhoea and vomiting (D&V) leading to increased ADH secretion
- Inappropriate water retention due to high ADH e.g. syndrome of inappropriate ADH secretion (SIADH), hypothyroidism, post-operative state, heart failure (HF)
- Acute stress, such as surgery, anaesthesia or pain, causing ADH release
- Inappropriate natriuresis e.g. cerebral salt-wasting, Addison's disease, diuretic use, renal failure
- Exercise induced hyponatraemia, especially in long distance runners (eg marathon runners) is precipitated by combination of above factors, please see the document "Guidance for Emergency Department".

Clinical Features:

Symptoms can vary and are primarily neurological, reflecting change in brain volume. It is now increasingly clear that even asymptomatic patients can have subtle clinical abnormalities e.g. gait disturbance, falls, concentration or cognitive deficits, when analysed in detail. Additionally, patients with chronic hyponatraemia more often have osteoporosis and sustain bone fractures more frequently.

Indications to consider HDU/ITU admission:

- Symptomatic hyponatraemia **(see below)**
- Acute admission with profound hyponatraemia **(see below)**
- Worsening hyponatraemia following the initiation of treatment.
- Using higher strength 'hypertonic' saline infusions e.g. 2.7% saline.
- Managing overly rapid correction of hyponatraemia **(see below)**
- Difficult to manage patients due to other contributing factors, e.g. agitation or low GCS due to drug/alcohol toxicity, patients with head injury, etc.

STEP 1: CLASSIFICATION OF HYPONATRAEMIA

Classify hyponatraemia based on the duration, biochemical severity and symptoms of hyponatraemia.

Table 1: Based on duration of hyponatraemia	
Acute	Documented to exist < 48 h
Chronic	Documented to exist for at least 48 h All undocumented / unclassified cases are considered chronic unless strong clinical evidence of the contrary

Table 2: Based on biochemical severity (serum sodium levels)	
Mild	130 – 135 mmol/L
Moderate	125 – 129 mmol/L
Profound*	< 125 mmol/L
**Term 'profound' is used instead of severe to avoid confusion with 'severe' symptoms.*	

Table 3: Based on symptoms	
Moderately severe*	- Nausea without vomiting
	- Confusion
	- Headache
Severe	- Vomiting
	- Cardiopulmonary dysfunction
	- Deep somnolence or Glasgow Coma Scale ≤8
	- Seizures
Moderately severe to severe symptoms may suggest a degree of brain oedema **This list is not exhaustive as other symptoms may be present.*	

STEP 2: DIAGNOSIS OF HYPONATRAEMIA (see Flowchart A)

1. Repeat an urgent sample to exclude an artefactual sample, especially in an acute hyponatraemia. This should not delay treatment.
2. Review history for known conditions (such as heart failure, cirrhosis, nephrotic syndrome) or any recent event, e.g. D&V, excessive IV dextrose use, polydipsia, recent new medication, recreational drugs use (e.g. ecstasy), recent mannitol use, recent bladder irrigations with glycine, etc. Please contact the Toxicology team if there is likely recreational drug related hyponatraemia.
3. Check serum lipids and proteins to exclude pseudo-hyponatraemia (especially triglycerides and multiple myeloma related).
4. Check serum urea, lactate and alcohol levels to exclude other ineffective osmoles.
5. Check venous glucose and if raised, calculate the corrected (the value of sodium concentration if the glucose was not elevated) serum sodium by using the following formula:

$$\text{Corrected serum } Na^+ \text{ (mmol/L)} = \text{Measured serum } Na^+ \text{ (mmol/L)} + 2.4 \times \frac{[(\text{serum glucose (mmol/L)} - 5.5]}{5.5}$$

6. Review drug history (including recreational drugs) that may be contributing to hyponatraemia and current medications (see Table 4) and discontinue when possible.
7. Check random (ideally 9AM) cortisol, thyroid function tests, liver function tests and serum osmolality.
8. Send spot urine sample at the same time as serum, to check for urinary sodium, potassium and osmolality and interpret results as follow:
   - Urine osmolality < 100 mOsm/kg implies that the kidney's ability to excrete free water is unimpaired. The likely cause is relative excess water intake.
   - Urine osmolality > 100 mOsm/kg and urine sodium < 30 mmol/L implies (biochemically) a low effective arterial volume, which may be associated with expanded (e.g. HF, cirrhosis or nephrotic syndrome) or contracted (e.g. GI losses) extracellular volume.
   - Urine osmolality > 100 mOsm/kg and urine sodium > 30 mmol/L is likely to represent excessive natriuresis (e.g. diuretics, renal salt wasting, cerebral injury) or inappropriate water retention (e.g. SIADH).
9. Clinically assess the extracellular fluid volume (ECF) status.
   - Contracted ECF (Hypovolaemia): History of GI or renal fluid losses, signs of dehydration, such as hypotension, tachycardia, oliguria, dry mucous membrane, reduced skin turgor, reduced central venous pressure.
   - Normal ECF (Euvolaemia): Normal blood pressure, pulse rate, central venous pressure.
   - Expanded ECF (Hypervolaemia): History of chronic fluid overload, raised central venous pressure, pedal oedema/ascites.

