Hyponatraemia - Full Clinical Guideline

Reference no.: CG - ELEC/2023/001

Introduction

Hyponatraemia can be defined as a plasma sodium below 133 mmol/L. The clinical significance of hyponatraemia depends on its severity, its speed of onset and its underlying etiology. It is potentially life threatening that carries risks for serious errors in treatment.

Patients generally require measures to improve hyponatraemia if they are symptomatic or have sodium less than 125mmol/L. Mild hyponatraemia should never be ignored as it is a significant risk factor for developing severe hyponatraemia.

Aim and Purpose

The guideline is to ensure that treatment for hyponatraemia is safe and appropriate for patients.

Scope

All adult inpatients for general assessment, and first line management

Classification of hyponatremia:

ONSET

Acute hyponatraemia - defined as onset within 48hrs
Chronic hyponatraemia - defined as onset longer than 48hrs

NB: Exact onset can be difficult to ascertain and where there is uncertainty, a duration of >48 hours should be assumed. This is because after 48 hours, physiological adaptation to the hyponatraemia occurs and there is a risk of osmotic demyelination with rapid correction.

SEVERITY

Mild hyponatraemia - asymptomatic

Moderate hyponatraemia - moderate symptoms:

- Nausea without vomiting
- Confusion,
- Headache,
- Drowsiness,
- General weakness,
- Myalgia

Severe hyponatraemia - severe symptoms:

- Vomiting,
- Seizures,
- Glasgow Coma Scale ≤8

Diagnosis:

STEP 1: Rule out artefactual causes:

- Always recheck U&E's from a non-intravenous drip arm,
- Measure serum osmolality; if it is ≥275mOsm/kg then this is suggestive of an artefactual cause to the hyponatraemia e.g. hyperglycemia, hypertriglyceridemia, hyperproteinemia, recent radiocontrast or Mannitol administration. Otherwise known as pseudohyponatraemia.

STEP 2: Rule out drug induced causes:

- Drug induced causes of hyponatremia are common. They usually occur a couple of weeks after the start of the medication OR occasionally drug induced hyponatremia can be exacerbated by an acute illness.
- A drug history timeline should be sought and where possible potential offending drugs known to induce hyponatremia should be temporarily stopped.
- Common drugs known to induce hyponatraemia:
    - **Thiazide & potassium sparing diuretics.**
        - Bendroflumethiazide, Metolazone, Indapamide, Chlortalidone, Amiloride, Spironolactone, Triamterene, Eplerenone, acetazolamide
    - **ACEi or Angiotensin II receptor antagonists**
        - Ramipril, Lisinopril, Perindopril, Enalapril, Valsartan, Losartan, Candesartan, Irbesartan
    - **Sulphonamides**
        - Trimethoprim, co-trimoxazole,
    - **Anti-inflammatory agents**
        - Ibuprofen, Diclofenac, Naproxen, COX-2 inhibitors
    - **Proton pump inhibitors**
        - Omeprazole, Lansoprazole, Pantoprazole
    - **Antidepressants**
        - Citalopram, Fluoxetine, Paroxetine, Sertraline, Amitriptyline, Clomipramine, Dosulepin, Trazodone, Venlafaxine
    - **Anti-epileptic Medications**
        - Carbamazepine, Sodium valproate, Oxcarbazepine, Lamotrigine

STEP 3: Rule out common medical conditions that causes:

- Take a thorough medical history and complete a physical examination specifically looking for oedema or signs of dehydration.
- Treat all underlying medical conditions as usual. Normally hyponatraemia that has been exacerbated by a medical condition will start to correct within 48hrs of initiating treatment of the medical condition.
- If there is evidence of excessive fluid intake or peripheral oedema, then fluid restriction of 1-1.5L per day could be considered with monitoring for intravascular dehydration or AKI.
- Common medical conditions known to induce hyponatraemia (through either GI sodium loss or urinary sodium loss inc SIADH or ECF dilution):
    - **Post-operative**
        - Following major surgery, take a history to identify excessive oral water intake, which alongside the stimulation of water conservation by the kidneys by the stress of surgical intervention, leads to a rapid fall in serum sodium
    - **Respiratory**
        - Pneumonia, TB, lung cancer, cystic fibrosis
    - **Gastrointestinal**
        - Diarrhea, vomiting, colorectal cancer, ileus
    - **Neurological**
        - Brain trauma, stroke, subarachnoid hemorrhage, meningitis, encephalitis
    - **Oedema related conditions** (consider fluid restriction)
        - Nephrotic syndrome, Congestive cardiac failure, Cirrhosis

