Approach to Hyponatremia

Learning Objectives

Knowing when to apply diagnostic algorithm for hyponatremia

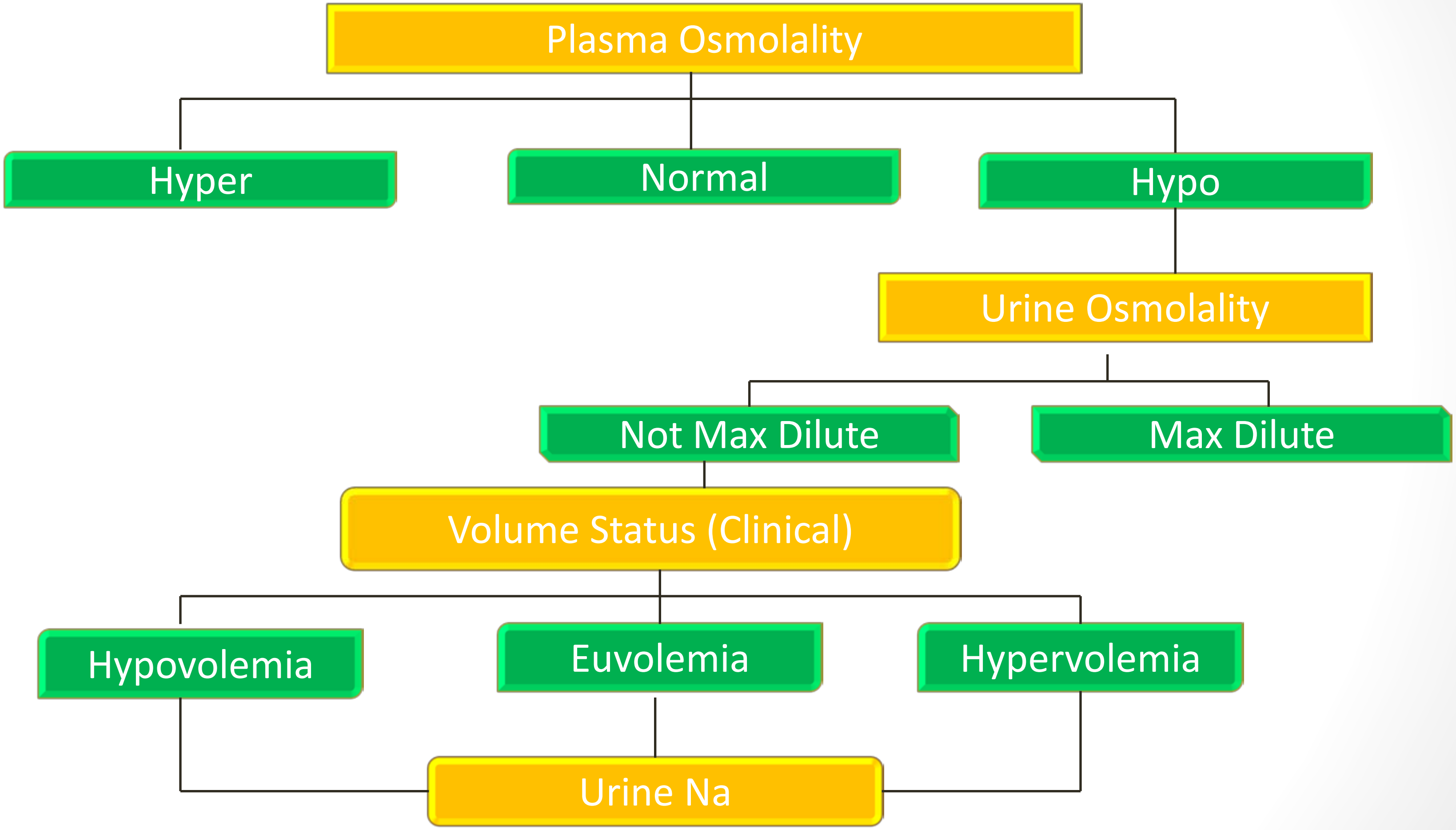
Understanding better the physiological basis

