# Hyponatremia – Clinical Significance

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# Case of hyponatremia

- 70 years old male
- Past medical history: DM, HTN
- Heavy smoker (20 packs/day)
- Recently: epigastrial pain, poor appetite, body weight decreased by 3 kg
- When specifically asked: complains of weaknes, dizziness, unsteady gait → family doctor arranged an appointment for head CT

# Physical examination

- RR 148/72 mmHg, P 89/min
- Some wheezes above the chest
- Mild epigastrial tenderness
- No edema
- Conscious, oriented, no focal neurological abnormality

# Laboratory results on admission

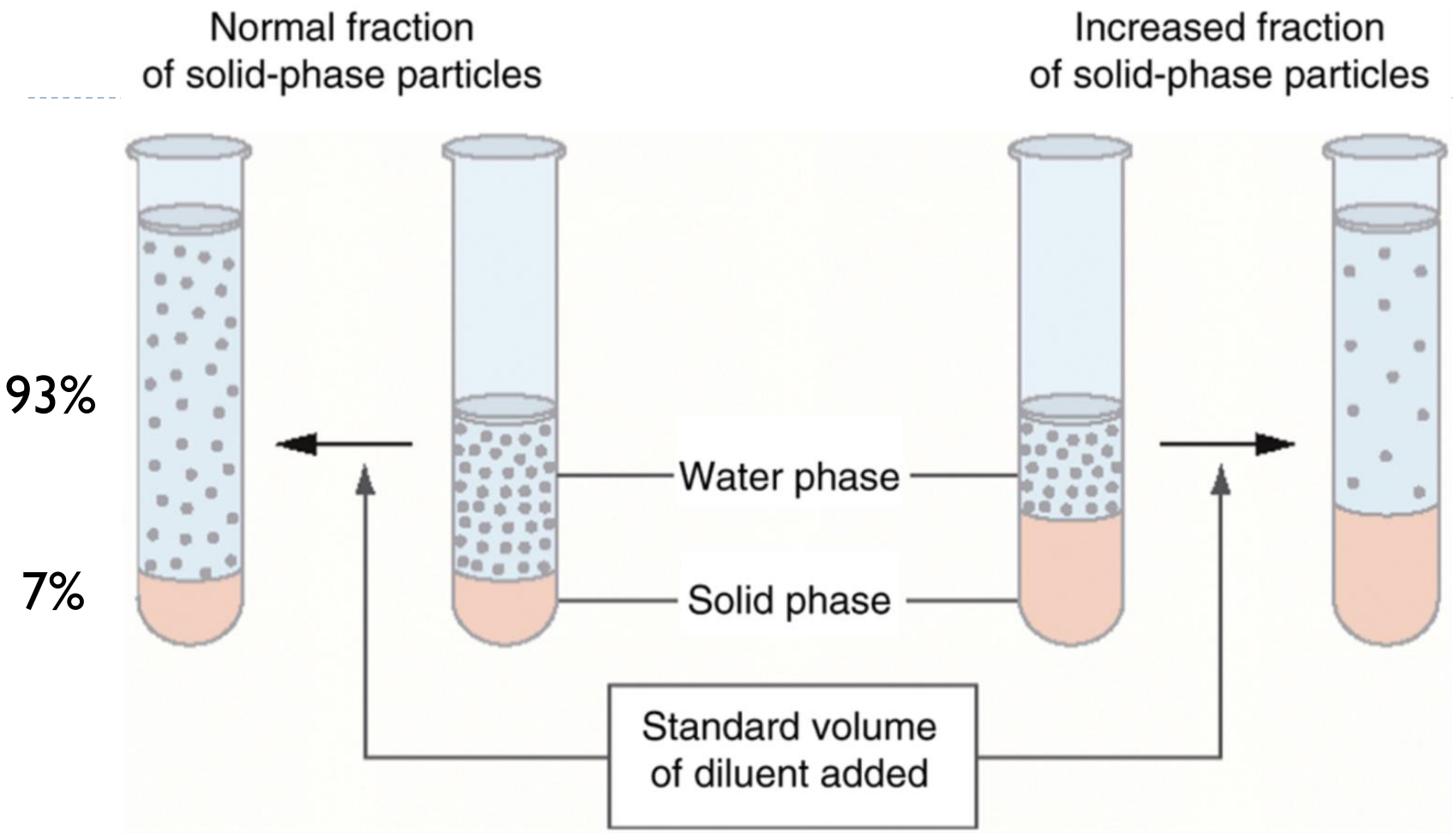
| | |
|---|---|
| Na | 114 mmol/l |
| K | 4,7 mmol/l |
| Cl | 82 mmol/l |
| Blood sugar | 7,1 mmol/l |
| CN | 3,8 mmol/l |
| Creatinine | 52 umol/l |
| Uric acid | 138 umol/l |
| Urinary sodium | 86 mmol/l |
| Urinary potassium | 63 mmol/l |
| Urinary osmolality | 577 mOsm/kg |

# What is your approach?

1) Is this a true hyponatremia?
   - Can it be pseudohyponatremia?
   - Measurement of serum osmolality

2) Is this an acute or chronic hyponatremia?

3) What is the most appropriate treatment?




# Pseudohyponatremia

Clinical practice guideline on diagnosis and treatment of hyponatraemia. NDT 2014



*Our pt's serum lipid and protein levels were normal.

# Hyperglycemia - Role of blood sugar

- „Translocational" hyponatremia! Serum osmolality in not low!
- **Corrected serum Na = measured serum Na + 2.4 x actual glucose - 5.5 (mmol/l) / 5.5 mmol/l**
- Quick, approximate calculation:
  - Each 5 mmol/l increase of blood sugar above normal alters serum sodium concentration by 2 mmol/l
  - e.g. blood sugar = 25 mmol/l → 20 mmol/l increment
  - serum Na decreases by 20/5x2 = 8 mmol/l