STEP 4: Investigations:

- If plasma sodium is <125 mmol/L or if the hyponatremia is not responding after 48hrs to initial management then the following investigations should be considered.
        - Paired urine and serum osmolality
        - Urine sodium (Interpret with caution if within 5 days of diuretic or ACEi dosing)
        - Urine Protein: Creatinine ratio (to rule out nephrotic syndrome)
        - Liver function tests (to rule out severe hypo-albuminuria)

        - Creatine kinase (to rule out rhabdomyolysis)
        - TSH (to rule out severe hypothyroidism)
        - 9am Cortisol if not on exogenous steroids (to screen for hypoadrenalism).
        - Stool chart
    - Other tests that might be considered if deemed clinically appropriate early in investigation.
        - MRI Brain – only if worsening headaches or confusion
        - CT Chest, Abdomen & Pelvis – only if unexplained weight loss
        - SST if clinical suspicion of hypoadrenalism is high or 9am cortisol in a stable patient is <350nmol/L.

Interpreting urine and serum osmolality & electrolytes

True hyponatraemia - Serum sodium <133 mmol/L with serum osmolality <275mOsm/kg
Artifactual hyponatraemia - Serum sodium <133 mmol/L with serum osmolality >275mOsm/kg
Psychogenic polydipsia / excess oral or IV fluid intake (including peri-operatively) - Serum sodium <133 mmol/L with urine osmolality <100mOsm/kg

Urine Sodium (interpretation can be confounded by diuretics and ACE inhibitors):

- **<30** is suggestive of a condition with low effective circulating volume or pathological activation of the renin- angiotensin system, or low body sodium with malnutrition:
    - **Hypovolaemic** e.g. diarrhoea, vomiting, diuretic use or 3rd space losses, malnourishment
    - **Hypervolaemic** e.g. cirrhosis, heart failure or nephrotic syndrome. Urine sodium should be low due to pathological activation of the renin- angiotensin system in these pathologies.
- **>30** is suggestive of a condition with high renal sodium losses
    - **Hypovolaemia** e.g. primary adrenal insufficiency, cerebral salt wasting or renal salt wasting such as diuretic use.
    - **Euvolaemia or hypervolaemia e.g.** adrenal insufficiency, hypothyroidism or SIADH, post-operative, or concurrent/recent medications as above.

For Flow Chart see Appendix 1

Syndrome of Inappropriate ADH (SIADH)

SIADH is a diagnosis of exclusion defined by the unsuppressed release of antidiuretic hormone leading to impaired water excretion and hyponatremia in either a hypervolaemia or euvolaemia state. Biochemically it is characterized by a serum sodium <133 mmol/L, serum osmolality <275mOsm/kg, urine osmolality>100mOsm/kg, urine sodium >30 mmol/L. Already listed above are the most common drug & medical causes of SIADH which should respond to appropriate drug withdrawal or usual treatment of those medical causes.

Once SIADH is confirmed with no identified cause, the patient should be considered at minimum for Chest and Head imaging.

Treatment

IF THE PATIENT HAS SEVERE SYMPTOMS WITH Na <125mmol/L

THEN START URGENT TREATMENT

The initial principle to treat hyponatraemia is to treat the underlying cause. Cessation of culprit medications, controlling hypervolaemic states and managing underlying medical conditions will be all that is required in most cases. Perversely aggressive treatment of very low serum sodium levels (Na <125mmol/L) is potentially more dangerous for the patient than conservative interventions due to the risk of Central Pontine Myelinolysis (also known as osmotic demyelination syndrome).

The rapid but cautious correction of hyponatremia should only be considered in patients with severe symptoms (eg intractable vomiting, unconsciousness, seizures, Glasgow Coma Scale ≤8).

