Hyponatremia

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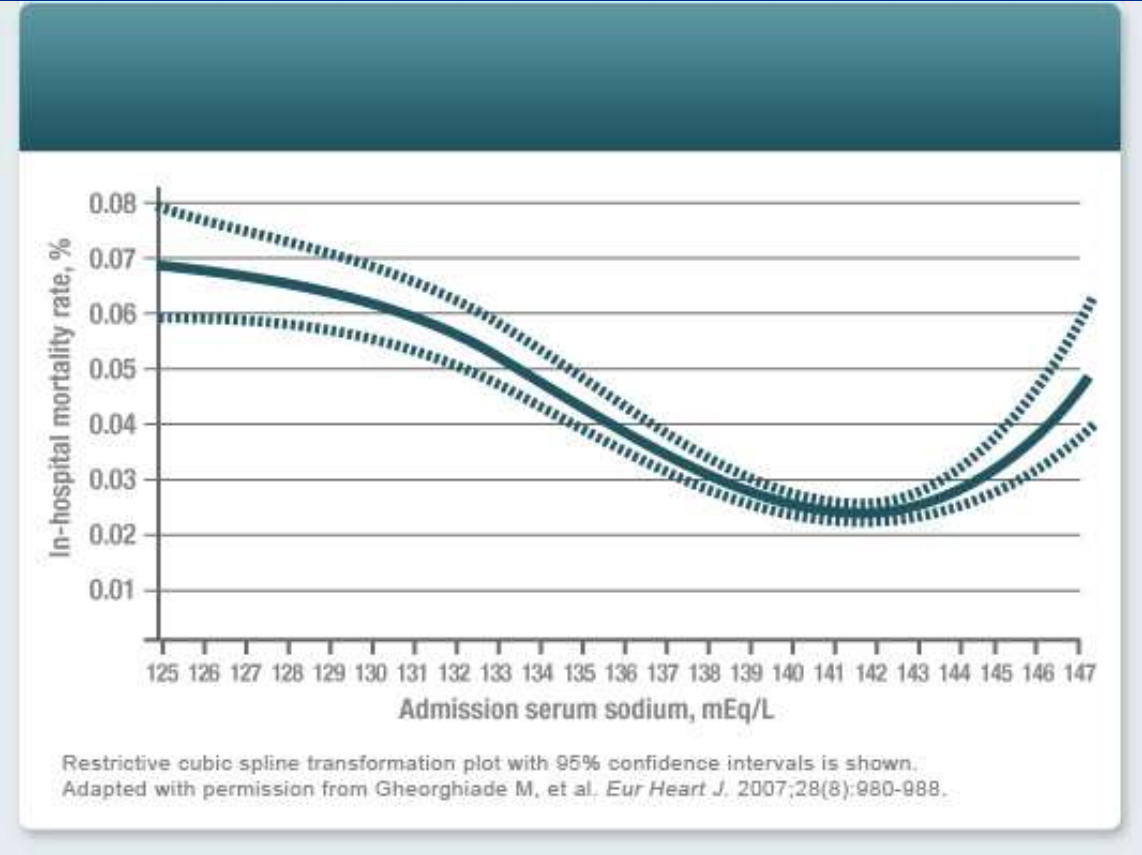
September 22nd, 2021

Studies have demonstrated that mortality was significantly increased among hospitalized patients with hyponatremia



Restrictive cubic spline transformation plot with 95% confidence intervals is shown.
Adapted with permission from Gheorghiade M, et al. *Eur Heart J.* 2007;28(8):980-988.