# What do the urinary lab results tell us?

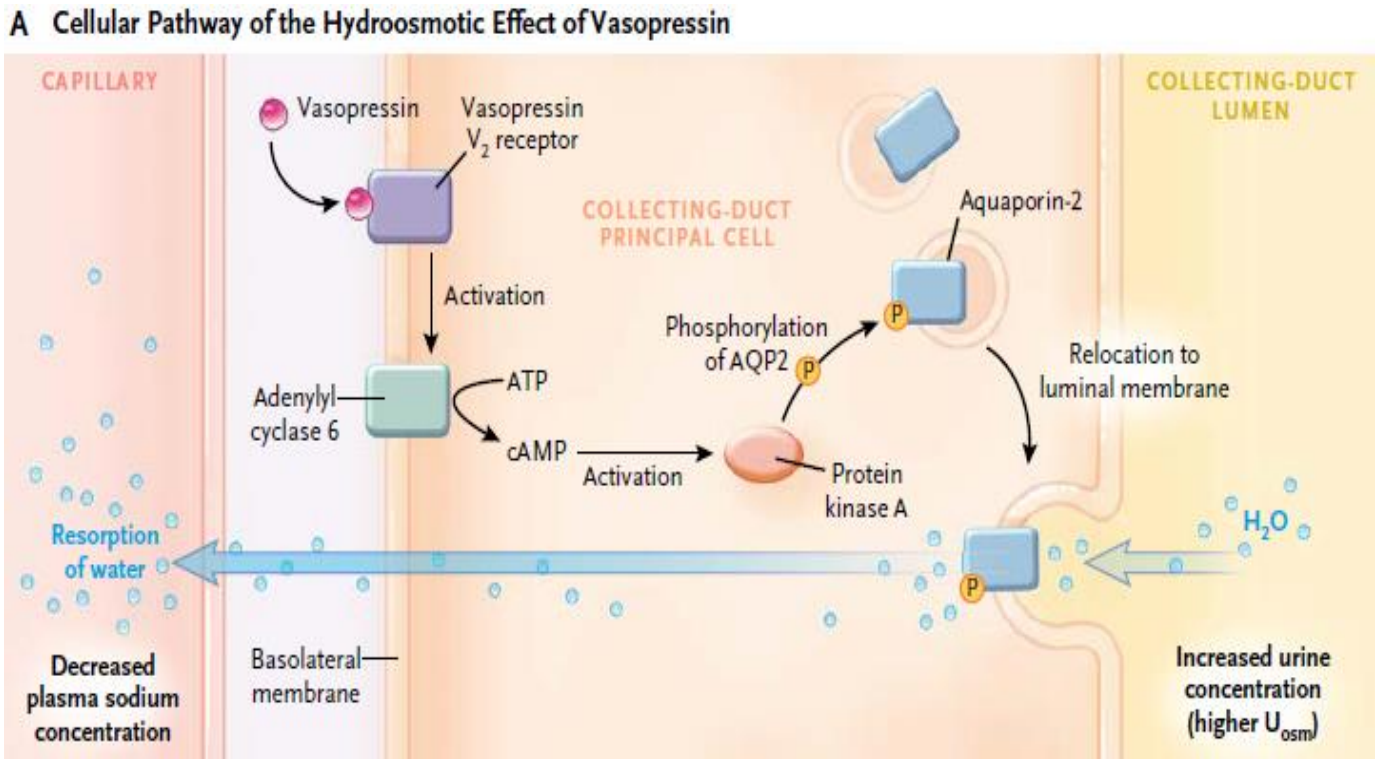
- Urinary sodium 86 mmol/l

- Based on the physical examination and the urinary Na concentration he was normovolemic.

* He did not get any diuretics –
  Diuretic drugs alter urinary Na excretion, regardless of volume status

- Uosm: 577 mOsm/kg = strong ADH effect - Why ???

# Action of ADH on the tubular water reabsorption - urinary concentration




Tomas Berl, M.D.

N Engl J Med 2015;372:2207-16.
DOI: 10.1056/NEJMra1403672

If Uosm > 100 mOsm/kg = ADH is acting

# Other labs to pay attention

- Blood sugar — 7,1 mmol/l – rules out pseudohypoNa (also serum lipids, protein levels)
- CN — 3,8 mmol/l – no signs of volume depletion, renal failure
- Creatinine — 52 umol/l - no sign of renal failure
- Uric acid — 138 umol/l – not enchanced tubular reabsorption (as in volume depletion)
- TSH — 1,155 mIU/l - rule out hypothyroidism
- Cortisol — measure if clinical suspition - rule out hypocorticism

# Acute or chronic?

**Table 1. Acute Versus Chronic Hyponatremia**

| | Acute | Chronic |
|---|---|---|
| Number of patients | 14 | 52 |
| Duration | <12 h | 3 d |
| Serum Na level (mmol/L) | 112 ± 2 | 118 ± 1 |
| Stupor or coma | 100% | 6% |
| Seizures | 29% | 4% |
| Mortality | 50% | 6% |
| Low Na level deaths | 36% | 0% |

Consults at 1 hospital in 1 year; Na <128.
Data from Arieff et al.[22]

These laboratory observations led to the clinical distinction between acute and chronic hyponatremia; a classic series found that deaths attributable to cerebral edema were limited to patients whose hyponatremia developed over the course of 12 hours, whereas patients who had become hyponatremic over 3 days or more were much less likely to have seizures and did not die from hyponatremia (Table 1).[22]

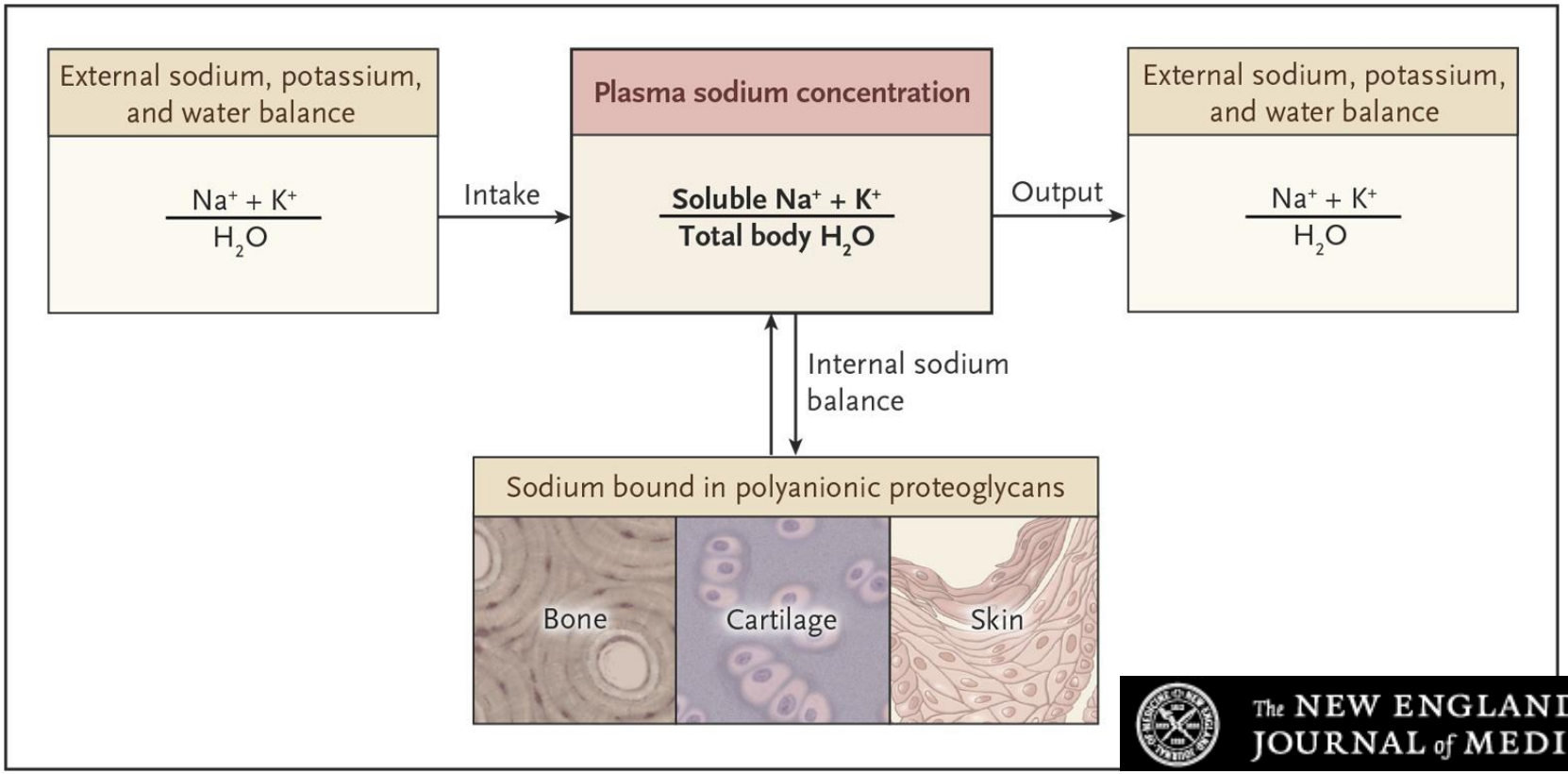
22. Arieff AI, Llach F, Massry SG. Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. Medicine (Baltimore). 1976;55:121-9.