Rapid correction of acute hyponatreamia (known drop in less than 48 hours) is at a lower risk of Central Pontine Myelinolysis compared to chronic hyponatraemia. However, when actively correcting any form of hyponatraemia with intravenous hypertonic saline, senior decision makers should be involved in deciding aim and frequency of biochemical reassessment.

Hypertonic saline (e.g. Sodium chloride 1.8% or 2.7%) should not be used outside of ED RESUS/HDU/ICU settings except under exceptional circumstances which would only follow specialist advice from endocrinology or nephrology or ICU.

Management of Severe Symptomatic Hyponatraemia

- Manage patients with severely symptomatic hyponatraemia in an environment where close biochemical and clinical monitoring can be provided e.g. ED RESUS/HDU/ITU and under guidance of renal/endocrine/intensive care team.
- First hour management regardless of whether acute or chronic hyponatraemia
    - Prompt i.v. infusion of 150 ml 2.7%$^{+}$ hypertonic saline over 20 min
    - Check the blood sodium concentration after 20 min **urgently*** and consider repeating another infusion of 150 ml 2.7% hypertonic saline over 20 min
- Repeat therapeutic treatment until a strongly recommended cap of 5 mmol/l increase in serum sodium concentration is achieved or if symptoms improve prior to reaching 5mmol/L increment.
- If neurological symptoms are still profound despite increase in sodium, possibly because of acuity of drop of sodium – a senior decision maker is responsible for directing further management.
- *VBG Direct anion measurement of sodium is more accurate and more rapid than serum sodium. Looking for a precise increment measurement should be kept to same ABG machine^{++} for trend

$^{+}$1.8% can be used if only concentration available $^{++}$All ABG machines are calibrated

For Flow Chart see Appendix 2

Supply of 2.7% NaCl at RDH can be located in appropriate management settings of Renal HDU/ICU and ED (children's resus)
Supply of 2.7% NaCl at QHB can be located in appropriate management settings of ICU and ED RESUS as well as Pharmacy OOH cupboard
Alternatively call the on-call pharmacist through switch if OOH

Management of Mild or Moderate symptomatic hyponatraemia

- **HYPERVOLAEMIA:** treat the underlying cause and consider fluid restriction with strict fluid balance charting, renal function monitoring and daily weights.
- **HYPOVOLAEMIA:** treat the underlying cause.
    - If serum sodium ≥125mmol/L then consider prescribing intravenous 0.9% normal saline.
    - If serum sodium <125mmol/L then consider using either Hartmanns Solution or a combination of 500ml normal saline followed by 1L 5% dextrose solution. Serum sodium should be monitored after every 1.5L of fluid resuscitation.
    - Consider more cautious fluid resuscitation to prevent rapid sodium correction in at risk groups eg. malnourished patients, patients with alcoholism. Aim for <8mmol/L increase in serum sodium every 24hrs in order to minimize the risk of Central Pontine Myelinolysis.

- **EUVOLAEMIA:** treat the underlying cause. If serum sodium is not improving within 48hrs then investigate for SIADH.
    - If post-operative fluid excess is suspected, ensure the patient keeps to intake of 1.5-2L a day with fluid balance monitoring and the sodium will gradually improve.
    - In cases where SIADH has been excluded then oral sodium replacement with Sodium Chloride M/R 600mg tablets BD for 7 days can be given.
    - In SIADH fluid restriction should be initially instigated <1L per day. Intravenous sodium replacement may exacerbate hyponatraemia so should not be used unless under instructions from endocrinology.
    - Other treatment options may be available but not widely used. Endocrinology or Nephrology advice should be sought if SIADH is not improving with fluid restriction of <1L per day

Over-correction of Sodium

Patients who have hyponatraemia for more than 48 h are at risk of neurological sequelae if the correction of serum sodium occurs too rapidly due to the development of osmotic demyelination (central pontine demyelinosis- irreversible neurological complication usually occurring 1-6 days after correction.)

A safe limit for the treatment of hyponatraemia is a rise of no more than 10 mmol/L in the first 24 h and 8 mmol/L in the subsequent 24 h (18 mmol/L in 48 h).