http://hyponatremiaupdates.com/risk-of-mortality

Hyponatremia: Important Big Picture

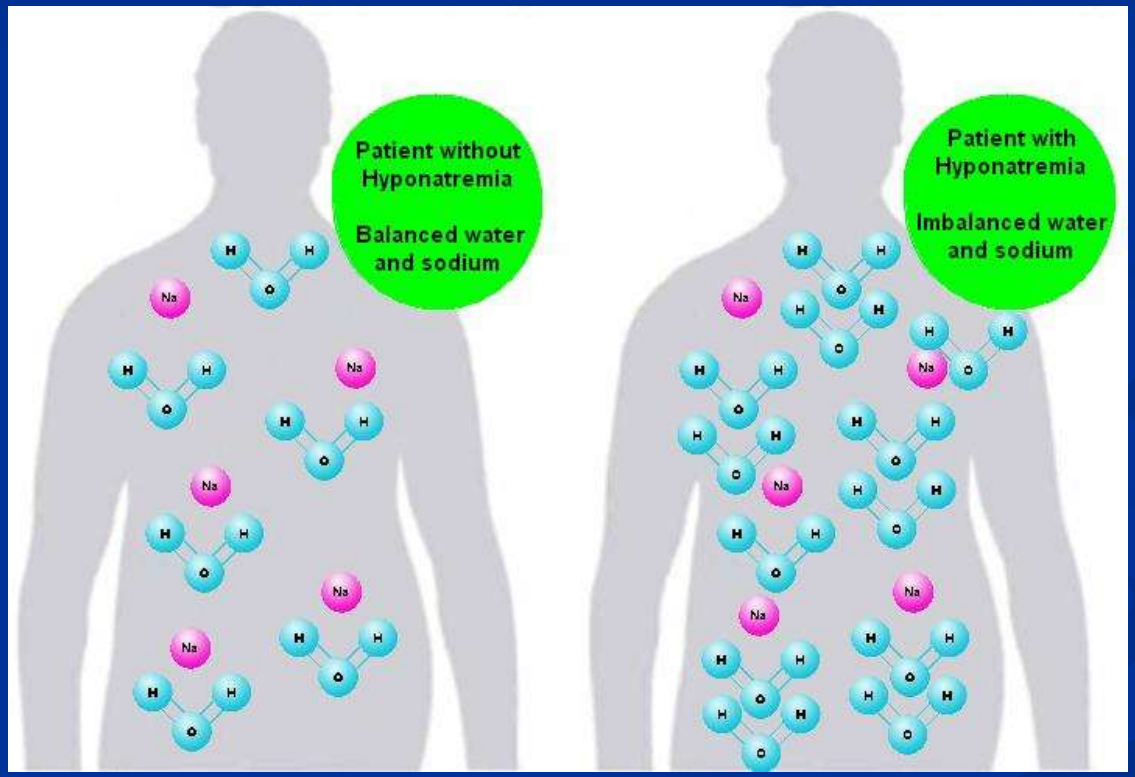
- Degree of hyponatremia does not predict outcomes in association studies
  - Lower serum Na at admission does not predict increased mortality
  - Possible U shaped mortality distribution so very low serum Na is actually not predictive of poor outcomes
  - Data was excluded from prior graph

Outline

- Sodium content versus sodium concentration
- Regulation of sodium content
- Regulation of water content
- Hyponatremia classification
- Treatment of hyponatremia
- Desalination

