Hyponatremia

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RENAL PHYSICIANS

- Most common electrolyte abnormality in hospitalized patients
- Increased likelihood of hospital death
- Inpatient mortality rates reported 10 - 30% Na < 120
- Most patients dying in the hospital with hyponatremia succumb to their underlying disease

Sterns, RH Treatment of Severe Hyponatremia, CJASN 2018

Critical for osmotic forces

Na major determinant of plasma osmolality

$$2[\text{serum Na}] + \frac{[\text{Glucose}]}{18} + \frac{[\text{BUN}]}{2.8}$$

Osmolar gap
Measured > calcuated by 10
Ethanol, methanol, isopropranol, ethylene glycol, mannitol and glycine

It’s a water problem

- Normal serum sodium 136-144 mEq/L
- Hyponatremia: serum sodium <135 mEq/L
  - Represents inappropriately low ratio of Na:H2O
    - Na loss
    - Water gain

•Intracellular [potassium] 140 mEq/L.
•Extracellular [potassium] 5 mEq/L.
•Intracellular [sodium] 12 mEq/L.
•Extracellular [sodium] 140 mEq/L.

Severe Hyponatremia

< 120 mEq/L

Occurred < 24 hrs is acute; rapid correction tolerated

Occurred > 48 hrs is chronic; risk of osmotic demyelination

Hyponatremia with Hyperglycemia

- 1.6:100 ratio applied when the serum glucose concentration < 400 mg/dL
-
- 4:100 ratio applied when the serum glucose concentration > 400 mg/dL

- Can use approximate ratio of 2:100

  Na 129 with BS 396

  396 – 100 = 296 (call it 300);

  3x 2 = 6

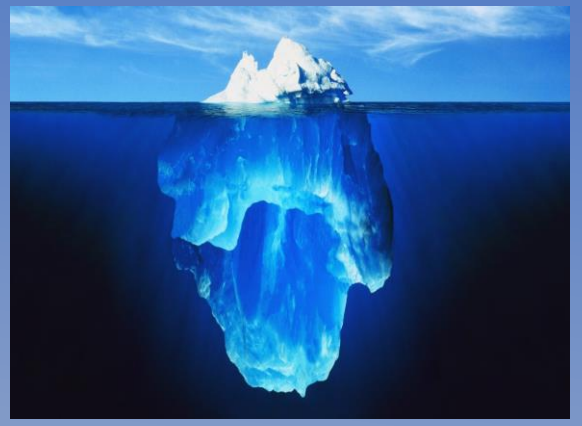
  129 + 6 = 135

Why address hyponatremia

- Increased mortality
- Neurocognitive deficits
- Gait disturbance
- Falls
- Bone fractures
- Osteoporosis

Patients die **with** rather than **from** hyponatremia

- Hyponatremia is often the tip of the iceberg



- Marker for severe heart and liver disease
- Often associated with chronic illness
- Acute kidney injury, brain tumors and other malignancies, and intracerebral hemorrhage