- Of some of the important tests in algorithm
- Of some of the major groupings in algorithm
- Of some of the important causes leading to hyponatremia

Case

- 30 yr old male
  - Known case of epilepsy (on valproate) and autism
  - Admitted for fracture of femur
  - Found to have serum Na 120 mmol/l; clinically euvolemic
- Other tests:
  - Serum urea 2.8 mmol/l, creatinine 36μmol/l
  - Serum osmolality: 248 mOsm/kg
  - Urine osmolality: 387 mOsm/kg
  - Urine sodium: 86 mmol/l
  - Serum cortisol, TFT: normal
- Diagnosis: SIADH, possibly secondary to valproate
  - But, despite significant fluid restriction and NaCl tablets persistent hyponatremia (120-125 mmol/l)
  - Referral for cause of hyponatremia and management

Diagnostic Algorithm for Hyponatremia



Hyponatremia: Preliminaries to Diagnostic Algorithm

Severely symptomatic?	• Start urgent treatment before diagnosing cause
If asymptomatic, is cause fairly obvious?	• E.g. volume depletion, cardiac failure, thiazides • No need algorithm, start appropriate treatment
Asymptomatic, but cause not obvious	• Apply diagnostic algorithm

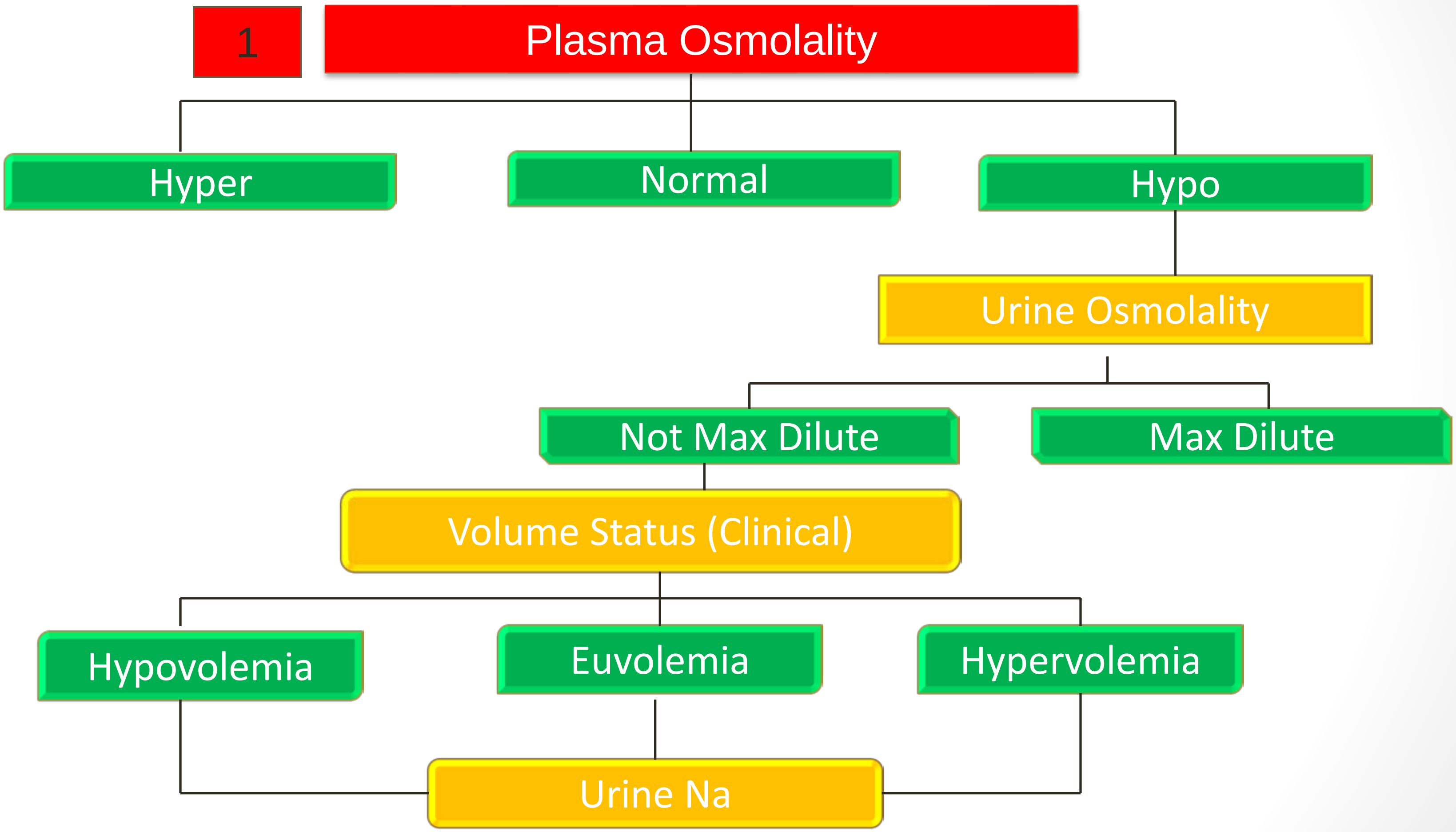
Diagnostic Algorithm (1)