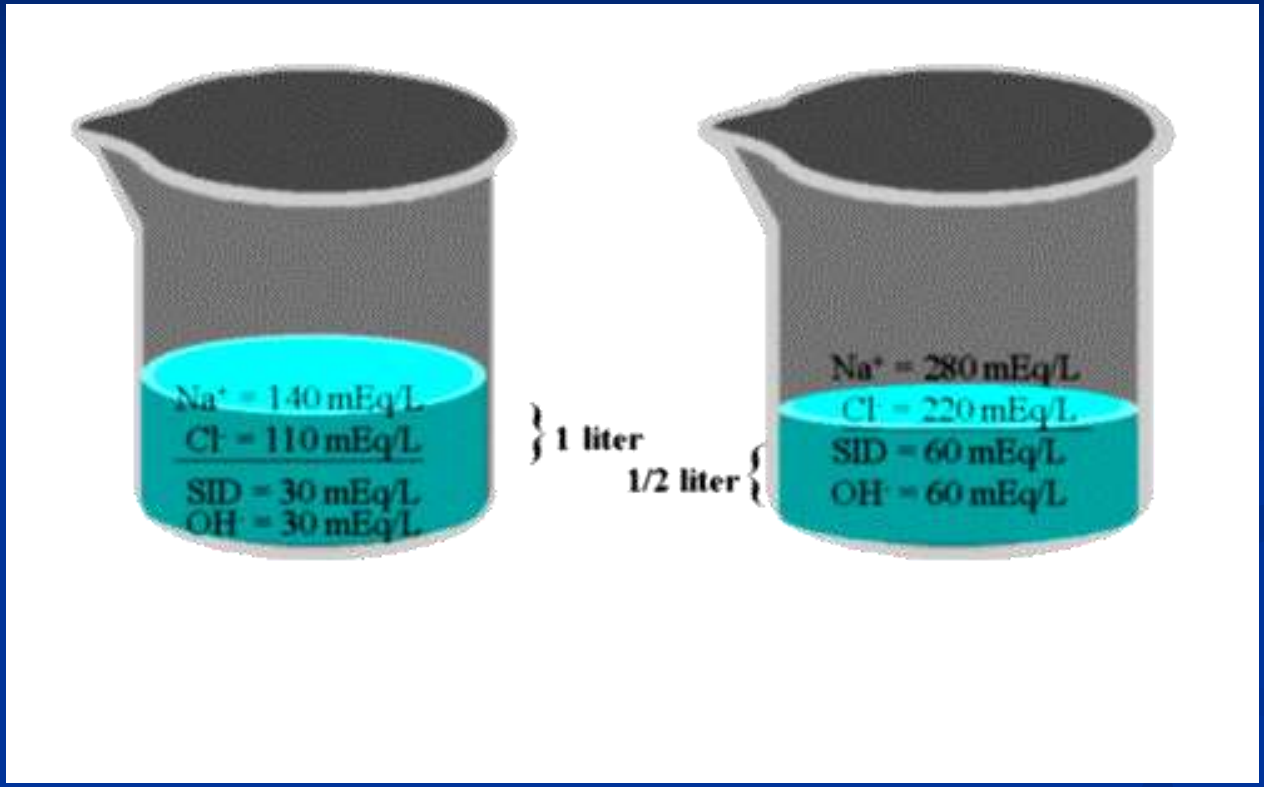
Hyponatremia background

- Hyponatremia means hyperaquaremia



http://ucrt.info/resources/CK-LX3430_Hyponatremia_cm.html

Sodium Content Versus Concentration



Total amount of Na in both beakers is 140 mEq but measured concentration is different due to difference in water content

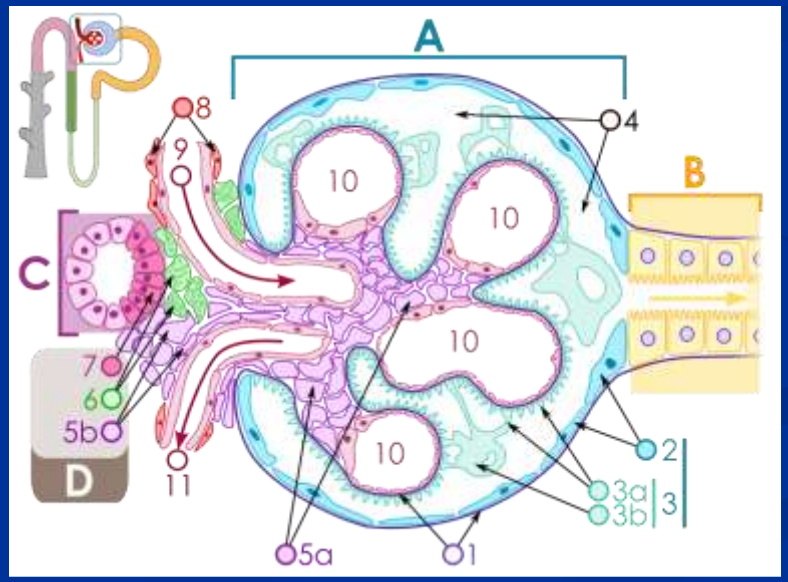
http://www.anaesthetist.com/icu/elec/ionz/Findex.htm#useful1.htm