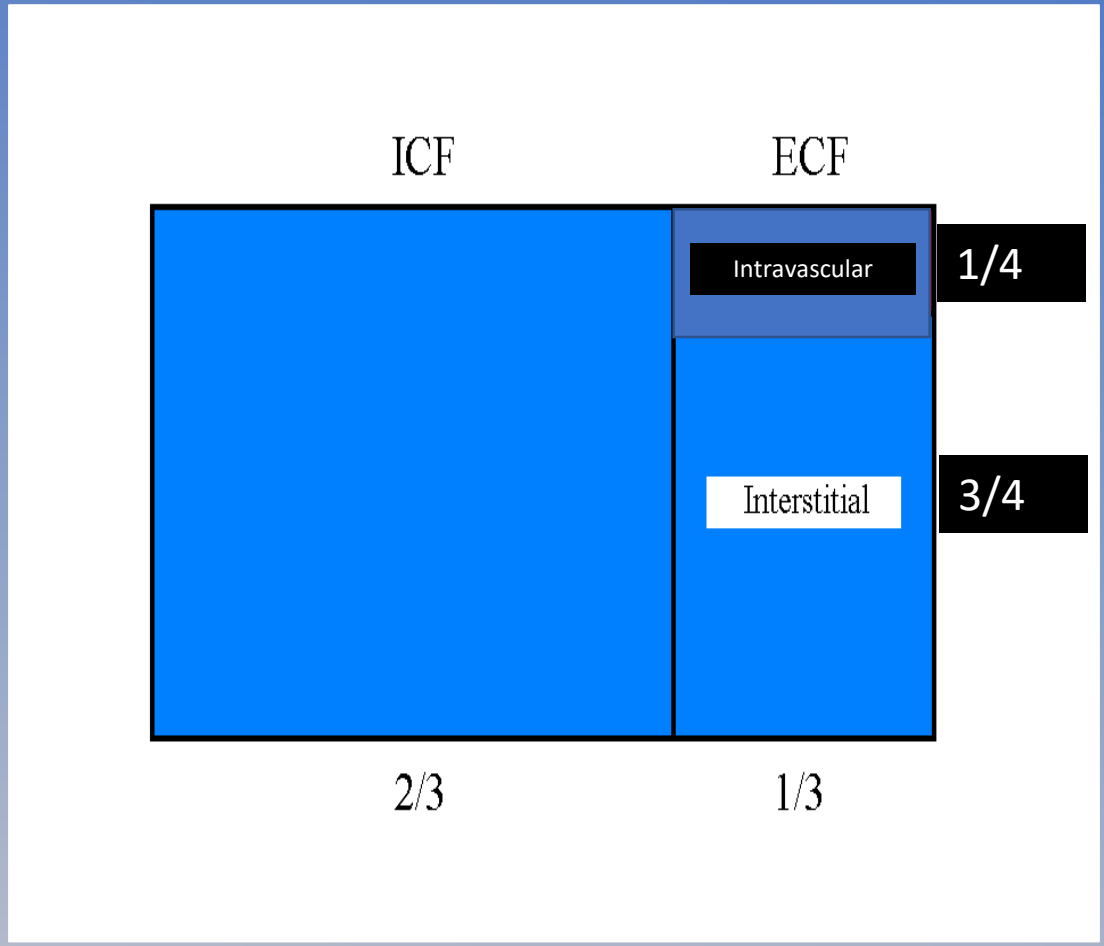
Water

- Total body water
  - 50-60% body weight
  - 2/3 intracellular
  - 1/3 extracelluar
    - ¼ Intravascular
    - ¾ Interstitial