- Hyponatremia: a state of relative water excess in relation to body sodium
- Algorithm: to ascertain which major physiological grouping of water excess patient best belongs to, before deciding underlying cause
- More than one cause possible

Diagnostic Algorithm (2)

- Generally, symptomatic hyponatremia is hypo-osmolar
  - Neurological symptoms from hypotonicity-induced cerebral oedema
- But hyponatremia also seen in hyper-osmolar and normo-osmolar states
  - Less common than hypo-osmolar group
- Therefore Step 1: serum osmolality
  - Main aim: to exclude normo- and hyper-osmolar hyponatremia

Diagnostic Algorithm for Hyponatremia



Hyper-osmolar Hyponatremia

- Effective osmoles
  - Hyperglycaemia
  - Mannitol
- Osmoles cause hyper-osmolality and trans-locational hyponatremia (TBW remains same)
- True hyponatremia but does not cause osmotic cerebral oedema
- Osmolal gap > 10 with mannitol (but not glucose)

- Ineffective osmoles
  - Uremia
  - Alcohol intoxication
- Osmoles cause hyper-osmolality but not the hyponatremia (which develops because of other reasons)
- Hyponatremia can be true and symptomatic
- Osmolal gap > 10 with alcohol (but not uremia)

Normo-osmolar Hyponatremia

- Factitious or pseudo-hyponatremia
  - Asymptomatic
  - Measured osmolality normal
  - Osmolar gap > 10 (because calculated osmolality falsely lower than measured osmolality)
- Less severe hyperglycaemia, uremia
- Use of sodium-free irrigants during TURP, laprascopic surgery
  - Though normo-osmolar, hyponatremia can still be symptomatic for other reasons (e.g. irrigant toxicity)
  - Osmolar gap > 10