# Clinical course

- Chest XR
  - widening of the left hilus + 2 cm wide mass
  Suspected pulmonal malignancy
  - CT scan is suggested
- Treatment of hyponatremia: fluid restriction
  (< 750 ml fluid intake/day)
  and generous amount of salt consumption with meals
- Serum sodium on the following days:
  114-114-113-123-125-129-135 mmol/l

# Internal and External Solute and Water Balance and the Plasma Sodium Concentration

Sterns RH. N Engl J Med 2015;372:55-65




Plasma Na concentration: Na and K in the body to total body water. This concentration is altered by net external balances (intake minus output) and by internal exchange between Na that is free in solution and Na that is bound to polyanionic proteoglycans in bone, cartilage, and skin.

# Summary of the basic approach to chronic hyponatremia

1) Differentiate acute and chronic hyponatremia
2) Look for the reason of ADH secretion
   - determine what the patient volume status is
   - check urinary electrolytes and osmolality
   - initiate work up to determine etiology
3) Decide about treatment
   - in case of chronic hypoNa be moderate and slow

# HypoNa in euvolemic patients -Medications

- One of the most frequent cause of hypoNa
- Caused very often by **thiazides**
  - increased urinary solute excretion
  - no increase in free water excretion
    - medullary concentration gradient remains intact
  - especially risky in elderly patients with low solute intake
  - ADH stimulation by diuretic caused volume depletion contributes to some extent
  - volume depletion causes increased thirst, fluid intake

- Many other drugs associated with hypoNa:
  SSRI-s, carbamazepin, narcotics, cyclophosphamide, desmopressin, etc.

# HypoNa in euvolemic patients -SAH

- Frequently seen in neurosurgical departments

*Hannon at al. J Clin Endocrinol Metab 2014*

- 100 patients suffered SAH, 49 developed hypoNa, serum Na <135 mmol/l, 14% < 130 mmol/l
- ADH, BNP, cortisol were measures, based on these:
- Etiology of hypoNa was SIAD in 71%

- (Rarely other intracranial hemorrhages, infections, or pulmonary infections cause hypoNa)

# Hyponatremia following mild/moderate SAH Hannon at al. J Clin Endocrinol Metab 2014

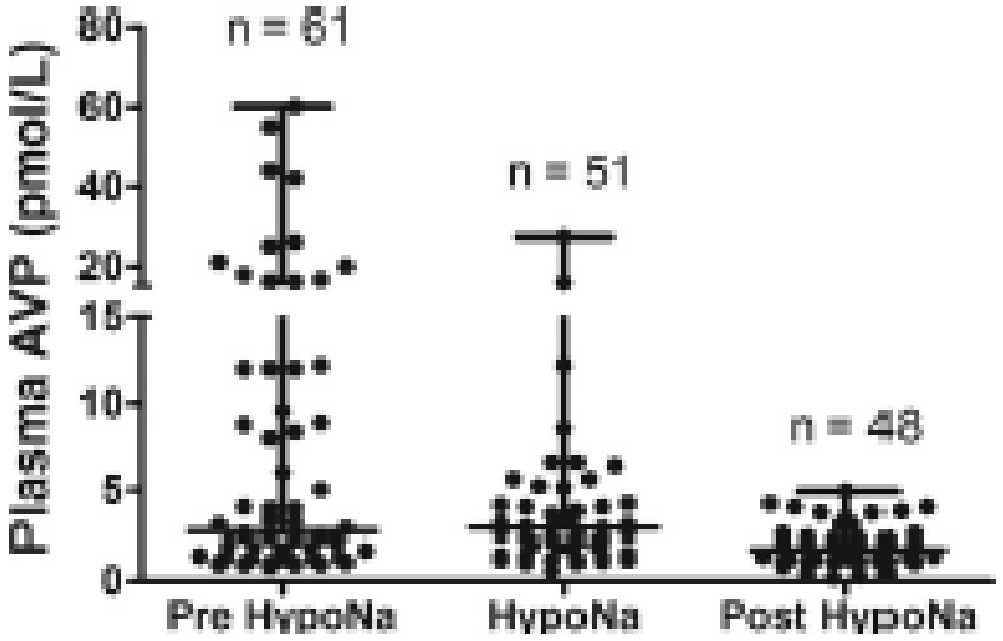



**Figure 2.** Comparison of AVP levels before development of hyponatremia, during hyponatremic episode, and after resolution of hyponatremia, in patients with SIAD. AVP levels are significantly higher before and during episode of hyponatremia when compared with after resolution of hyponatremia ($P = .03$).