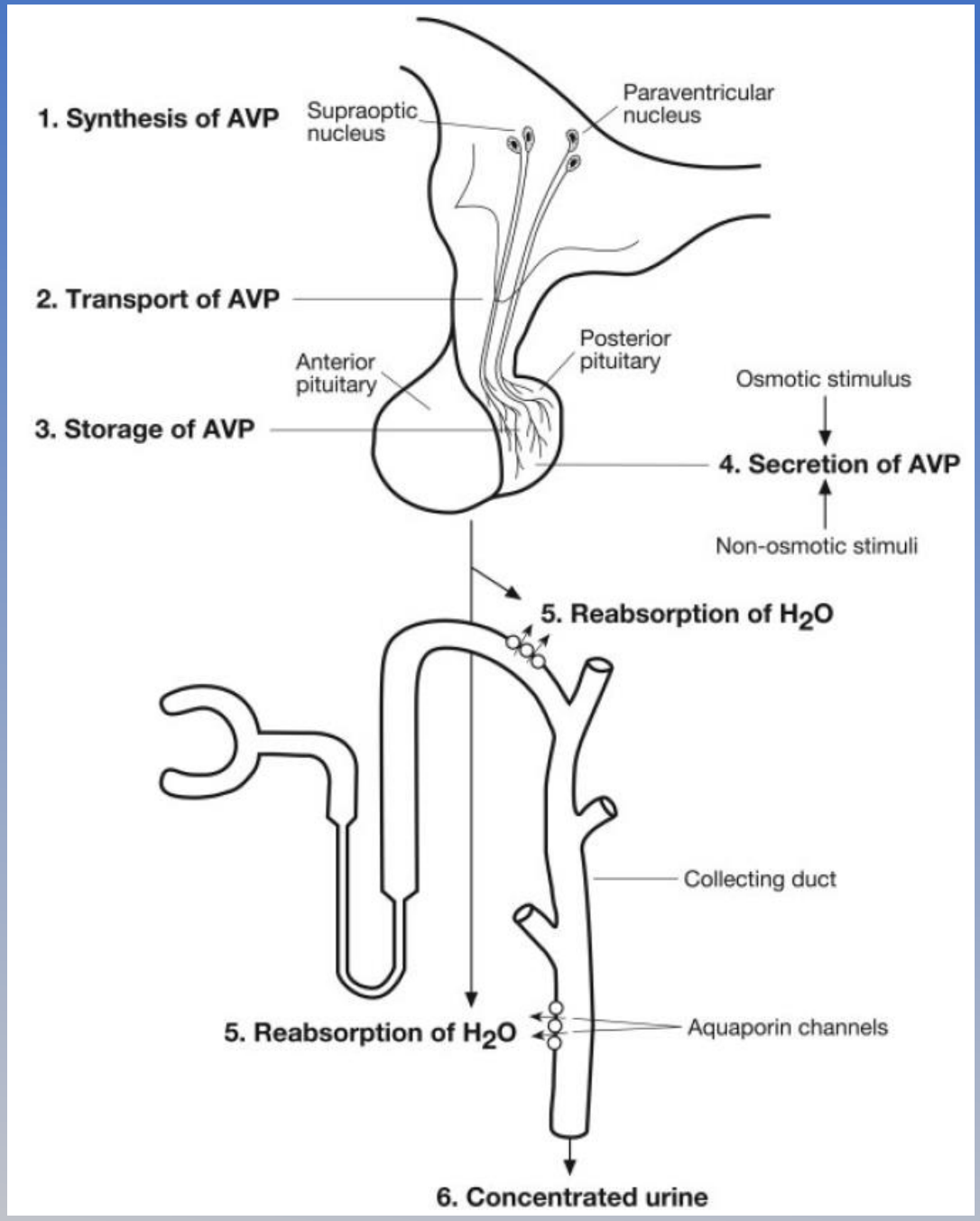
70 kg man 42 L TBW

28 L intracellular; 14 L extracelluar

3.5 L intravascular (8%)



Vasopressin
Antidiuretic Hormone
Arginine vasopressin

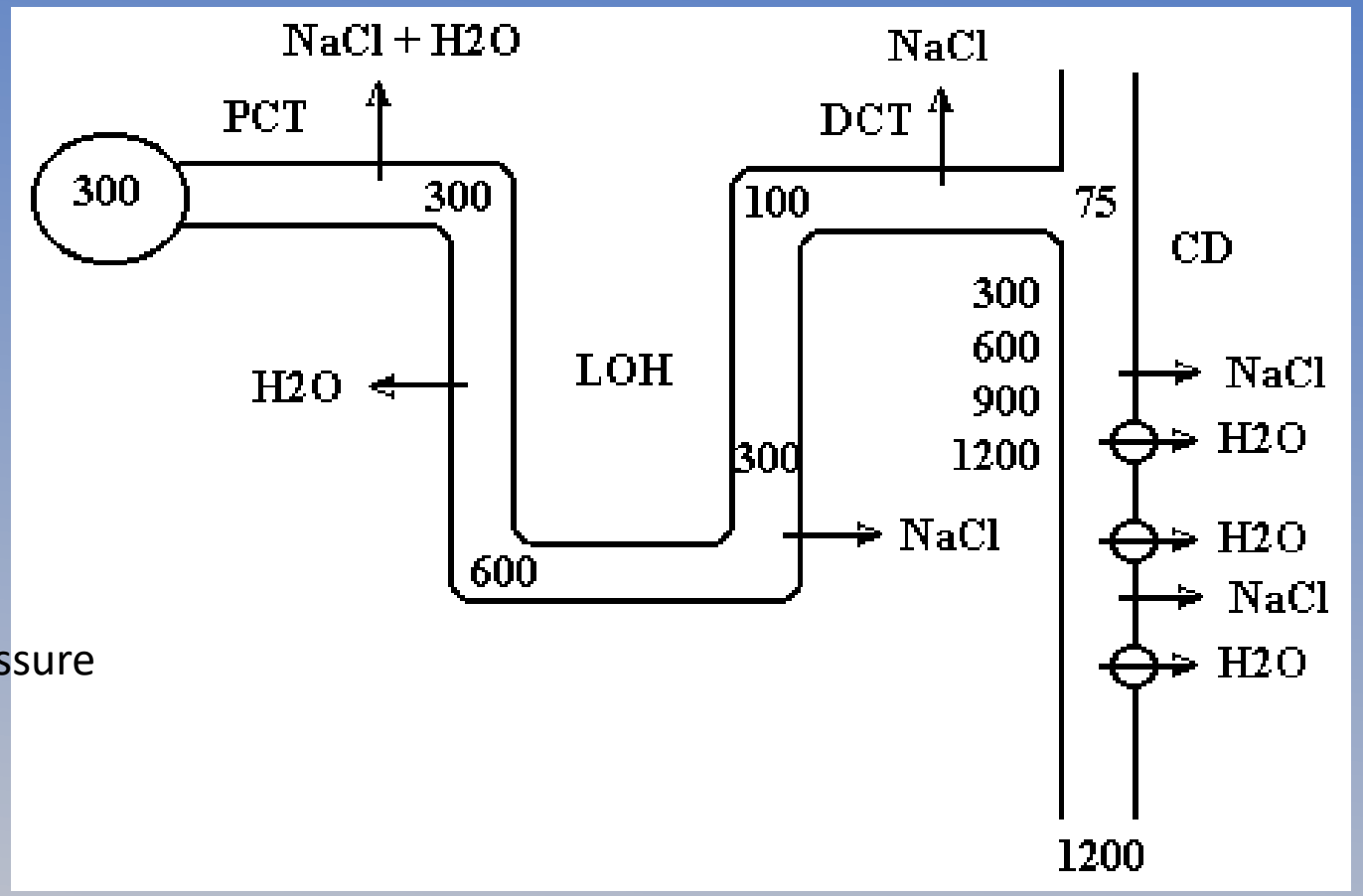


Hyperosmolarity
Decreased atrial pressure
Angiotensin II
SNS

Bhardwaj, Ann Neurol 2006

ADH present

Iso-osmolar