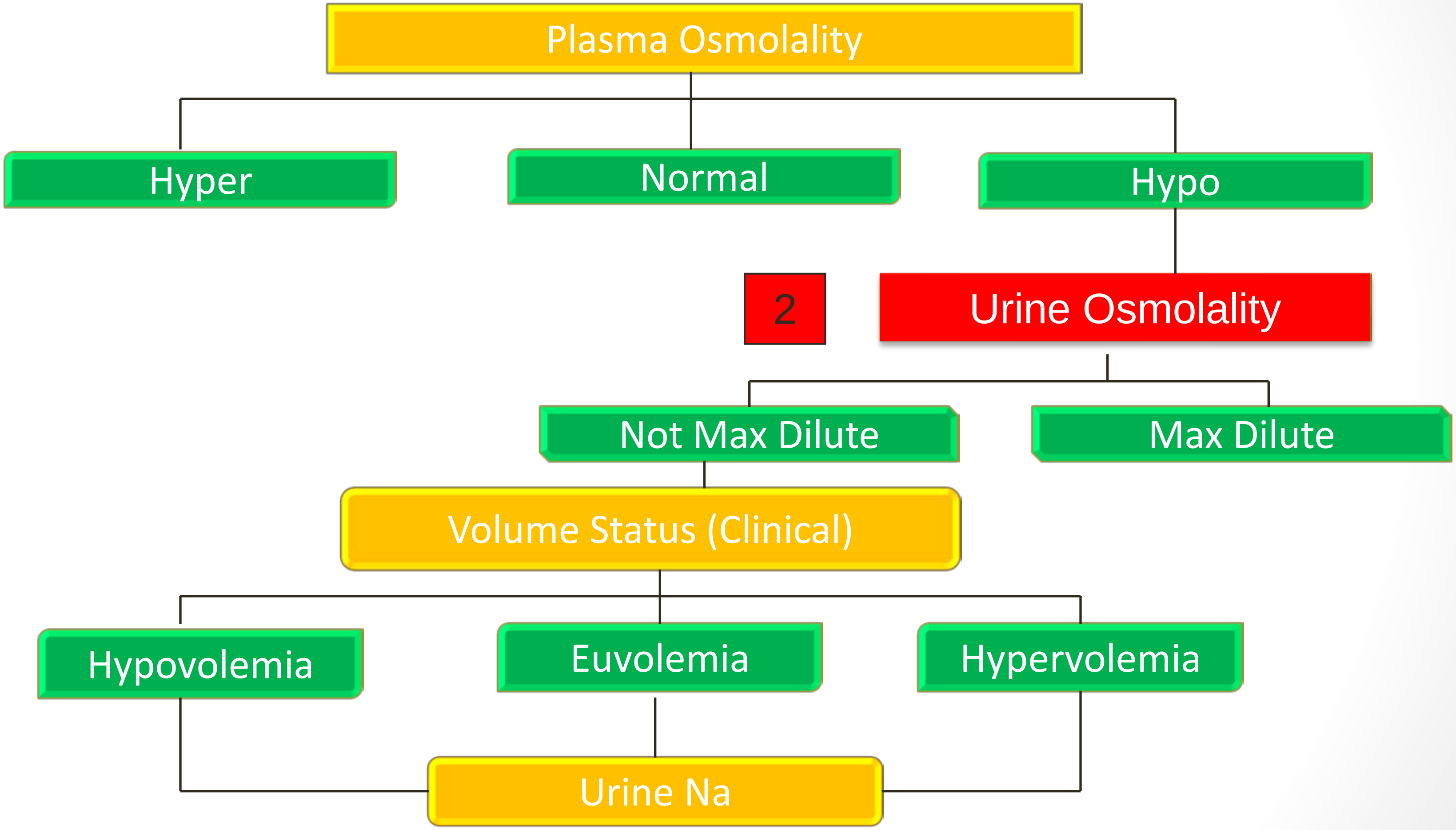
Hypo-osmolar Hyponatremia: Pathophysiology

- Biggest group of hyponatremia
- Osmolar gap: normal typically
- Hypo-osmolar state can cause symptomatic cerebral oedema
- Excess water in relation to sodium in ECF = excess total body water in relation to total body sodium
  - Water intake exceeds impaired renal water excretion (majority of causes)
  - Water intake exceeds normal renal water excretion capacity (primary polydipsia)
  - Total body sodium can be decreased, normal or increased; basic problem is with water balance, not sodium balance

Hypo-osmolar Hyponatremia: Overview of Diagnostic Strategies

- Combination of establishing ADH status and volume status
- ADH status
  - Small group of causes with suppressed ADH
  - Bigger group with non-suppressed ADH
- Non-suppressed ADH group
  - Causes in this group associated with different volume status
  - Determining clinical volume status narrows down possible causes
  - Applying urine sodium to each volume group further refines diagnosis of cause