# Hyponatremia following mild/moderate SAH
# Hannon at al. J Clin Endocrinol Metab 2014

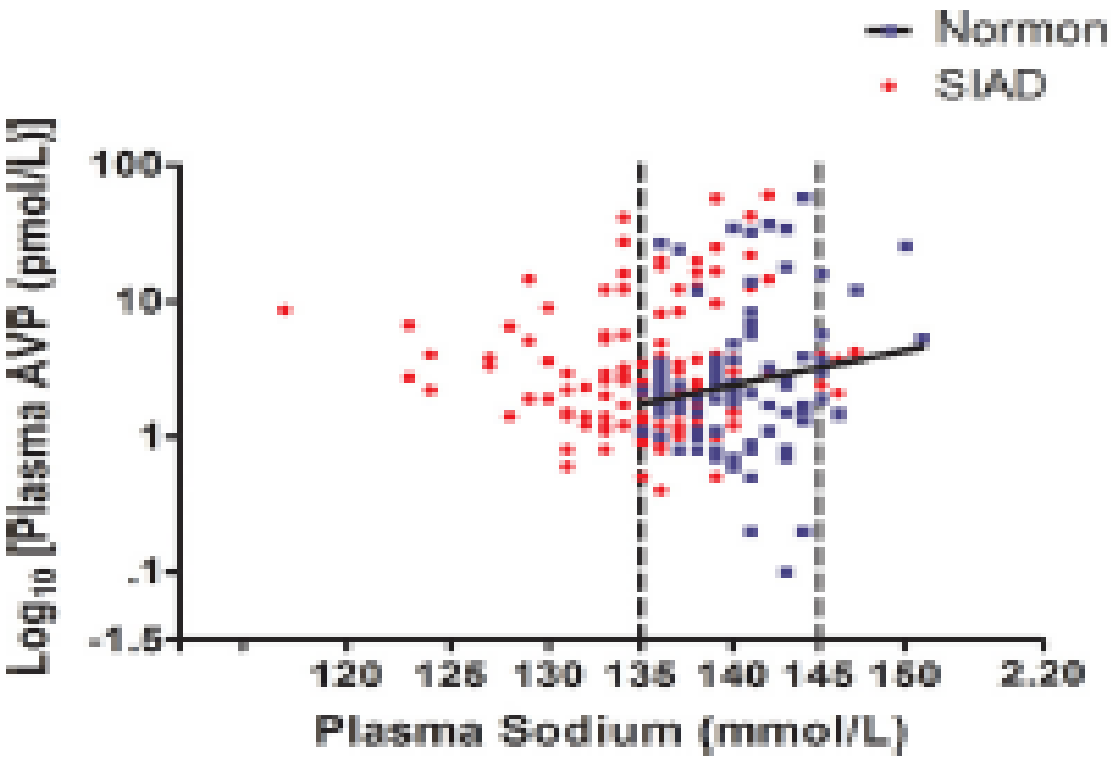



**Figure 3.** Relationship between plasma sodium and AVP secretion. The association between plasma sodium and AVP release is maintained in those patients with normonatremia ($R = 0.51$, $P = .04$), but lost in those with SIAD ($R = -0.02$, $P = .93$).

# HypoNa in euvolemic patients - Malignancy

- Although this was the original description of SIADH by Schwartz and Bartter in 1957, it is a relatively rare cause of hypoNa
- Several tumors can cause:, e.g. lung, oropharynx, GI, genitourinary, carcinomas, lymphomas, sarcomas, neuroblasoma

# Hyponatremia in hyperhydrated patients – liver cirrhosis

- In 15-20% of alcoholic patients
- High level of vasopressin due to
  **decreased effective circulatory volume**
  (systemic vasodilatation, arteriovenosus shunting)
  → neurohormonal activation, baroreceptor mediated vasopressin release
- HypoNa means **„more water than salt"**
  Poor prognostic sign
- **Treatment**: water restriction, salt restriction, diuretics
- Potential role of vaptans?

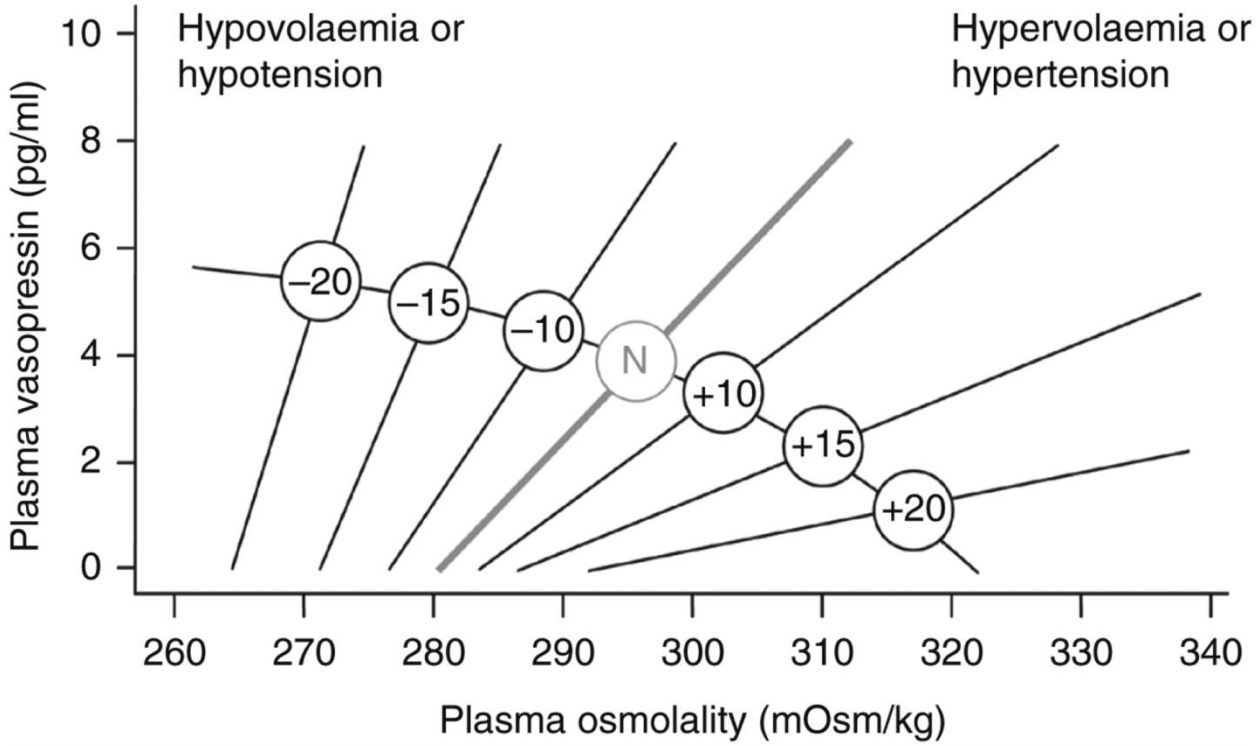
# Hyponatremia in hyperhydrated patients – heart failure

- In 20-30% with NYHA III-IV → decreased cardiac output → baroreceptor mediated neurohormonal activation
- High level of vasopressin due to **decreased effective circulatory volume**
- HypoNa means **„more water than salt"**
  Poor prognostic sign
- **Treatment**:
  water restriction, salt restriction, loop diuretics; treatment of the cardiac disease
- Potential role of vaptans (?)