Table 4: Common causes of Drug-induced hyponatraemia	
Diuretics	- Thiazides (can cause even after chronic use) e.g. bendroflumethiazide - Thiazide-like e.g. indapamide - Potassium-sparing e.g. spironolactone, amiloride - Loop diuretics (usually only a contributory factor) e.g. furosemide
Antihypertensive drugs	- ACE inhibitors e.g. ramipril, lisinopril - ARBs e.g. losartan, candesartan
Proton pump inhibitors	- e.g. omeprazole
Antidepressants	- Tricyclic e.g. amitriptyline, dosulepin - SSRI e.g. citalopram, paroxetine - SNRI e.g. venlafaxine - MAOi
Anti-epileptic drugs	- Carbamazepine - Oxcarbazepine - Sodium valproate
Anti-psychotic drugs	- Phenothiazines e.g. chlorpromazine, prochlorperazine - Butyrophenones e.g. haloperidol
Anti-cancer drugs	- Platinum agents e.g. cisplatin, carboplatin - Alkylating agents e.g. cyclophosphamide, melphalan, ifosfamide
Miscellaneous	- Vasopressin and analogues*, oxytocin - NSAIDs - Amiodarone
ACE inhibitors: Angiotensin-coverting enzyme inhibitor, ARBs: Angiotensin-II receptor blockers, SSRIs: Serotonin-selective reuptake inhibitors, MAOi: Monoamine oxidase inhibitors, NSAIDs: Non-steriodal anti-inflammatory drugs. **Desmopressin – must be discussed with endocrinology prior to discontinuing if there is diabetes insipidus*	

STEP 3a: MANAGEMENT OF ACUTE (SYMPTOMATIC OR ASYMPTOMATIC) AND CHRONIC SYMPTOMATIC HYPONATRAEMIA

Medical Emergency (For list of symptoms, see Table 3):

- For **Exercise induced hyponatraemia**, see the document "Guidance for Emergency Department".
- Consider other causes for the aforementioned symptoms, but if these symptoms are considered likely due to hyponatraemia or if the serum sodium has acutely dropped over 10 mmol/L in less than 48h, call Clinical Response Team (CRT) on 0610 to arrange urgent critical care admission. 2.7% hypertonic saline infusion must only be given in HDU or ITU (other than exceptional cases in ED or under the supervision of the MET/CRT team).
- Symptomatic hyponatraemia mostly result from brain oedema, which may lead to permanent brain damage or death if left untreated. In acute hyponatraemia, absence of any symptoms excludes clinically significant brain oedema, but it may be precipitated by any further drop in serum sodium.
- Fluid restrict until decision for further treatment is made.
- Discontinue medications contributing to hyponatraemia, if possible.
- In symptomatic (acute or chronic) hyponatraemia or in any case of an acute drop in serum sodium of more than 10mmol/L in less than 48h, infuse 150 ml of 2.7% hypertonic saline over 20 minutes (can be given through a large peripheral line). For extremes of body compositions (BMI < 15 kg/m2, or > 40 kg/m2) consider using weight-based dose (2 ml/kg) of 2.7% hypertonic saline.

    - In symptomatic (acute or chronic) hyponatraemia, check serum sodium 30 minutes after the above infusion and repeat the infusion until symptoms are improving, or serum sodium has increased by 5 mmol/L or serum sodium has reached 130 mmol/L, whichever comes first. Monitor serum sodium every 6h, until stable. If the symptoms do not improve after a 10 mmol/L increase in serum sodium, it is very likely they are caused by something other than hyponatraemia.
    - In asymptomatic acute hyponatraemia, monitor serum sodium every 6h after the single infusion, until stable.

- Initiate prompt assessment by following the diagnosis algorithm (see Flowchart A) and start cause-specific treatment.
- Increase in serum sodium should be limited to 10 mmol/L in the first 24h (regardless of baseline sodium) and 8 mmol/L during every 24h thereafter, until serum sodium of 130 mmol/L is reached.