Diagnostic Algorithm for Hyponatremia



Hypo-osmolar Hyponatremia

- Step 2: urine osmolality
  - Main aim: to decide if state of relative water excess (i.e. hyponatremia) is with
    - ADH suppression (urine maximally dilute, i.e. < 100 mOmol/kg)

    = dilute urine group in this presentation

    OR

    - ADH secretion (urine not maximally dilute, i.e. > 100 mOsmol/kg)

    = concentrated urine group in this presentation

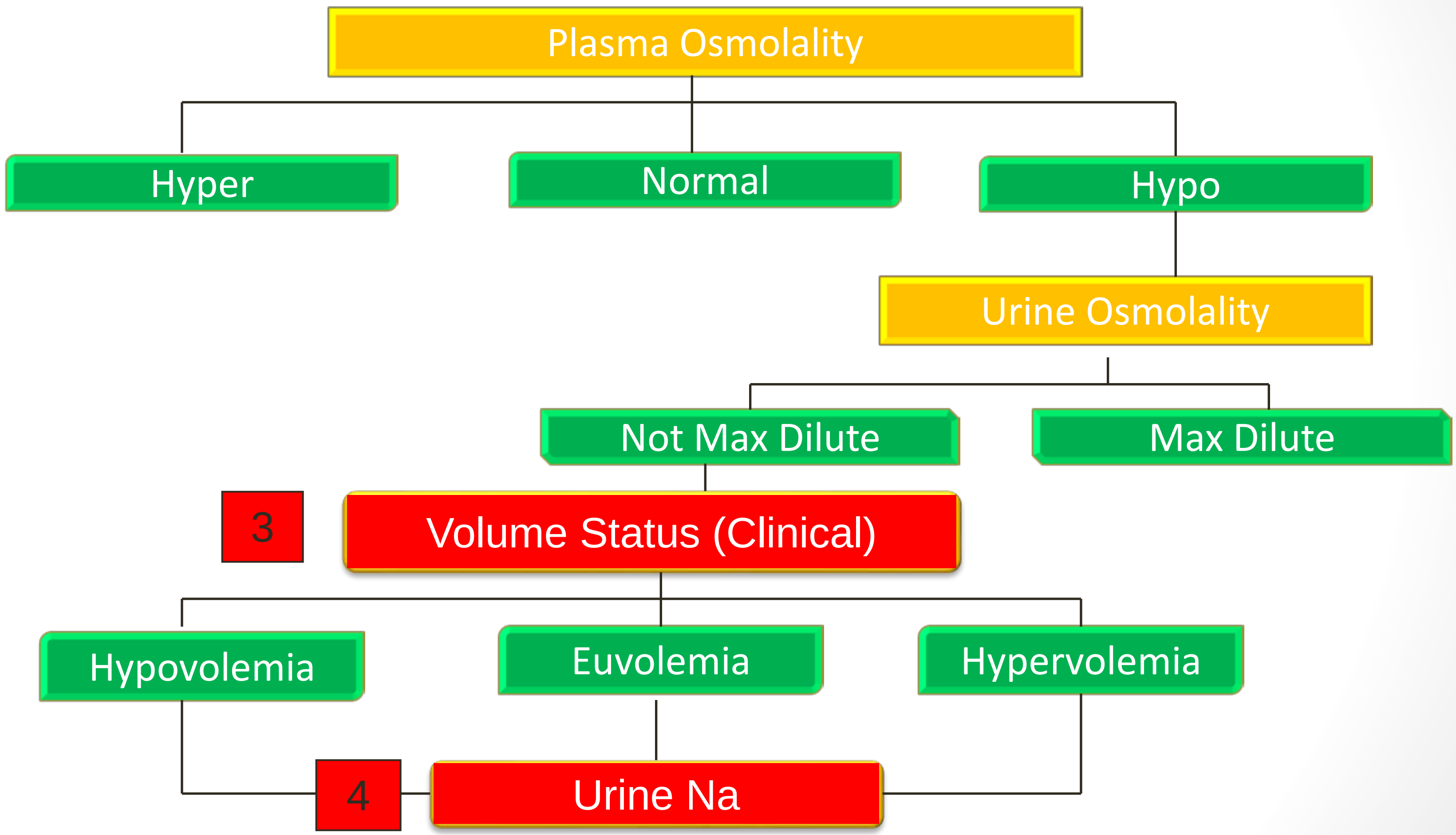
Hypo-osmolar Hyponatremia with Dilute Urine