Sodium Content aka Volume

- Total amount of Na in the body
- Determines extracellular fluid volume
- There is no way to directly measure this
- This is determined by physical exam for volume status

Regulation of Sodium Content

- Sensors
  - Baroreceptors
    - Arterial- carotid sinus and aortic arch
    - Venous- right atrium
  - Juxtaglomerular Apparatus

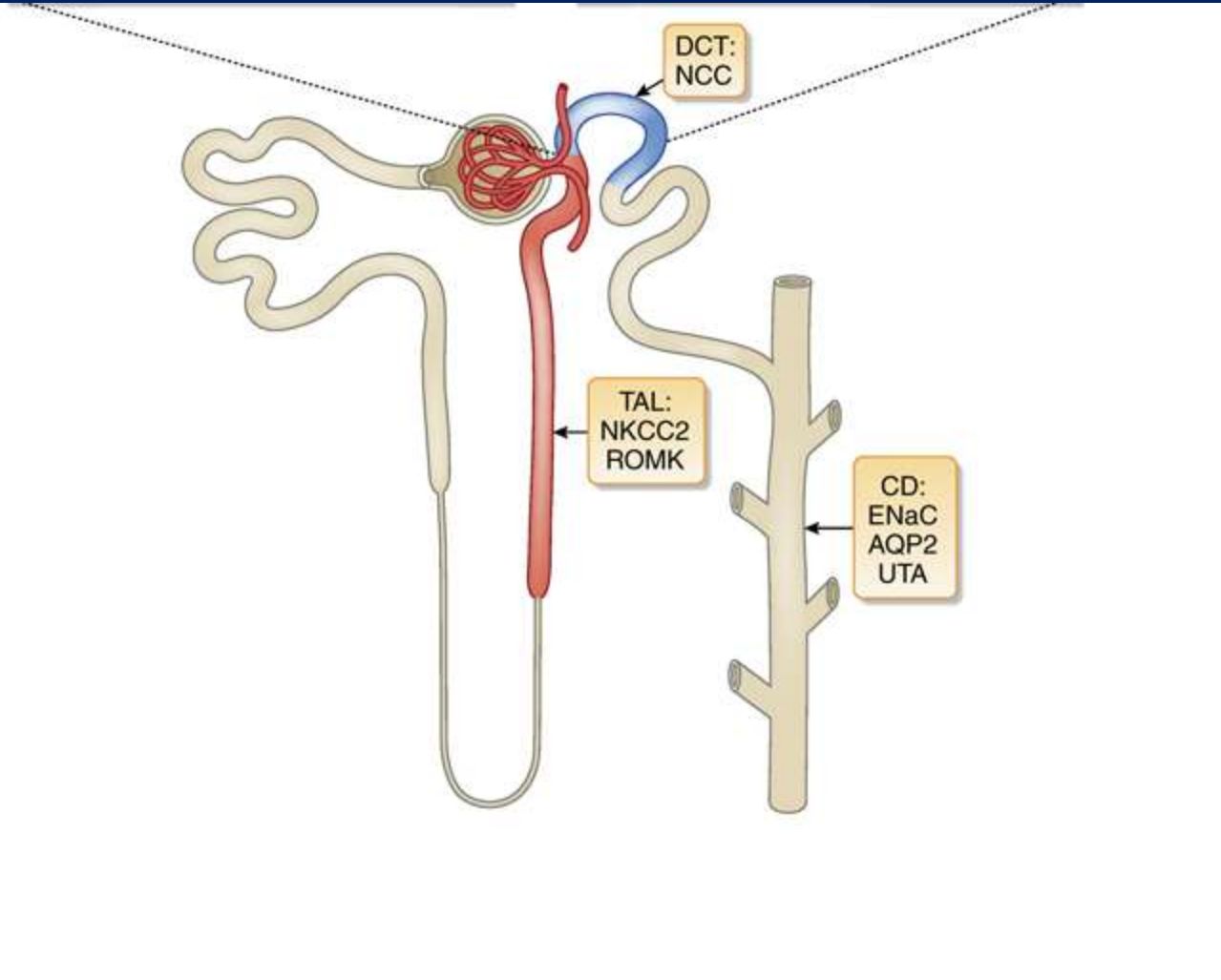


http://en.wikipedia.org/wiki/File:Renal_corpuscle.svg

Regulation of Sodium Content