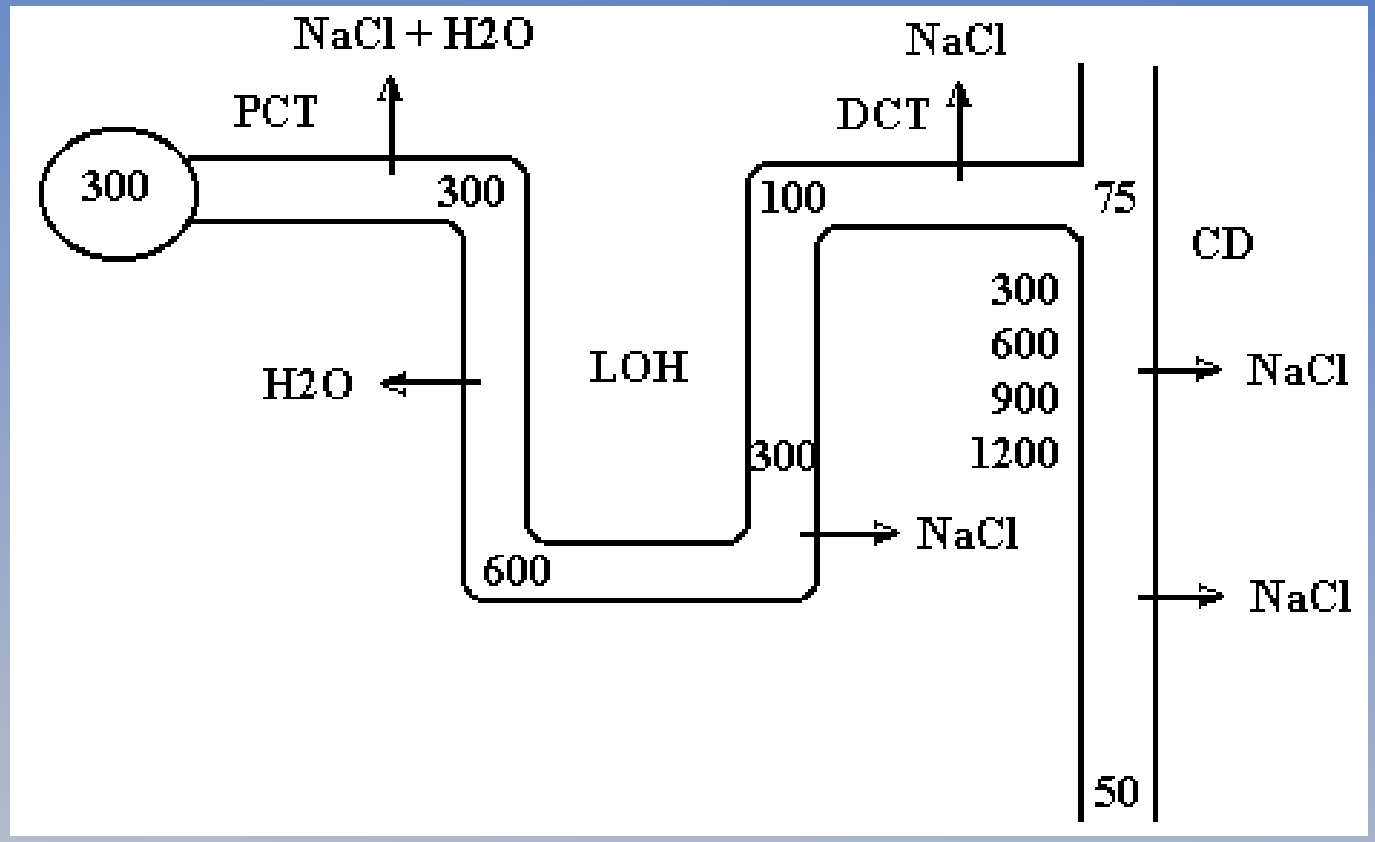


Hyperosmolarity
Decreased atrial pressure
Angiotensin II
SNS

CD
V2
AQP

ADH absent

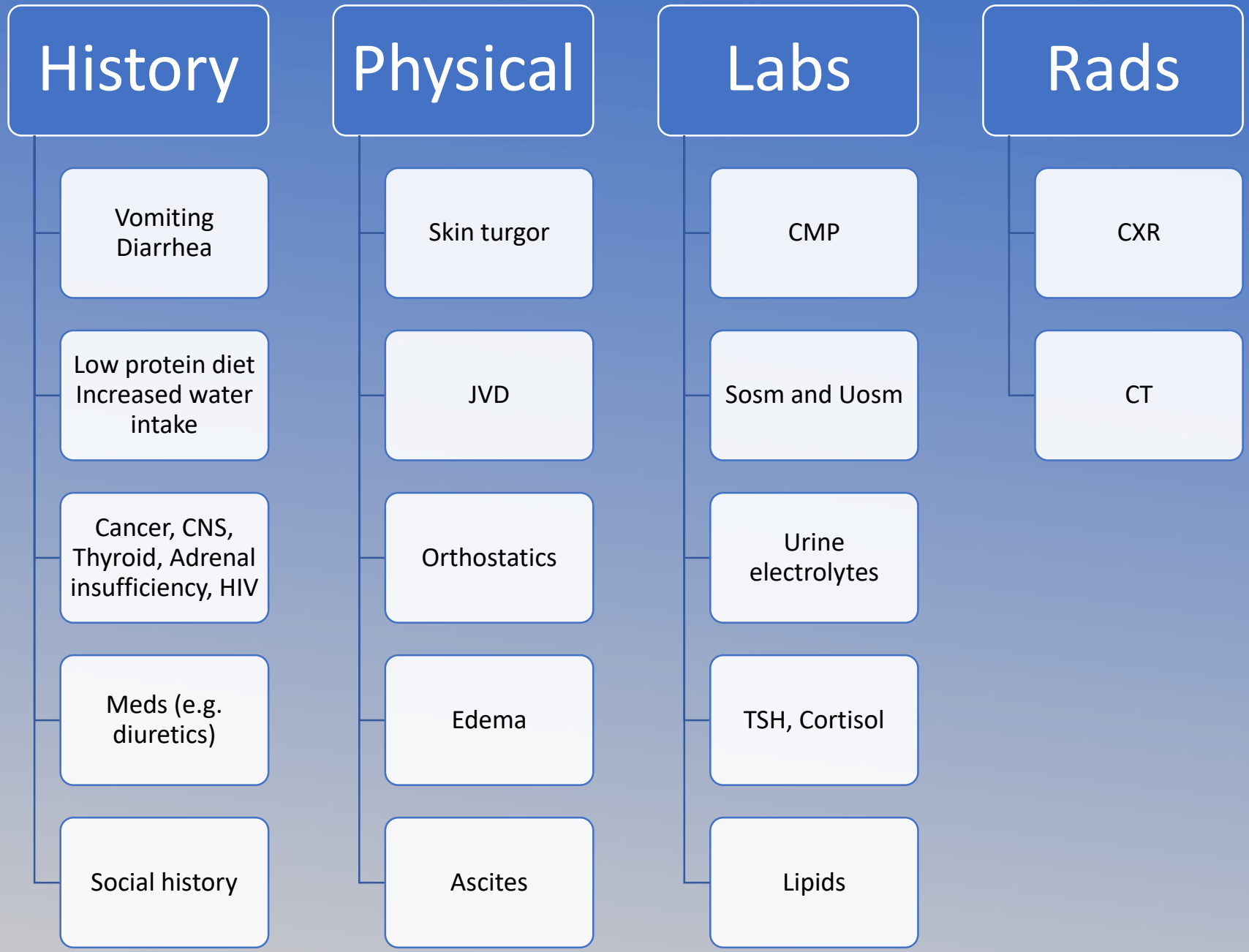
Iso-osmolar



CD
V2
AQP

Renal water excretion is…

- Impaired – ADH
  - Urine is concentrated
  - Serum sodium falls
- Overwhelmed – polydipsia
  - Urine is dilute
  - Serum sodium falls