- Main causes
  - Primary polydipsia
  - Poor solute intake / Beer potomania
  - Reset osmostat (with recent significant water load)
- Water retention in this group occurs through ADH-independent pathways

Poor Solute Intake

- Normal solute intake: 600 to 900 mosmol/day
- In malnourished: can be 200 to 250 mosmol/day
  - Maximum daily urine volume = urine solute per day / minimum urine osmolality
  - With maximally dilute urine, maximum urine output in malnourished can fall below 2 to 3 litres/day
  - Hyponatremia begins as fluid intake (including heavy alcohol use) exceeds this excretory capacity

Diagnostic Algorithm for Hyponatremia



Hypo-osmolar Hyponatremia with Concentrated Urine

- ADH-mediated hyponatremia
  - Exception: Advanced renal failure → ADH suppressed in this condition
- Explanation of persistent ADH secretion can be linked to body's volume status
  - Hypovolemia and hypervolemia →ECV ↓ →ADH↑
  - Euvolemia →unregulated ADH↑ (i.e by neither osmotic nor ↓ECV stimuli)
- Steps 3 and 4: assessment of volume status (clinically) and urinary sodium
  - Main aim: to ascertain underlying causes of hyponatremia in this hypo-osmolar group with concentrated urine

Clinical Volume Status

- Should be done but to be aware of its potential unreliability
- Best diagnostic signs for hypovolemia
  - Postural dizziness or increased postural pulse (Sn 60 – 98%, Sp 99%)
  - Poor skin turgour - subclavicular area (LR 3.5, but less specific in elderly)
  - Dry mouth (LR 3.1)
- Supplementary feature: serum urea to creatinine ratio > 100 (in SI units, both in mmol/L)

Clinical Volume Status (2)

- Best diagnostic signs for CCF
  - Positive hepato-jugular reflex (LR 8)
  - Displaced apex beat (LR 5.8)
  - Elevated JVP (LR 3.9)
  - S_3 gallop (LR 3.9)
- To note: serum urea to creatinine ratio can also be elevated (cardio-renal syndrome)

Urinary sodium

- An attempt to ascertain underlying cause within each volume status group
- True hypovolemic group
  - Urine sodium <20 mmol/l → extra-renal loss of sodium (e.g. diarrhoea); exception: vomiting with metabolic alkalosis
  - Urine sodium >20 mmol/l → renal loss of sodium (e.g. renal salt wasting, diuretics, cerebral salt-wasting)
- Hypervolemic group
  - Urine sodium <20 mmol/l → e.g. CCF, cirrhosis
  - Urine sodium >20 mmol/l → renal failure
- Euvolemic group
  - Urine sodium >20 mmol/l (with normal sodium intake)

Urinary sodium (2)

- Also affected by
  - Prior sodium intake
  - Ongoing sodium infusion
  - Ongoing diuretic effect
  - Ongoing osmotic diuresis
  - Ongoing bicarbonaturia (metabolic alkalosis)
- Interpetation of urinary sodium regarding causes of hyponatremia must consider these confounders, if present
- Generally, urine FENa is better than spot urine Na concentration to assess urine sodium status

Hypervolemic hyponatremia: Renal failure

- Main mechanisms for impaired renal water excretion
  - ↓ GFR →this ↓ delivery to diluting segment
  - Rising of minimum urine osmolality to as high as 200 to 250 mOsm/kg in <u>advanced</u> renal failure (despite ADH suppression) because of ↑ solute excretion → this ↓ urinary dilution
- Approximate urine volume in renal failure
  - Around 10% of GFR
  - E.g. advanced renal failure patient with GFR 5 ml/min (around 7l/day) cannot excrete >800 ml/day
- Water intake exceeding this urine volume capacity results in dilutional hyponatremia