- Effectors:
  - Vasoconstriction
    - Sympathetic nervous system
    - AII
  - Renal Na reabsorption
    - Proximal tubule via sympathetic nervous system and AII
    - Collection tubule via aldosterone and *decreased* ANP

A quick reminder of the renal tubule

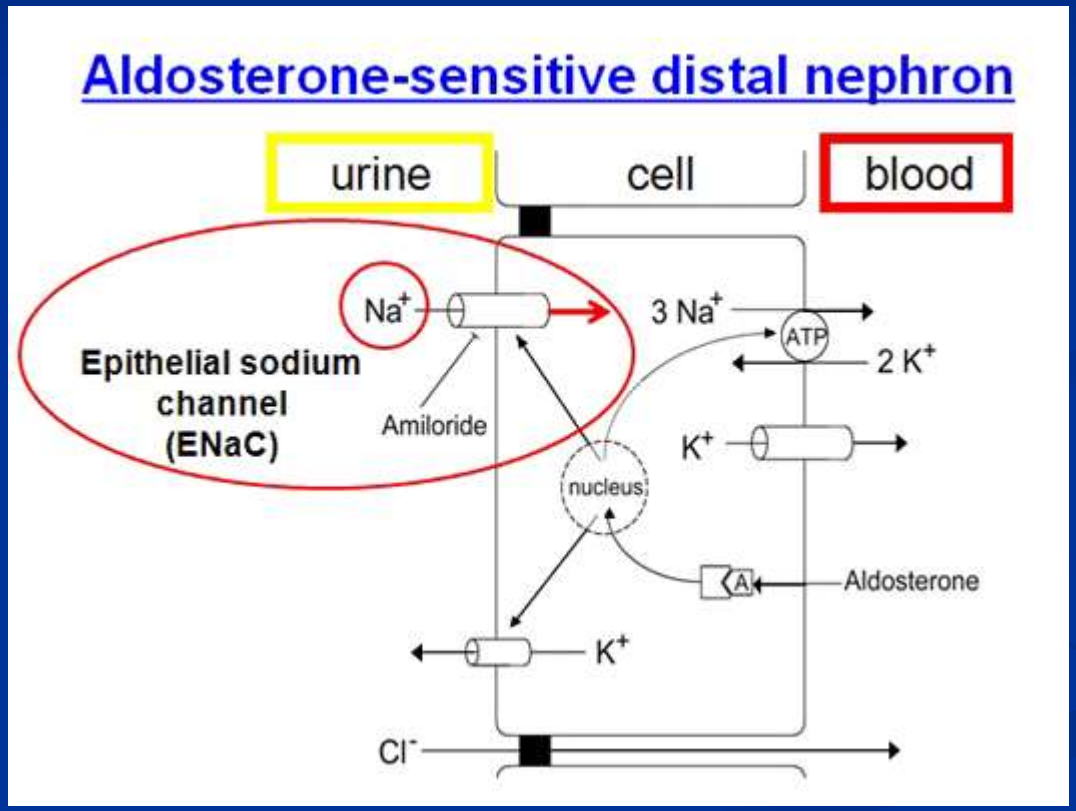


Gamba G.The nanopeptide hormone vasopressin is a new player in the modulation of renal Na(+)-Cl(-) cotransporter activity. Kidney Int. 2010 Jul;78(2):127-9.