History
Vomiting
Diarrhea
Low protein diet
Increased water intake
Cancer, CNS, Thyroid, Adrenal insufficiency, HIV
Meds (e.g. diuretics)
Social history
Physical
Skin turgor
JVD
Orthostatics
Edema
Ascites
Labs
CMP
Sosm and Uosm
Urine electrolytes
TSH, Cortisol
Lipids
Rads
CXR
CT

TB Na ↓↓
TB H_2O ↓

TB Na ↔
TB H_2O ↑

TB Na ↑
TB H_2O ↑↑

Hypotonic Hyponatremia

Hypovolemic	Euvolemic	Hypervolemic
Hypotonic Hypovolemic Hyponatremia	Hypotonic Euvolemic Hyponatremia	Hypotonic Hypervolemic Hyponatremia
UNa > 20 Renal losses: -Diuretics -salt wasting	UNa < 10 Extra-Renal losses -GI losses -3rd spacing -insensible	UOsm > 100 SIADH
		UOsm < 100 Polydipsia
		UOsm > ? Reset osmostat
UNa < 10 CHF Low C.O. Cirrhosis		
UNa > 20 Renal failure		

Urine electrolytes

- Indirect measure of volume status
- Reflects state of kidneys

- When effective circulatory volume reduced
  - SNS, RAAS = sodium retention

- Random urine sodium < 15 mEq/L (Fe_{Na} < 1%)
  - Suggest volume down status
- When does urine sodium no longer accurately reflect volume status?
  - Severe CHF, advanced cirrhosis, extensive burns
  - Diuretic use

SIADH causes

Tumors

- Pulmonary/mediastinal (bronchogenic carcinoma, mesothelioma, thymoma)
- Non-chest (duodenal carcinoma, pancreatic carcinoma, ureteral/prostate carcinoma, uterine carcinoma, nasopharyngeal carcinoma, leukemia)

Central Nervous System Disorders

- Mass lesions (tumors, brain abscesses, subdural hematoma)
- Inflammatory diseases (encephalitis, meningitis, systemic lupus, acute intermittent porphyria, multiple sclerosis)
- Degenerative/demyelinative diseases (Guillain-Barré, spinal cord lesions)
- Miscellaneous (subarachnoid hemorrhage, head trauma, acute psychosis, delirium tremens, pituitary stalk section)

SIADH Causes

Drugs

- Stimulated AVP release
  - nicotine, phenothiazines, tricyclic antidepressants
- Direct renal effects or potentiation of AVP antidiuretic effects
  - desmopressin, oxytocin, prostaglandin synthesis inhibitors
- Mixed or uncertain actions
  - ACE inhibitors, carbamazepine and oxcarbazepine, chlorpropamide, clofibrate, clozapine, cyclophosphamide, 3,4-methylenedioxymethamphetamine [“Ecstasy”], omeprazole, serotonin reuptake inhibitors, vincristine)

SIADH Causes

Pulmonary Diseases

- Infections
  - tuberculosis, acute bacterial or viral pneumonia, aspergillosis, empyema
- Mechanical/ventilatory
  - acute respiratory failure, COPD, positive-pressure ventilation

Other

- AIDS and AIDS-related complex
- Prolonged strenuous exercise (marathon, triathlon, hot-weather hiking)
- Postoperative state
- Senile cerebral atrophy
- Idiopathic

Drugs associated with SIADH

ADH analogues	Antineoplastics	Cardiovascular agents	Psychotropics	– paroxetine – sertraline Tranylcypromine Trazodone Tricyclic antidepressants – amitriptyline – amoxapine – clomipramine – desipramine – dothiepin – doxepin – imipramine – nortriptyline Venlafaxine Viloxazine
Desmopressin (DDAVP) Oxytocin Vasopressin	Alemtuzumab Aminoglutethimide Chlorambucil Carboplatin Cisplatin Cyclophosphamide Docetaxel Etoposide Ifosfamide Levamisole Melphalan Rituximab Thiotepa Vidarabine Vinblastine Vincristine Vinorelbine	Amiodarone Cilazapril Clofibrate Clonidine Enalapril Hydrochlorothiazide (and other thiazide diuretics) Lisinopril Lorcainide Methyldopa Phenoxybenzamine Propafenone Ramipril	Antipsychotics – amisulpride – aripiprazole – chlorpromazine – clozapine – fluphenazine – haloperidol – pimozide – risperidone – thioridazine – trifluoperazine – thiothixene Bupropion Reboxetine Duloxetine Lorazepam Mirtazapine Phenelzine SSRIs – citalopram – escitalopram – fluoxetine – fluvoxamine	
Analgesics				
Diclofenac Fentanyl Ibuprofen				
Anticonvulsants				
Carbamazepine Levetiracetam Oxcarbazepine Valproic acid				
Anti-infectives		**Hypoglycemic agents**		**Other**
Azithromycin Dalfopristin/quinupristin Lopinavir Miconazole Rifabutin		Chlorpropamide Glimepiride Tolbutamide		Interferon-alpha Metrizamide MDMA (ecstasy) Nicotine Omeprazole Tacrolimus Theophylline
	Antiparkinson agents			
	Amantadine Levodopa Pramipexole Trihexyphenidyl			