- Similar situation in nephrotic syndrome

# Hyponatremia in volume depleted patients

- Vasopressin secretion is mediated by volume depletion
  - **non-osmotic baroreceptor mediated ADH secretion**
- **Treatment**:
  In this case **isotonic saline** infusion will correct serum Na as the stimulus for vasopressin secretion is stopped
- Do not give hypertonic Na infusion!
  - risk of overcorrection!
- Watch for dilute urine
  - increased free water excretion!
  - it predicts the serum Na increase




From: Clinical practice guideline on diagnosis and treatment of hyponatraemia

Nephrol Dial Transplant. 2014;29(suppl_2):i1-i39. doi:10.1093/ndt/gfu040

# „Beer potomania" or „Tea and toast" hyponatremia - Impact of solute intake

- Maximal urinary diluting capacity > 50 mOms/kg
- (We cannot pee „tapwater")
- Sodium, potassium and protein consumption determines solute excretion
  (10 g of protein results in 50 mmol urinary urea excretion)
- **Solute excretion determines water excretion**
- Beer potomania – minimal solute intake (salt, protein)
- **Treatment**: hypertonic saline administriation depens on acuteness and severity;
  **Aim to normalize salt and protein consumption**
- Be carefull with serum osmolality measurement – alcohol increases it! – calculated osmolality is better

# Impact of Solute Intake on Urine Flow and Water Excretion

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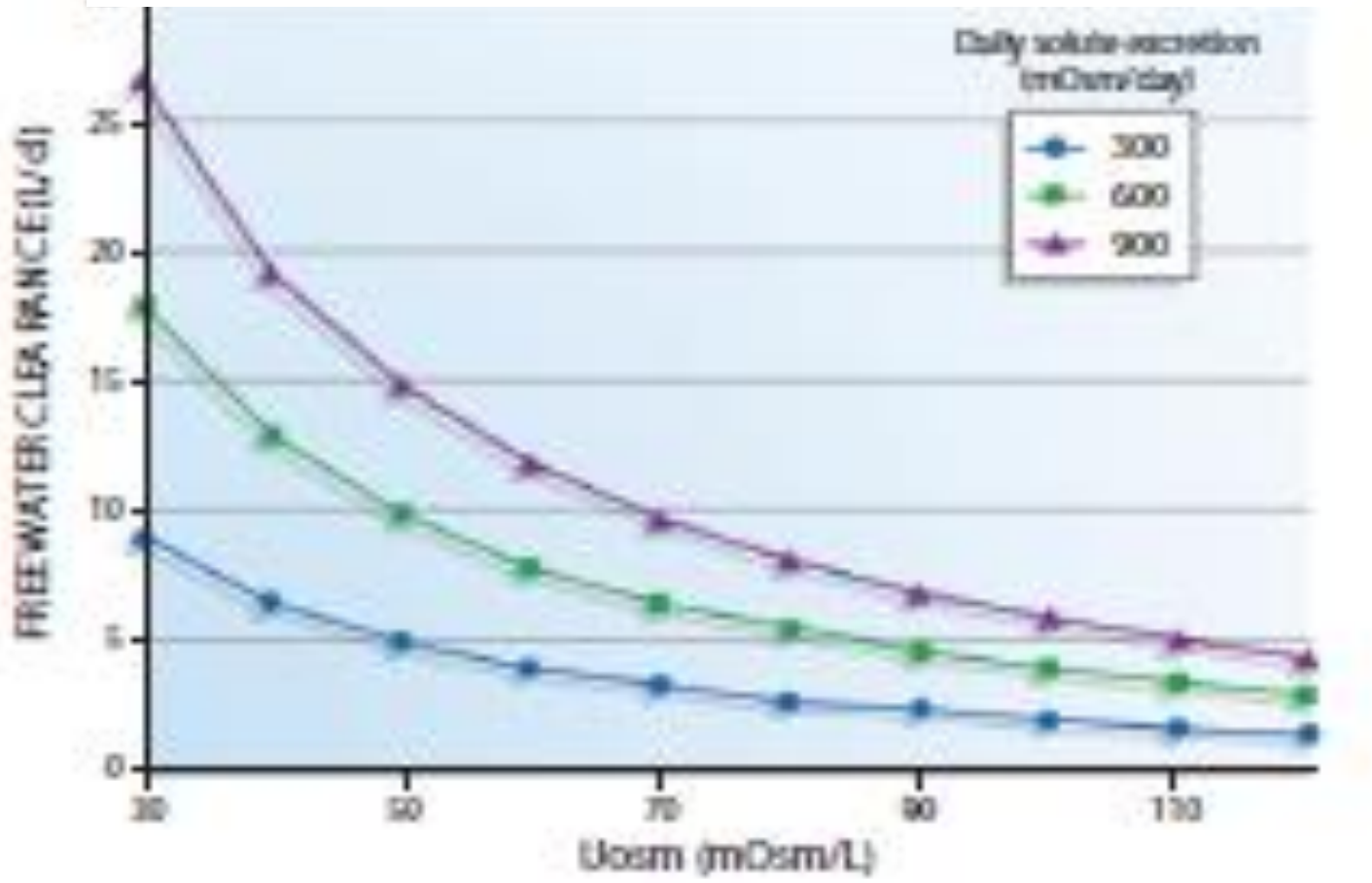



**Figure 1.** Dependence of water clearance on daily solute excretion at low urinary osmolalities. Data from reference 7, with permission.

# Hyponatremia in chronic renal failure

- Limited diluting capacity:
  urinary osmolality ~ serum osmolality (isostenuria)

- On low protein, low salt and low potassium diet
  → Limited solute excretion

- **Treatment**:
  adjust fuid intake to solute intake and renal diluting capacity

# Acute hyponatremia

# Acute hypoNa is a rare condition

- You may diagnose it in
  - Postoperative state:
    excesive ADH secretion due to pain, stress, nausea, narcotics + inappropriate hypotonic fluid administration
  - Recent introduction of a thiazide diuretic
  - Psychogenic polydypsia
  - Endurance exercise
  - Use of ecstasy

# Acute hypoNa causes severe symptoms

- **Signs of cerebral edema:**
  vomiting, confusion, seizures, stupor, coma, noncardiogenic pulmonary edema
- (In case the patient does not have such symptoms hyponatremia is very likely chronic!)