Hypervolemic hyponatremia: Renal failure (2)

- With mild to moderate renal impairment (till around stage 3 CKD), there is generally sufficient urinary dilution and free water excretion to maintain normonatremia

Euvolemic hyponatremia

- Main considerations
  - SIADH and reset osmostat variant
  - Hypoadrenalism (via ADH)
  - Hypothyroidism (via ADH)
  - Thiazide use
- Generally, all these causes are associated with urine Na >20 mmol/l
  - Unless they also have poor sodium intake

Diuretic-induced Hyponatremia

- Primarily with thiazides; uncommon with loop diuretics
- Two types of presentation
  - Hypovolemia
  - Euvolemia – especially with thiazides
- Many thiazide hyponatremia cases present clinically like SIADH
  - Unlike loops, thiazides do not impair medullary osmolality (that can cause more water excretion)
  - Thus, though natriuretic, more water retention occurs with thiazides than with loops

SIADH: Main Diagnostic Criteria

- Decreased effective serum osmolality (<275 mOsmol/kg)
- Urine osmolality > 100 mOsmol/kg during serum hypotonicity
- Urine sodium > 40 mmol/L with normal salt intake
- Normal thyroid/adrenal function
- Supplementary features
  - Serum urea < 3.6 mmol/L, low normal serum creatinine
  - Serum uric acid < 0.24 mmol/L
  - Abnormal water loading test (excretion < 80% of 20 ml/kg of water load in 4 hr)
- SIADH still diagnosable with concurrent mild to moderate renal impairment
  - Such renal impairment can still dilute urine sufficiently to avoid hyponatremia

SIADH vs Mild Hypovolemia/Low Sodium Intake

- SIADH suspected but volume status uncertain clinically, and urinary sodium < 20 mmol/l or 20-40 mmol/l
- To note: hypovolemia or low sodium intake can co-occur in SIADH patient
- Saline infusion test (if no clinical contraindications)
- IV N/S 1 to 2 litres for 1 to 2 days with pre- and post-measurements

	Mild Hypovolemia	SIADH
Serum Na increase	≥ 5 mmol/l	<5 mmol/l
Urine FENa increase	< 0.5%	> 0.5%
Urine osmolality change	Drops	Remains elevated

Reset Osmostat

- Downward resetting of osmostat
- Regarded as one form of SIADH
- Seen in various conditions including
  - Normal pregnancy, quadriplegia, psychosis, TB, chronic malnutrition
- Suspected when
  - Mild hyponatremia (generally between 125 to 130 mmol/l)
  - Stable (i.e. not progressively worsening) hyponatremia despite variations in salt and water intake
- Urine osmolality may be maximally dilute or otherwise – depending on set point and water-load (plasma tonicity) status
- No treatment (including fluid restriction) needed

SIADH vs Reset Osmostat

- Water loading test
- Not to do in patients with severe hyponatremia (especially ≤ 120 mmol/l) or potential fluid overload problems
- Method
  - Supine position
  - Water load 20 ml/kg (oral or IV) over 30 min
  - Observe 4 hours
  - Monitor urine output, serum sodium, urine osmolality
- Key variable: urine output
  - Reset osmostat behaves as normal person: >80% of water load excreted
  - SIADH shows abnormal response: <80% excreted

Case Review & Summary

- Preliminary considerations
  - Asymptomatic hyponatremia and cause not immediately obvious
- Diagnostic algorithm
  - Step 1: Hypoosmolar hyponatremia
  - Step 2: Urine concentrated (not maximally dilute) → ADH-mediated hyponatremia
  - Steps 3 and 4: Clinically euvolemic with high urine Na
- Cause
  - SIADH, reasonable initial diagnosis
  - However, subsequent behaviour of serum sodium with fluid restriction and salt tablets → suggestive of reset osmostat
  - Confirmed by water load test
  - Off fluid restriction and NaCl tablets; serum Na two weeks later stable at 126 mmol/l and patient asymptomatic