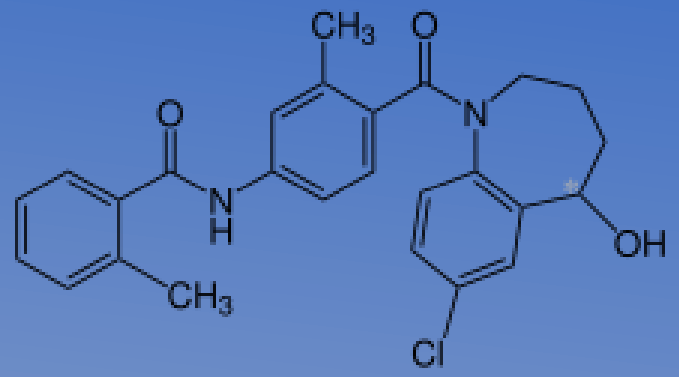
SIADH

- Decreased effective osmolality of the ECF ($\mathbf{P_{osm}}$ **< 275** mOsm)
- Inappropriate urinary concentration ($\mathbf{U_{osm}}$ **> 100** mOsm with normal kidney function)
- Clinical euvolemia, as defined by the absence of signs of hypovolemia (orthostasis, tachycardia, decreased skin turgor, dry mucous membranes) or hypervolemia (subcutaneous edema, ascites)
- Elevated urinary sodium excretion despite a normal salt and water intake
- Normal thyroid, adrenal, and kidney function

SIADH Treatment

- Treat the underlying disease
  - Treatment of infections, Stop offending drugs
  - Treatment of adrenal insufficiency or hypothyroidism
- Fluid restriction
- IV Fluids with caution as NS can worsen SIADH
- 3% Saline
- Loop diuretic with Salt tabs
- V2 receptor antagonists
- Demeclocycline
- Urea

Tolvaptan



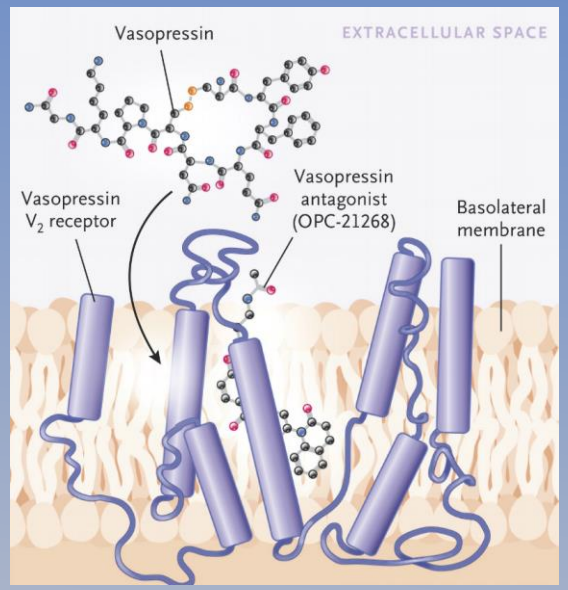
- Samsca – selective V2

  Euvolemic and hypervolemic indication

  Very expensive

  Some cost savings recovered with shorter admission time

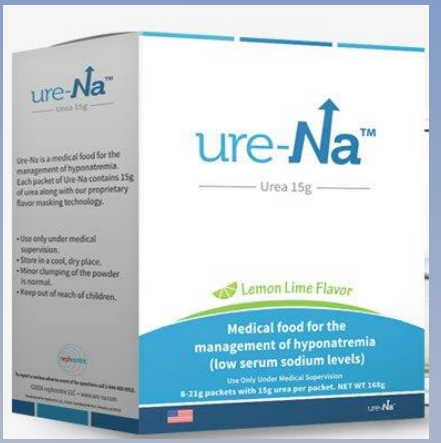
- Jynarque - PKD



Urea

- Osmotic agent that increases urinary free water excretion
- No risk of volume expansion like NaCl tabs
- Cheap
- Modest rise in BUN
- Relatively contraindicated in liver failure - can raise ammonia

Urea for the Treatment of Hyponatremia, Rondon-Berrios et al. JASN 2018



Desalination

- Hyponatremia may worsen serum Osm < urine Osm with .9% saline
  - Example:

    30 M HIV+ with PCP pneumonia and SIADH

    Serum Na 122; urine Osm 600 mOsm/kg

    0.9% saline given but repeat sodium is 118 mEq/L

1 L .9% saline

Na154 + Cl 154 mEq (~300 mOsm) excreted in urine

Urine osm fixed at 600 mOsm/kg

300 mOsm excreted in 0.5 L of free water

Net effect: 0.5 L of free water retained - > pts Na drops

Thiazide-associated hyponatremia

- Who gets it…
  - Elderly females
    - small body mass
    - baseline reduced ability to excrete free water
  - High water intake
  - Onset early, often within 2 weeks

Thiazide-induced

- Mechanisms
  - Impair renal diluting ability
    - Cause negative sodium balance – stimulates ADH release
    - Inhibit NaCl transport in DCT
      - raises minimum urinary osmolarity
      - increased distal Cl delivery to macula densa decreases GFR (TGF)

Treatment – know what your giving the patient

Infusate	Infusate Na
5% saline	855 mEq/L
3% saline	513 mEq/L
.9% saline	154 mEq/L
Plasma-Lyte	140 mEq/L
Ringer's lactate	130 mEq/L
.45% saline	77 mEq/L
.225% saline	34 mEq/L

Q1

A 20-year-old woman with von Willebrand disease treated with desmopressin is seen in the emergency department for headache, nausea, and vomiting. She is found to have a sodium level of 120 mEq/L. You are asked to advise on fluid management over the next 24 hours. Which of the following is the most appropriate management?