# Acute hypoNa during preparation for colonoscopy

- 84 years old female, admitted to hospital 12 days earlier because she had had **diarrhoea** for 3 days
- On admission she looked **volume depleted**, had low BP (90/50 mmHg)
- Laboratory results: Hgb 9,86 g%, serum **Na 134** mmol/l, K 3,0 mmol/l, **BUN 21,9 mmol/l**, creatinine 182 umol/l
- She got **0,9% NaCl infusion+KCl** for 3 days
  the BP normalized (118/59 mmHg),
  the labs: **Na 141 mmol/l**, K 3,6 mmol/l, **BUN 4,1** mmol/l, creatinine 86 umol/l
- The gastroenterology team decided to go on with GI work up in order to look for the cause of anemia

# Acute hypoNa during preparation for colonoscopy

- Scheduled for colonoscopy on Monday (plan to preparing her by Fleet enema on Sunday evening)
- Instruction by the nurse on Sunday morning: „**no solid food to eat, only fluids to drink**”
- On Sunday morning – complaints free, ambulating, „**looked nervous**”
- In the afternoon: she suddenly **lost her consciousness,** had a **convulsion, did not respond** even **to pain,** had **uncoordinated movements** in all her extremities. Vomited repeatedly.

# Acute hypoNa during preparation for colonoscopy

- Urgent labwork:
  serum **Na 117 mmol/l, K 2,9** mmol/l,
  BUN 2,4 mmol/l, creatinine 98 umol/l
- Urinary osmolality **431 mOsm/kg**,
  urinary **Na 164** mmol/l, K 44 mmol/l hrs,
  900 ml/12 hrs
- Brain CT:
  -no major abnormality can be seen



32

# Approach of the case

- **Acute**, severe hyponatremia → very likely cerebral edema
- Urine osmolality: 431 mOsm/kg - **strong influence of ADH** (likely due to stress, anxiety, nausea)
- **Lots of fluid intake** according to the instructions
- Urine Na: 164 mmol/l means - no volume depletion
- Treatment: **3% NaCl** infusion



33

# Treatment plan

- Weight of the patient: 84 kg. Body water: 42 l
  - To elevate seNa by 1mmol/l, she needs 42 mmol Na
  - To elevate seNa by 5 mmol/l, she needs 210 mmol Na
  - It means 408 ml of 3% NaCl infusion
- Follow urinary Na loss and replace it
- Check electrolytes frequently


34

# Treatment on the 12th day

- She got **300 ml 3%** NaCl infusion (154 mmol) + 4 g KCl
- 4 hours later serum **Na 119** mmol/l, K 3,2 mmol/l
- During Sunday night **300 ml 3%** NaCl (154 mmol) + 4 g KCl
- On Monday morning **300 ml 3%** NaCl infusion (154 mmol) (still unconscious)
- By the afternoon: serum **Na 130 mmol/l**, K 3,9 mmol/l

- In summary she got 462 mmol Na in the 1st 24 hrs
- Urinary losses in 24 hrs: 230 mmol Na and 62 mmol K


35

# Full recovery

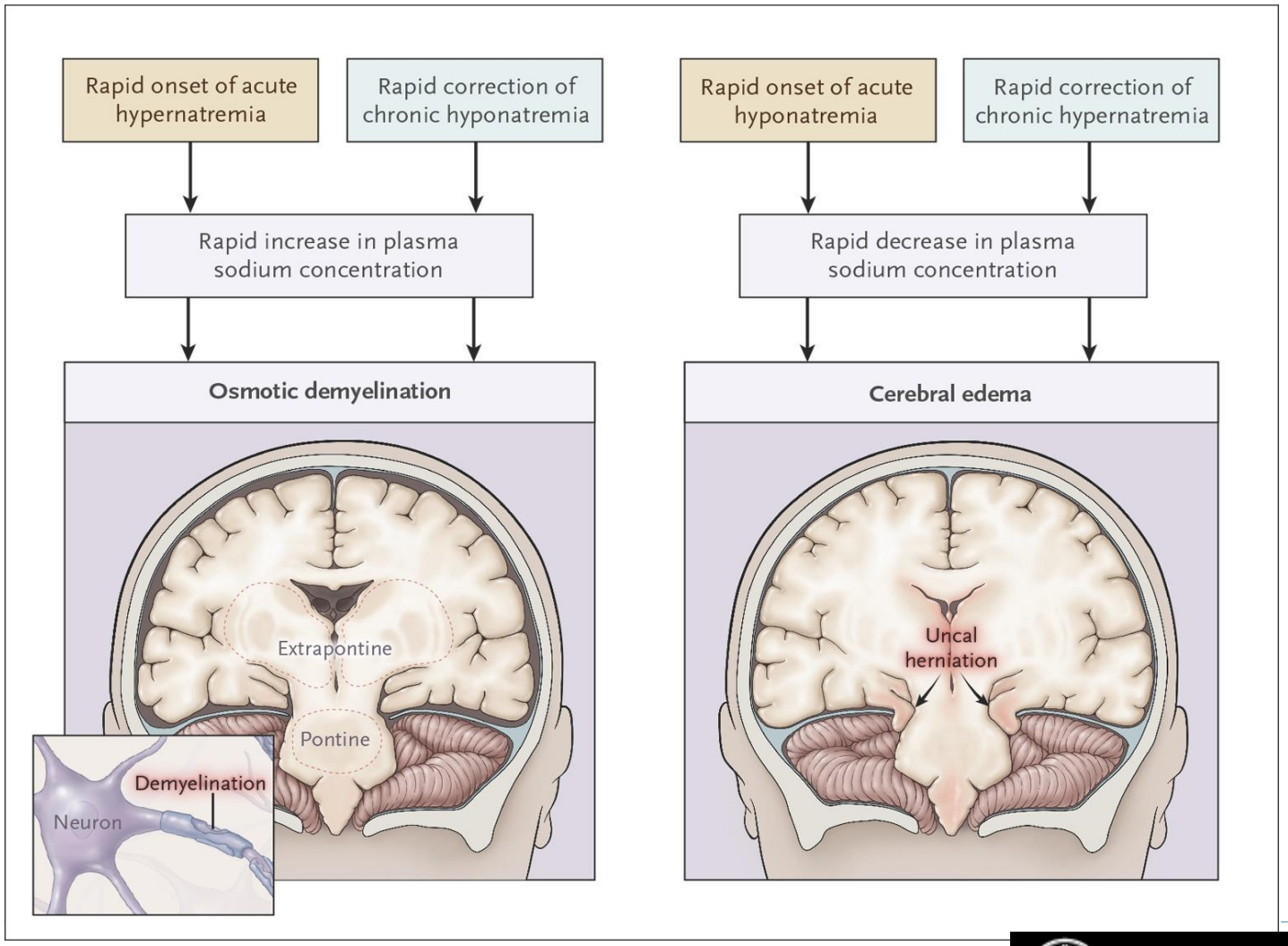
- Monday
  Neurological examination:
  - no primary neurological abnormality,
  - EEG: diffuse functional cortical abnormality