STEP 3b: MANAGEMENT OF CHRONIC ASYMPTOMATIC HYPONATRAEMIA

Chronic asymptomatic hyponatraemia (Na^+ ≤ 129 mmol/L):

- Assess using the diagnosis algorithm (see Flowchart A).
- Discontinue medications contributing to hyponatraemia, if possible.
- Further treatment is based on the ECF status (see below).
- Increase in serum sodium should be limited to 10 mmol/L in the first 24h (regardless of baseline sodium) and 8 mmol/L during every 24h thereafter, until serum sodium of 130 mmol/L is reached.
- Check the serum sodium every 6h until it has stabilised under the stable treatment.

1. Chronic hyponatraemia with contracted extracellular fluid volume:

- Decide the volume to be replaced and then select the type of fluid to be administered using the formula below. Higher strength saline may only be given in HDU or ITU. See calculation for predicted change in Na^+ concentration.
- Hartmann's solution (a balanced crystalloid solution) should be preferred provided patient does not have hyperkalaemia, alkalosis or hypercalcaemia, whereas 0.9% sodium chloride is used with upper GI loss (loss of hydrochloride) or serum chloride < 90 mmol/L.
- Restoring volume will suppress ADH secretion, causing free water excretion, which poses high risk of imminent overly rapid correction of hyponatraemia. Hence, if there is any increase in urine output, serum sodium should be checked every 2h until condition stable.

Predicted change in serum Na^+ with 1 L of fluid $= \dfrac{\text{Infusate } [Na^+] - \text{Serum } [Na^+]}{\text{Total body water (TBW)*} + 1}$

**TBW in young men = 0.6 x body weight (kg)*
**TBW in young women and elderly men = 0.5 x body weight (kg)*
**TBW in elderly women = 0.45 x body weight (kg)*

Infusate Na^+ =
154 mmol/L in normal (0.9%) saline
308 mmol/L in double strength (1.8%) saline
462 mmol/L in hypertonic (2.7%) saline
130 mmol/L in Hartmann's solution

For example:
80 year old male who weighs 70kg has serum sodium of 118mmol/L.

TBW = 0.5 (elderly man) x body weight (70kg) = 35 L

Predicted change in serum Na^+ with 1L 0.9% sodium chloride $= \dfrac{\text{Infusate } Na^+ (154) - \text{serum } Na^+ (118)}{35+1} = 1$ *mmol/L*

2. Chronic hyponatraemia with expanded extracellular fluid volume:

- Cause-specific treatment is the mainstay of treatment.
- Fluid restriction to prevent further fluid overload.
- Use of diuretics may sometimes be appropriate.

3. Chronic hyponatraemia with normal extracellular fluid volume (likely SIADH):

- Fluid restriction (500 - 750 ml/day) is the first line treatment. Calculate the urine to serum electrolyte ratio as below. A ratio > 1 will indicate fluid restriction may not be successful in increasing serum sodium level.

$$\text{Urine to serum electrolyte ratio} = \frac{\text{Urine } Na^+ \text{ (mmol/L)} + \text{urine } K^+ \text{ (mmol/L)}}{\text{Serum } Na^+ \text{ (mmol/L)}}$$

- Slow Sodium - Consider oral Slow Sodium 600 mg, using 2-4 tablets twice a day to increase the solute intake with low dose loop diuretics e.g furosemide 40mg.
- Demeclocycline – It interferes with ADH receptor activity in the kidneys and can be used in mild-moderate hyponatraemia, where fluid restriction is ineffective and the patient does not have liver impairment. Demeclocycline should be initated at a dose of 300mg QDS, then reduced to 300 mg BD for maintenance. It has a slow onset of action and the response can take up to 3-4 days.
- Vaptans - Contact Endocrinologist (bleep 1801 or via switchboard) to discuss vasopressin receptor antagonists (e.g. tolvaptan). These are sometimes considered in special circumstances, e.g. where the offending drugs may not be withdrawn, such as oncology patients on chemotherapy or in ADH producing tumours. Tolvaptan is approved on formulary in SIADH for oncology patients only. For all other indications, use of vaptan requires an individual funding request prior to initiation. If clinically urgent, Medical Director approval for use must be received before commencing treatment and a retrospective IFR must be completed.
- Consider investigations for the underlying cause of SIADH.