A. Discontinue desmopressin, because this would allow spontaneous water diuresis and resolution of hyponatremia

B. Discontinue desmopressin and replace urine output with normal saline

C. Continue desmopressin and replace one half of urine output with 1/2 0.9% saline solution

D. Continue desmopressin and infuse 3% saline at 50 ml/h

Q1

- The danger is rapid correction of serum sodium in a young woman who is at the highest risk for complications, including death. The correct answer is option D, because it is the treatment strategy that allows for controlled normalization of the serum sodium level.

- Desmopressin is used for treatment of central diabetes insipidus, von Willebrand disease, and increasingly, enuresis in children and adults. The major complication of desmopressin use is hyponatremia.

Q1

Desmopressin acetate (DDAVP)-associated hyponatremia and brain damage: a case series.

- Group 1: DDAVP withheld
  - Mean change in serum sodium at 48 hrs: 37.1 ± 8.1 mEq/L
  - 23% death, 69% severe brain damage, 8% moderate brain damage
- Group 2: DDAVP continued
  - Mean change in serum sodium at 48 hrs: 11.0 ± 0 mEq/L

Achinger, SG et al. Nephrol Dial Transplant 2014

Q2

- A 54-year-old man with known heart failure due to NICM is admitted with a change in mental status in the past day. His family states that he has been complaining of excess thirst and that he was drinking more water and soft drinks during the last 2 days. His medications include furosemide at 80 mg twice daily and metolazone at 2.5 mg twice daily. Oxygen saturation 95% on RA. He is disoriented and agitated with bibasilar rales and 2+ peripheral edema. Labs show sodium 118 mEq/L, potassium 2.9 mEq/L, chloride 79 mEq/L, CO2 29 mEq/L, BUN 36 mg/dl, and creatinine 1.2 mg/dl (baseline of 1.2 mg/dl). His serum sodium had previously been stable at 132 mEq/L

Q2

Which of the following is the MOST appropriate management?

A. Treat with 3% saline at 100 ml over the next 3 hours

B. Restrict water intake only

C. Use tolvaptan at 15 mg now and increase to 30 mg if serum sodium does not increase by 6 mEq/L in the next 6 hours

D. Restrict water intake and use tolvaptan as in option C

Q2

- Arginine vasopressin receptor blockers or vaptans have been approved for treatment of chronic hyponatremia in hypervolemic and euvolemic states.
- It is important to note that vaptans should not be used in treatment of symptomatic acute hyponatremia (especially in those with neurologic symptoms). There is usually a delay of several hours before an effective vaptan-associated aquaresis occurs, which may delay rapid correction of sodium concentration in these patients.
- These patients should be treated with hypertonic saline (1). Therefore, the best answer is option A.

Q3

A surgical colleague is planning to run in a marathon for the first time. He is concerned about developing an electrolyte complication and asks you how best to prevent such an event. What would you advise him to do?