- Next day: serum **Na 134** mmol/l,
  she regained consciousness

- Two days later: serum **Na 140** mmol/l

# Treatment

# Consequences of Rapid Changes in the Plasma Sodium Concentration




Sterns RH. N Engl J Med 2015;372:55-65

# Acute, or chronic hypoNa with severe symptoms

- Administer 150 ml 3% NaCl bolus infusion over 20 minutes (Na conc. 513 mmol/l)
- Check serum Na concentration
- Meanwhile repeate the 150 ml 3% NaCl bolus infusion once or twice
- Aim to increase serum Na concentration by 5 mmol/l
- Limite correction in 10 mmol/l in the first 24 hr, and in 8 mmol/l in the next 24 hr
- Check serum Na concentration in 4-6 hrs until severe symptoms have stopped and serum Na stabilised

# Role of potassium

- Loss of potassium → intracellular depletion
  → sodium is transferred from EC to IC space
- Therefore → **in hyponatremic patients potassium** administration **increases serum Na level -** 1 mmol of retained potassium elevates serum Na by 1 mmol

# Watch for urinary Na+K concentration

- Excretion of **hypotonic urine** will increase serum Na concentration: **lots of free water is excreted**
- Urinary Na+Urinary K/serum Na
  **-** if low, eg < **0,5** – lots of free water is excreted → **serum sodium will increase**
- If the electrolyte concentration of urine is higher than serum Na, serum Na ↓ is expected
- **Large increase of urine output** → predicts **water diuresis**

# Effect of furosemide

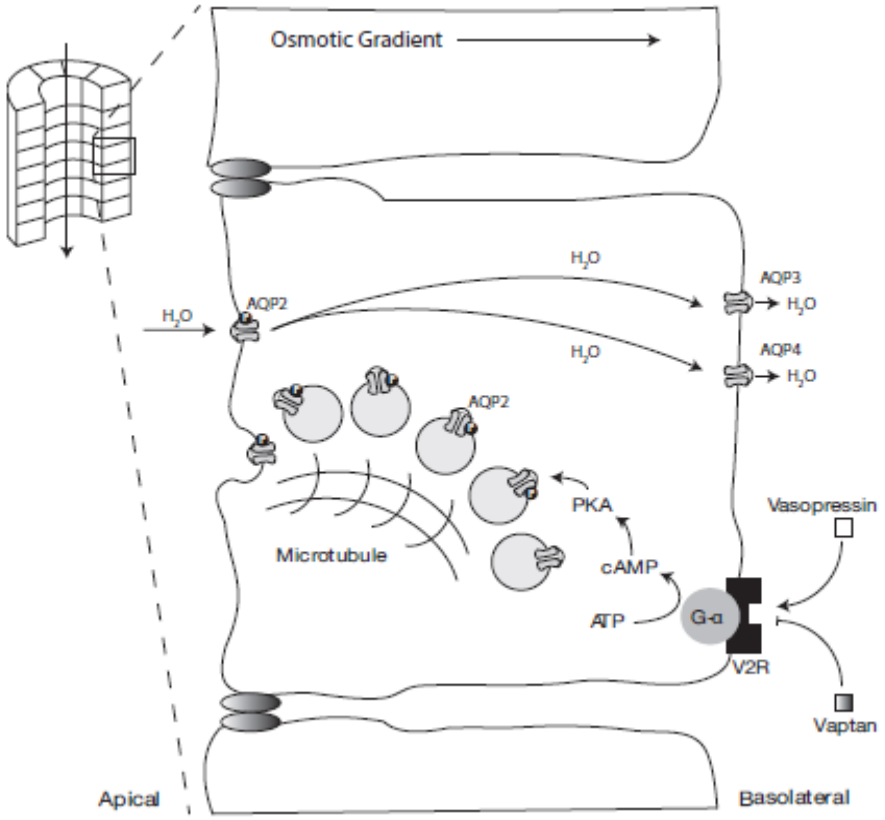
- Increases the volume of the urine
- Dilute urine is excreted
- Reduces the risk of the EC volume expansion
- Increase the speed of serum Na elevation

# Chronic hypoNa with moderate or mild symptoms

- **Fluid restriction**: <500-800 ml/day
- For patients with no edema: **increase solute intake** (protein, sodium and potassium)
- **Urea** – may be considered (good effect with 30 g/day in patients with NSIAD)
- In hyperhydrated patients: fluid + salt restriction! + **furosemide**
- Check the **medications** the patient was taking!

# Vaptans

- $V_2$ receptor antagonists
- Block the effect of ADH on collecting duct
- **May be** considered in heart failure, SIADH
- Contraindicated in acute hypoNa, volume depletion
- Potential liver toxicity
- Very expensive




*Ruediger W. Lehrich, MD, David I. Ortiz-Melo, MD, Mehul B. Patel, MD, and Arthur Greenberg, MD*

Am J Kidney Dis. 2013;62(2):364-376

# In case of overcorrection

- **D5W infusion** (adjust dose to urine output)
- **Desmopressin** (iv 1-5 ug in 6-8 hours)

  - consider if too rapid serum Na increase in hypovolemic hypoNa due to Saline infusion

# Osmotic demyelination

- In the pons CPM
- May extend to extrapontin structures
- Pseudobulbar palsy, hyperreflexia, quadriparesis, cerebellar ataxia, dysarthria, dysphagia, movement disorders or locked-in syndrome, even death
- Biphasic presentation – it develops 1-7 days after overcorrection
- MRI proves, but only approx 2 weeks later
- Higher risk in patients with very severe chronic hypoNa, in alhoholic patiens, in malnutrition, potassium depletion
- High disability, short and long term mortality rate