Individuals most at risk for developing osmotic demyelination syndrome are elderly patients, malnourished patients, patients with alcoholism, patients with central nervous system disease or hypoxaemia and patients in the post-operative setting.

A tighter safety limit for correction of 8 mmol/L in 24 h and 14 mmol/L in 48 h should be considered in such patients.

Symptoms of CPM that may ensue if these limits are exceeded are:

- Dysarthria, dysphagia, seizures, altered mental status and quadriparesis
- Often delayed by at least a couple of days and gradual in onset

To avoid exceeding the recommended limits of correction consider carefully the frequency of sodium monitoring – it should occur <u>at least once a day</u> however increased monitoring should reflect the severity of the hyponatraemia and the management being undertaken.

If there is concern regarding over-correction in an at-risk individual we recommend consulting a senior decision maker or Endocrinology or Nephrology who may wish to introduce hypotonic fluid (5% dextrose), with or without concurrent anti-diuresis (desmopressin).

Medication

Demeclocycline: Most recent guidelines from the European Society for Endocrinology do not recommend use of demeclocycline in SIADH due to the risks outweighing the benefits of the drug. It certainly should not be started without discussion with endocrinology.

Fluid restriction

This is an appropriate part of the management in hypervolaemic hyponatraemia, SIADH, post-operative hyponatraemia due to water excess, and some cases due to medications. It should not be used until hypovolaemia and hypoadrenalism have been excluded.

Severity of restriction varies- initially 1L per 24 hours but can be reduced to 500-750 ml/24 h. Often, this is poorly applied and patients access additional fluids in the ward environment (and at home). It is therefore very important to put in place strict monitoring of fluid intake and output.

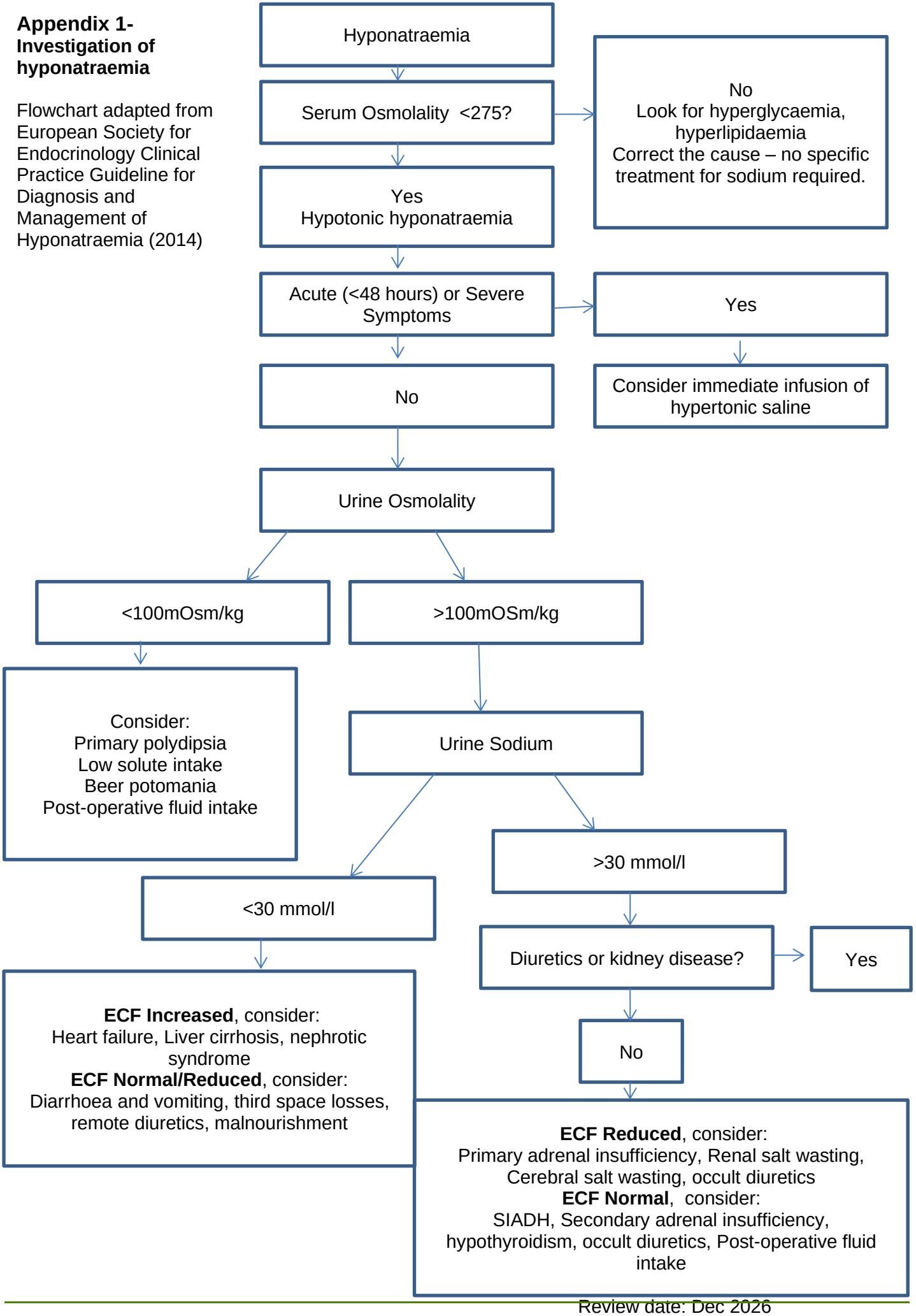
The Furst Formula can be used to predict how likely patients with SIADH will respond to fluid restriction:

$$\frac{(\text{Urine Sodium} + \text{Urine Potassium})}{\text{Serum Sodium}}$$

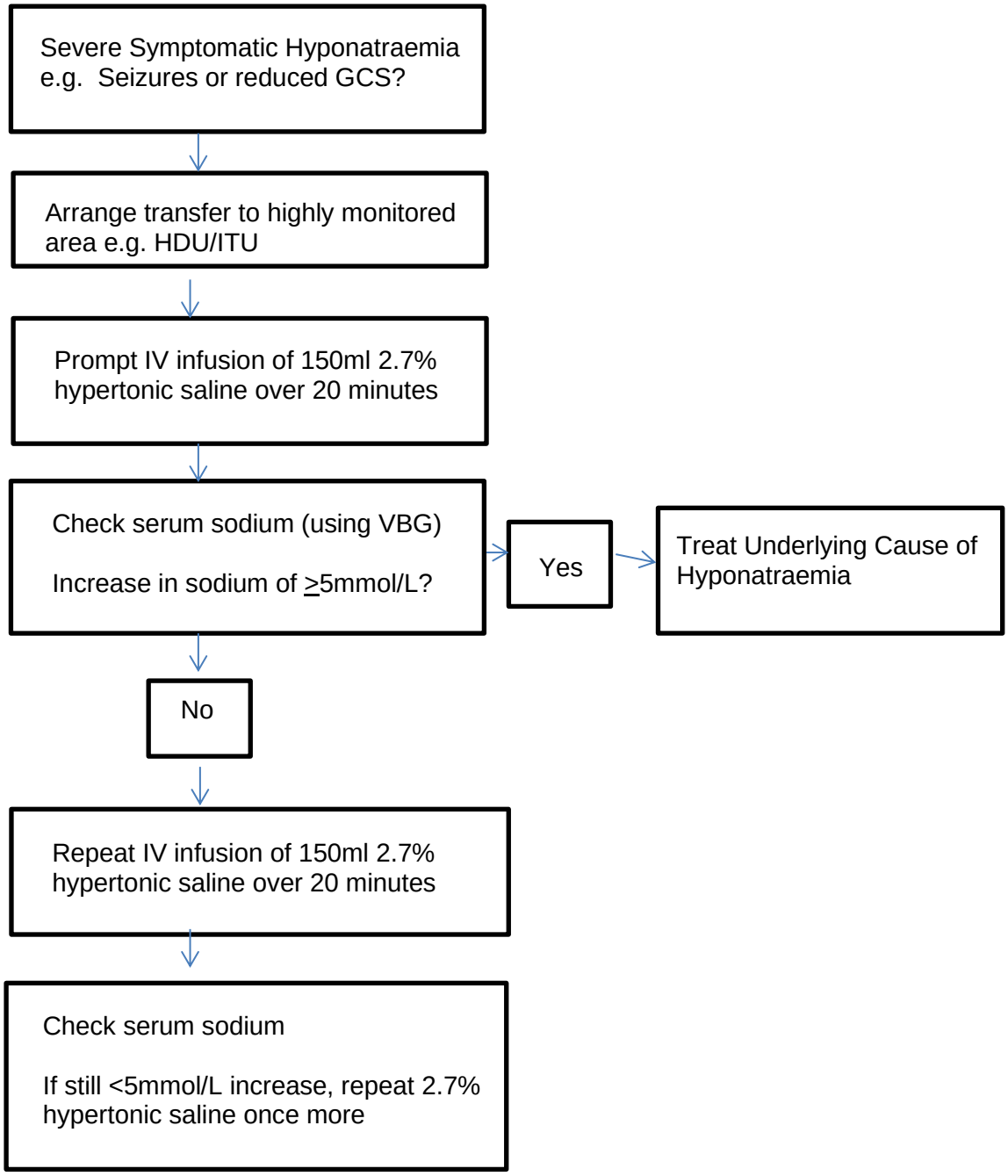
Ratio <0.5 - should respond with fluid restriction to 1L
Ratio 0.5-1.0 - requires tighter restriction (500ml)
Ratio >1.0 may not respond to fluid restriction alone. Medications used in SIADH discussed with Endocrinology