A quick reminder of the renal tubule

- Important points for this talk:
  - The distal convoluted tubule is the diluting segment of the tubule and dependent of flow for diltution
  - The collecting duct in the ADH sensitive section of the tubule for final water balance

ENaC: The only renal tubule channel a non-nephrologist needs to remember



https://www.elitenetzwerk.bayern.de/964.0.html

Regulation of Sodium Content Overview

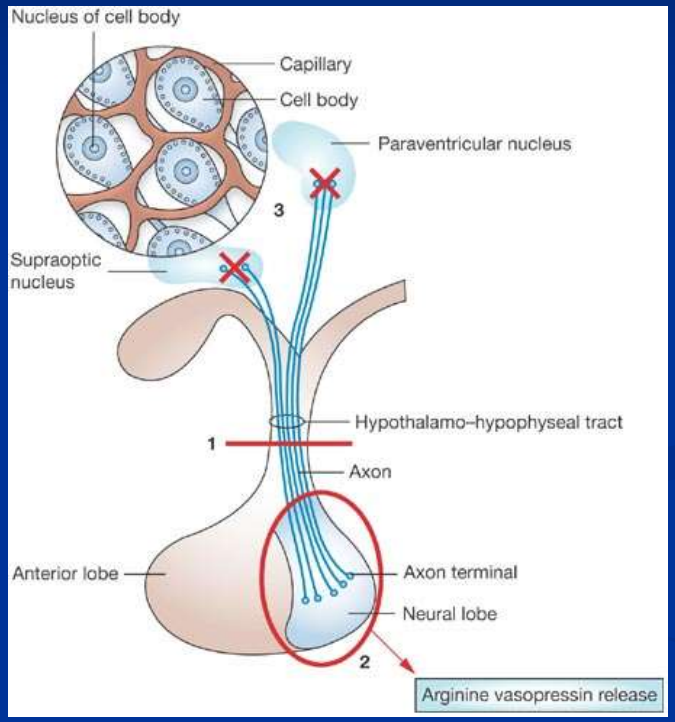
- In states of perceived hypovolemia, the sympathetic nervous system and RAAS work to increase Na retention
- **This results in a Na poor urine**
- **Low urine Na is a reflection of perceived hypovolemia from actions of SNS/Aldo**
- In dire situations the body will try to hold onto free water even though it is a poor volume expander through non-osmotic ADH mediated pathways

Regulation of Water Content

- Measurement
  - Serum Na concentration
  - Hyponatremia means hyperaquaremia
  - Hypernatremia means hypoaquaremia