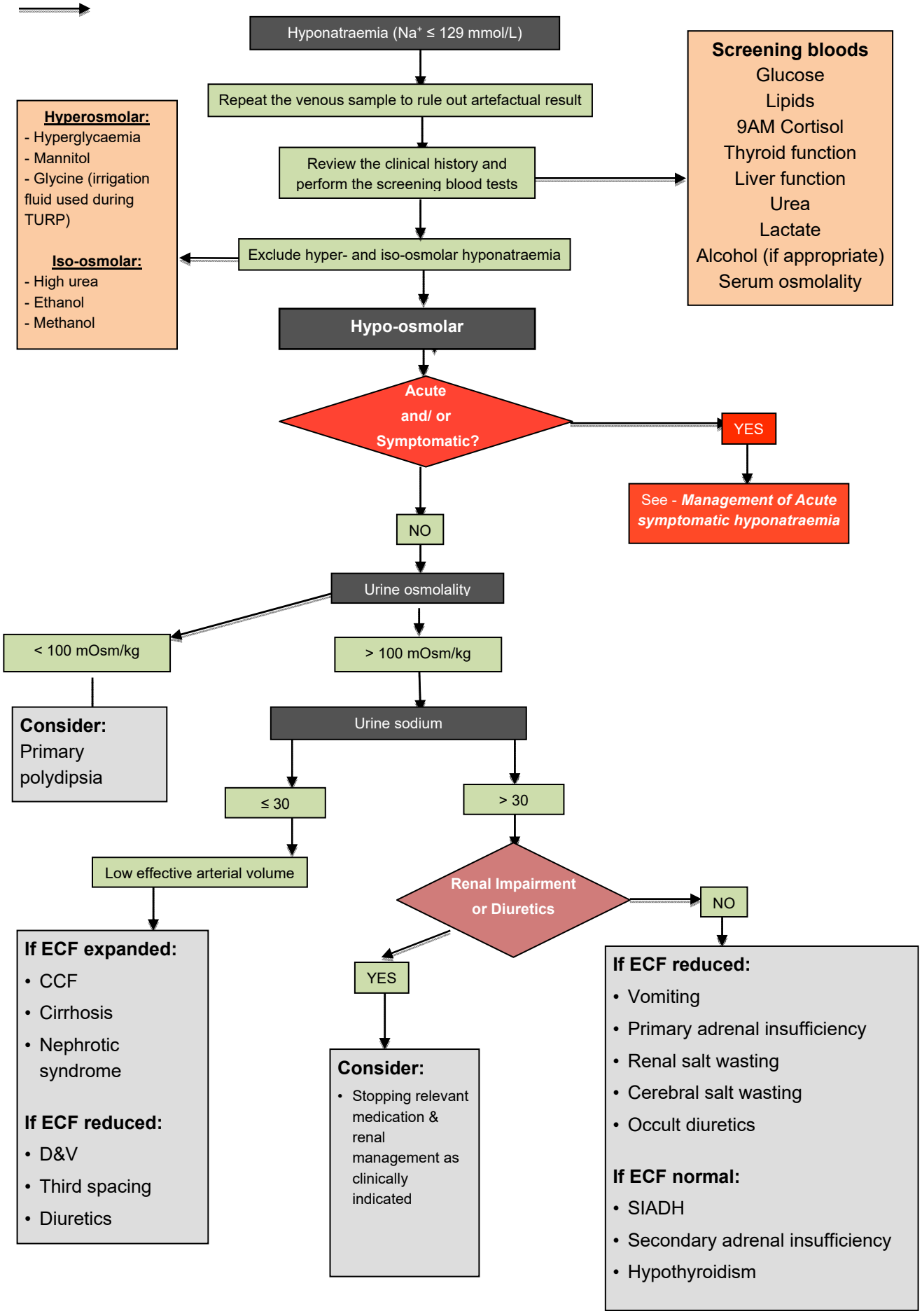
CRITERIA FOR THE DIAGNOSIS OF SIADH

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

STEP 4 (if required): MANAGING OVERLY RAPID CORRECTION OF HYPONATRAEMIA:

- The brain needs ~48h to adapt to a hypotonic environment. This is achieved mainly by extruding the electrolytes and organic osmoles from its cells, in order to avoid brain oedema from the water shift into the brain cells. Once adapted after 48h, brain cells can again sustain damage if the serum sodium rises too rapidly, causing osmotic demyelination syndrome.
- Situations mostly associated with rapid correction of hyponatraemia include:
    - Volume repletion in hypovolaemia
    - Treatment of glucocorticoid deficiency
    - Withholding thiazide diuretics
    - Withholding other drugs known to cause SIADH
    - Reducing fluid intake in primary polydipsia
- If the serum sodium rises more than 10 mmol/L in the first 24h or more than 8 mmol/L during every 24h thereafter, discontinue the ongoing treatment and discuss with the endocrinologist for consideration of IV 5% glucose (10 ml/kg over 1h followed by serum sodium measurement) and/or desmopressin therapy (SC/IV 1 - 2 micrograms).
- Continue to monitor renal function and electrolytes as appropriate.