Appendix 1- Investigation of hyponatraemia

Flowchart adapted from European Society for Endocrinology Clinical Practice Guideline for Diagnosis and Management of Hyponatraemia (2014)



Appendix 2- Management of Hyponatraemia with Severe Symptoms



Appendix 3- Formula for calculation of sodium replacement requirements in dehydration

LIMITATIONS- Please note that the formula is theoretical and assumes that sodium losses have ceased and that the body retains the appropriate quantity of free water during rehydration.

The formula does allow an initial rate of sodium containing fluid to be prescribed but it is unsafe to continue this without frequent biochemical reassessment- especially in the early stages.

Involvement of senior decision makers within the team is expected

The box below gives the formula for calculating the sodium deficit of a patient with hyponatraemia. Dividing this number by 150 (the number of mmol sodium chloride in a litre bag) calculates the number of litre bags of 0.9% sodium chloride to give in total to increase sodium from the current level to the 'desired' level.

The rate of initial correction should depend on the clinical status of the patient. The rate of correction of serum sodium concentration should be limited to increases of 8-12mmol/L in the first 24 hours or 18mmol/L over 48 hours. As such entering a desired sodium level 8 mmol/l higher than the current level will give an estimate of the treatment required to achieve such an increase

Replacing Sodium- hypovolaemic hyponatraemia or symptomatic patients

Sodium deficit (mmol/L) = Total body water x (Desired serum sodium- actual serum sodium)

Total body water = 0.6l/kg x weight (kg) Men

Total body water= 0.5l/kg x weight (kg) Women

Use adjusted body weight for overweight patients

Adjusted body weight=Ideal body weight ^{2} + (0.4 x (Actual body weight - Ideal body weight))

References

Clinical practice guideline on diagnosis and treatment of hyponatraemia. Goce Spasovski et al. European Journal of Endocrinology (2014) Vol 170 Issue 3

SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE Emergency management of severe symptomatic hyponatraemia in adult patients Endocrien Connections. (2016) Stephen Ball et al

The diagnosis and management of inpatient hyponatraemia and SIADH. Paul Grant et al.Eur Journal of Clinical Investigation (2015) Vol 45

Estimate Ideal body weight in (kg)
Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet.
Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.
Devine BJ. Gentamicin therapy. DICP. 1974; 8:650–5.

Allen J and Newland-Jones P (2012). How to manage adults with hyponatraemia. Clinical pharmacist vol 4; October 2012 262-264

Wakil A, Ng JM and Atkin SL (2011). Investigating hyponatraemia. British Medical Journal March 2011; vol342:d11182/11/2012

Documentation Controls

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