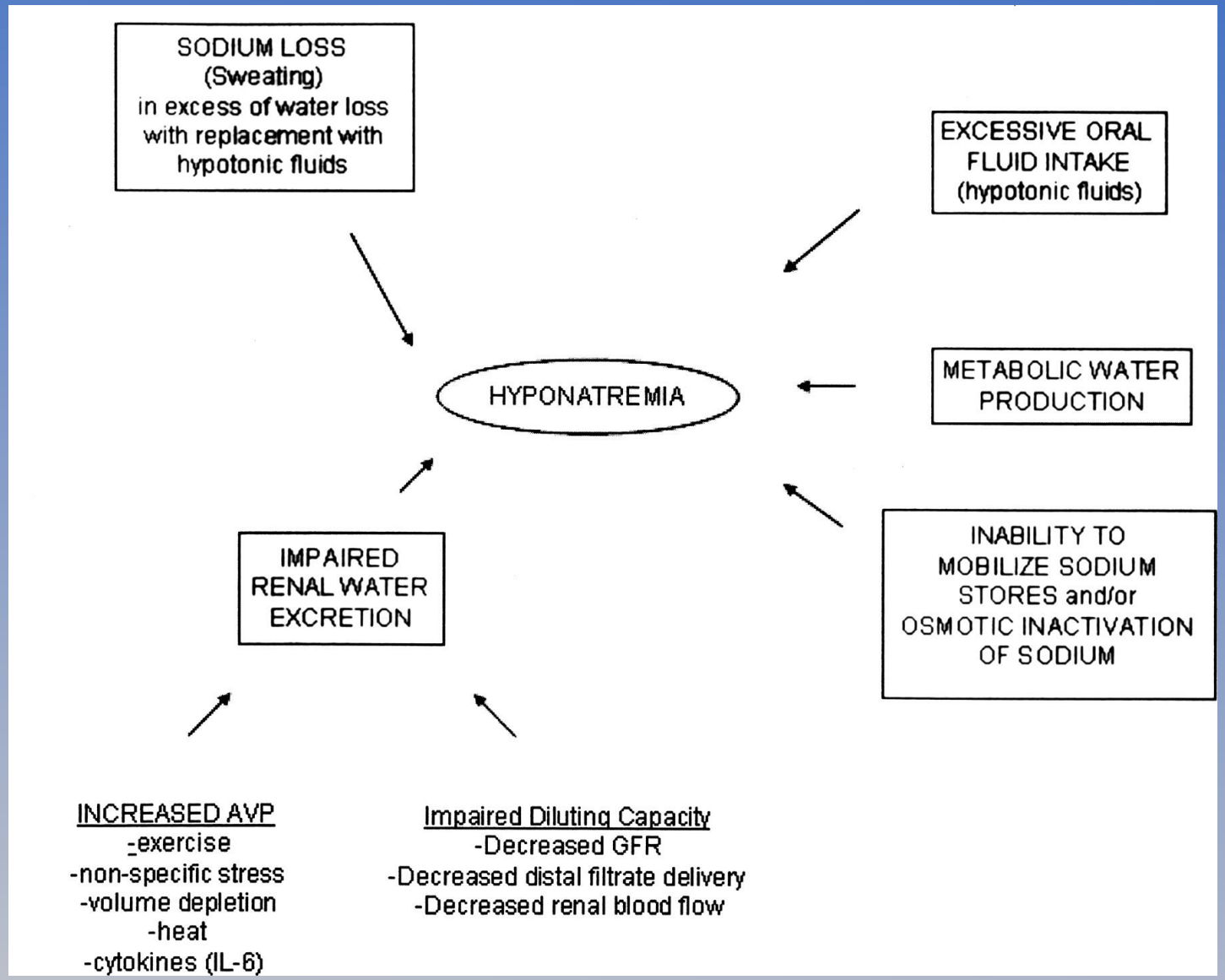
- A. Drink a regular glass of water for every mile
- B. Take salt tablet before and at least four times during the run
- C. Drink only when you feel thirsty
- D. Take a salt tablet before and during the run as well as a glass of water for every mile
- E. Consume fettuccini alfredo just prior to the race

Risk factors for EAH

- Exercise duration > 4 hrs, slow running
- Female gender
- Low body weight
- Excessive drinking (> 1.5L/hr) during event
- Pre-exercise overhydration
- Abundant availability of fluids during event
- NSAIDs
- Extreme hot or cold environment

Q3

- Although exercise-associated hyponatremia (EAH) is due to both water gain and salt loss, the major cause is excess water intake and decreased water excretion due to increased antidiuretic hormone release.
- The correct answer is, therefore, C – Drink when you feel thristy



Exercise-Associated Hyponatremia, Rosner et al. CJASN 2007

Q4

- A 74-year-old man is admitted from a skilled nursing facility because he has increased confusion. He had been on a hunger strike as part of a passive suicide plan but was still taking in water. He had a history of anxiety and a bipolar disorder. The patient stated that “Water is my favorite drink.” and “You should see how much water I can drink in a day”
- PE: elderly white man in no distress. Disoriented to time and place and intermittently refuses to answer questions

Q4

- **Na 106 mEq/L**, K 4.0 mEq/L, Cl 71 mEq/L, CO2 24 mEq/L, BUN 25 mg/dl, Cr 1.1 mg/dl and glucose 126 mg/dl.
- Urine studies: Na 10 mEq/L and osmolality 125 mOsm/kg.
- The patient received 2 L of normal saline and fluid restricted
- After 12 hrs Na increased to **126 mEq/L**. Urine osmolality 70 mOsm/kg
- D5W is ordered

Q4

- Which of the following is the best way to treat this patient at this time?
- A. Increase D5W to 110% of urinary loss per hour
- B. Use desmopressin and continue with D5W with goal of decreasing serum sodium to 112 mEq/L
- C. Use desmopressin and continue with D5W with the goal of stabilizing serum sodium at 120 mEq/L
- D. Desmopressin alone is adequate because he is now asymptomatic

Over correction options

- D5W
- Increased oral intake
- Matching urine water outpt with IV + PO - totally impractical
- DDAVP 1-2 mcg IV q 6 hrs

Sterns, RH et al. DDAVP Is Effective in Preventing and Reversing Inadvertent Overcorrection of Hyponatremia. CJASN 2008

Risk factors for rapid correction

- Increased risk for rapid correction
- Young age
- Female
- Schizophrenia
- Lower serum Na on presentation
- Urine Na < 30 mEq

Risk factors for ODS

- Serum sodium ≤105 mEq/L
- Concurrent hypokalemia
- Chronic excess alcohol intake
- Acute or chronic hepatic disease
- Malnourishment
- Chronic hyponatremia corrected > 10 mEq/L in 24 hours and/or 18 mEq/L in 48 hours

Treatment options for high risk ODS

1 - 2 mcg desmopressin, IV or SC q 6-8 hrs for 24 to 48 hours

Simultaneous infusion of 3% saline, 15 to 30 mL/hour.

A bolus of 3% saline can be given at the start of therapy to help relieve symptoms

Rate of infusion of hypertonic saline is then adjusted to achieve the desired rate of correction.

Desmopressin makes the rate of correction resulting from hypertonic saline more predictable because it prevents an unexpected water diuresis from occurring during the course of therapy.

Rafat C et al. Use of desmopressin acetate in severe hyponatremia in the intensive care unit. CJASN 2014