FLOWCHART A: DIAGNOSIS OF HYPONATRAEMIA



FLOWCHART B: MANAGEMENT OF SYMPTOMATIC OR ACUTE HYPONATRAEMIA

Symptoms? (Any of, Vomiting, Cardiorespiratory distress, deep somnolence, seizure, GCS < 8)

YES

See - ***Management of Symptomatic (acute or chronic) hyponatraemia (see page 6)***

1. Call CRT on 0610 to arrange critical care admission.
2. Consider other causes for the symptoms.
3. Infuse 150ml of 2.7% hypertonic saline over 20 minutes.
4. Check U&Es after 30 min.
5. Repeat step 3 & 4 until symptoms improve, or Na^+ rise by 5 mmol/L or Na^+ is ≥130mmol/L, whichever comes first.
6. Start cause-specific treatment using the diagnosis algorithm (see Flowchart A)
7. Discontinue medications contributing to hyponatraemia, if possible
8. Limit increase in Na^+ to 10mmol/L in the first 24h and 8mmol/L during every 24h thereafter.

NO

Acute (definitely < 48H) hyponatraemia?

YES

See - ***Management of Acute asymptomatic hyponatraemia***

1. Repeat U&Es to confirm an acute drop in Na^+.
2. Exclude any of the above symptoms.
3. Start cause-specific treatment using the diagnosis algorithm (see Flowchart A).
4. Discontinue medications contributing to hyponatraemia, if possible.
5. If the acute drop in Na^+ is >10mmol/L, call CRT on 0610 to arrange critical care admission to administer hypertonic saline.
6. Give a single infusion of 150ml of 2.7% hypertonic saline over 20 minutes.
7. Check U&Es every 6h until stable.

NO

Go to - ***Management of Chronic asymptomatic hyponatraemia***

FLOWCHART C: MANAGEMENT OF CHRONIC (>48H) ASYMPTOMATIC HYPONATRAEMIA

See - ***Management of Chronic hyponatraemia ($Na^+ \leq 129$) without severe or moderately severe symptoms***

1. Asses using the diagnosis algorithm (see Flowchart A).
2. Discontinue medications contributing to hyponatraemia, if possible.
3. Limit increase in Na^+ to 10mmol/L in the first 24h and 8mmol/L during every 24h thereafter.
4. Check U&Es every 6h until the Na^+ has stabilised under stable treatment.
5. Assess the ECF volume and proceed as below:

Reduced circulating volume?

YES

See - ***Management of Chronic hyponatraemia with contracted extracellular fluid volume***

1. Treat with 0.9% sodium chloride or Hartmann's solution.
2. Select type and rate of IV fluid to be given, using formula:

$$\text{Predicted change in } Na^+ \text{ with 1L IV fluid} = \frac{\text{Infusate } [Na^+] - \text{Serum } [Na^+]}{\text{total body water} + 1}$$

3. Monitor urine output to watch for excessive free water clearance, which risks overly rapid correction of Na^+

NO

Expanded circulatory volume?

YES

See - ***Management of Chronic hyponatraemia with expanded extracellular fluid volume***

1. Start cause-specific treatment.
2. Fluid restriction to prevent further fluid overload.
3. Sometimes, use of diuretics may be appropriate.

NO

Likely SIADH

YES

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

See - ***Management of Chronic hyponatraemia with normal extracellular fluid volume (likely SIADH)***

1. Fluid restriction (500 - 750 ml/day) is the main treatment.
2. Calculate U/P electrolyte ratio. Ratio >1 indicates fluid restriction may not improve serum sodium.
3. Oral Slow Sodium 1200-4800mg/day + Furosemide 40mg OD (if fluid restriction alone not effective).
4. Demeclocycline 600mg TDS/QDS initially then reduce to 300mg BD/TDS, if fluid restriction alone is ineffective.
5. Contact Endocrinologist to discuss vasopressin receptor antagonists (Vaptans) usually for oncology patients.
6. Investigate underlying cause of SIADH

References

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