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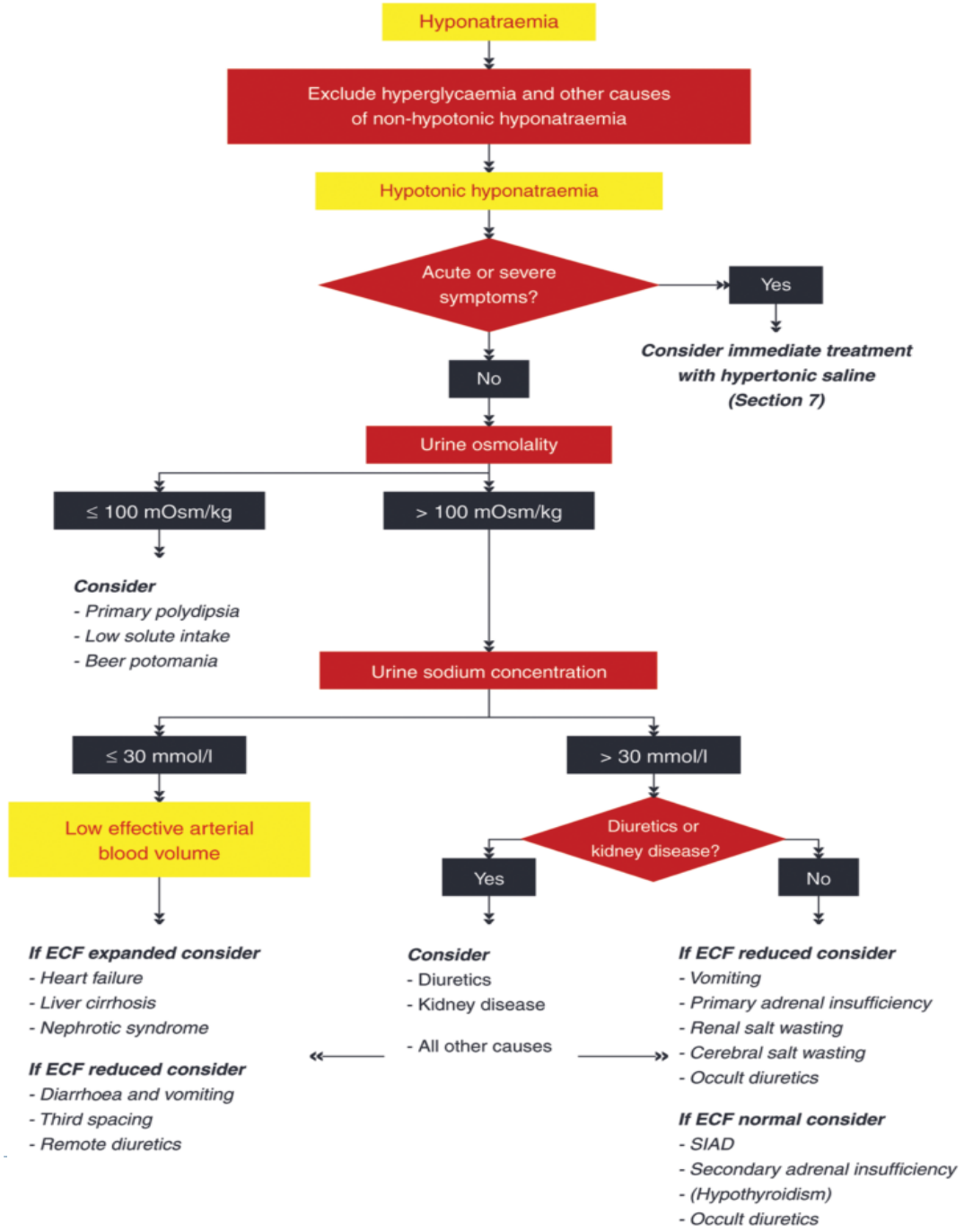

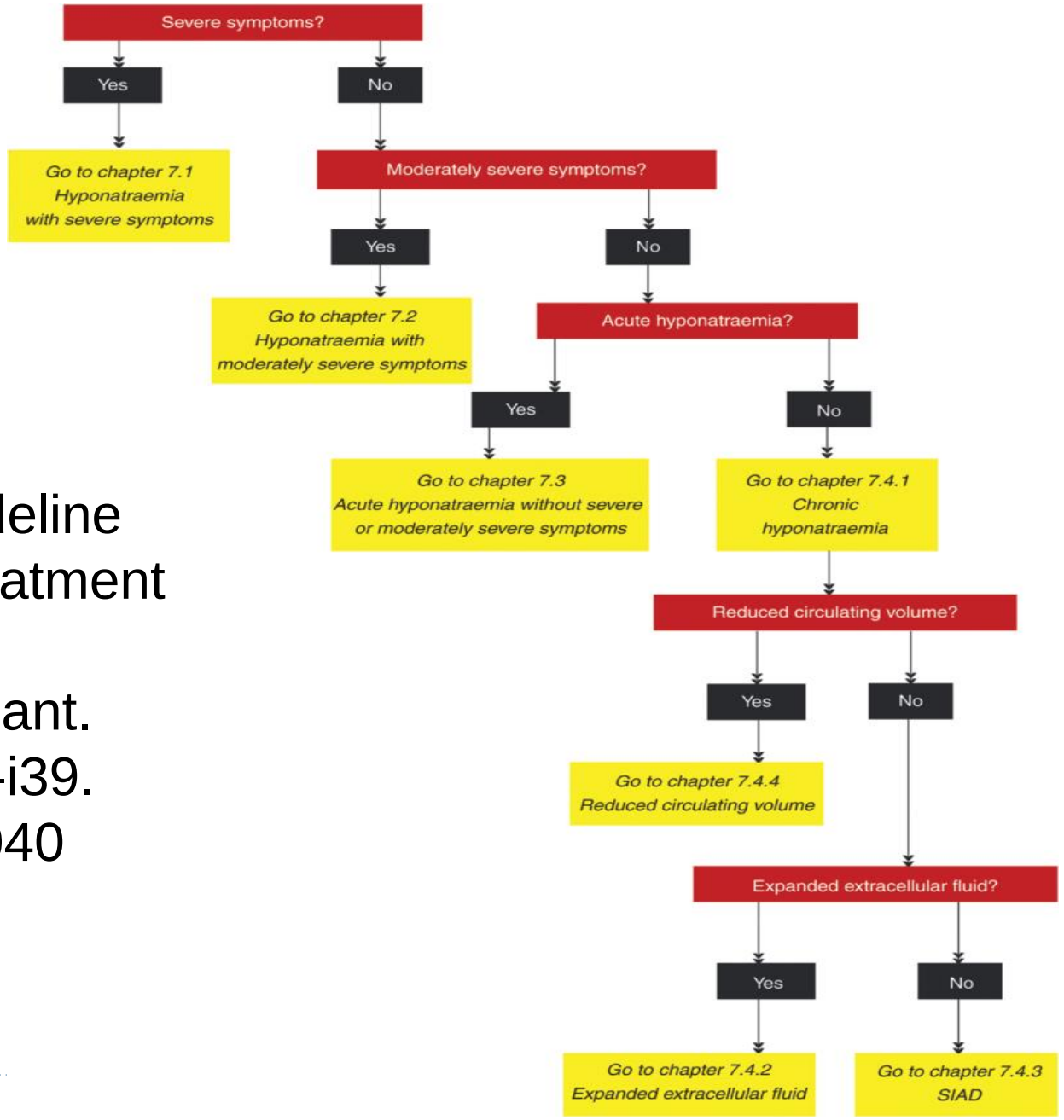


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# Thank you for your attention!