Regulation of Water Content: Sensors

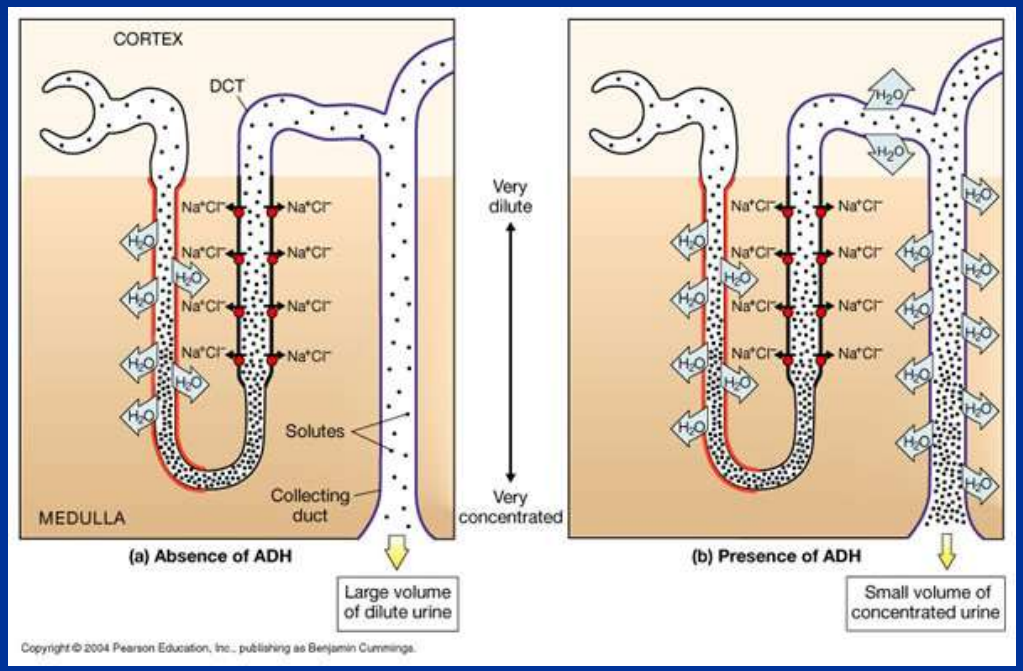
Figure 3 Mechanisms that underlie the pathophysiology of the triphasic pattern of postoperative diabetes insipidus



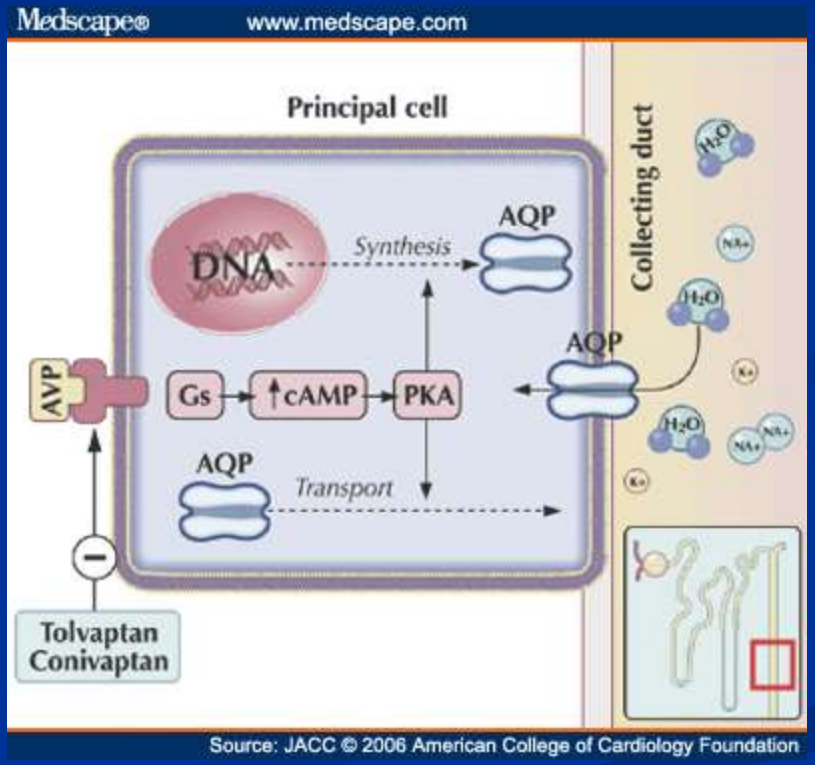
Loh JA and Verbalis JG (2007) Diabetes insipidus as a complication after pituitary surgery
Nat Clin Pract Endocrinol Metab **3:** 489–494 doi:10.1038/ncpendmet0513

nature CLINICAL PRACTICE ENDOCRINOLOGY & METABOLISM

Regulation of Water: Effectors



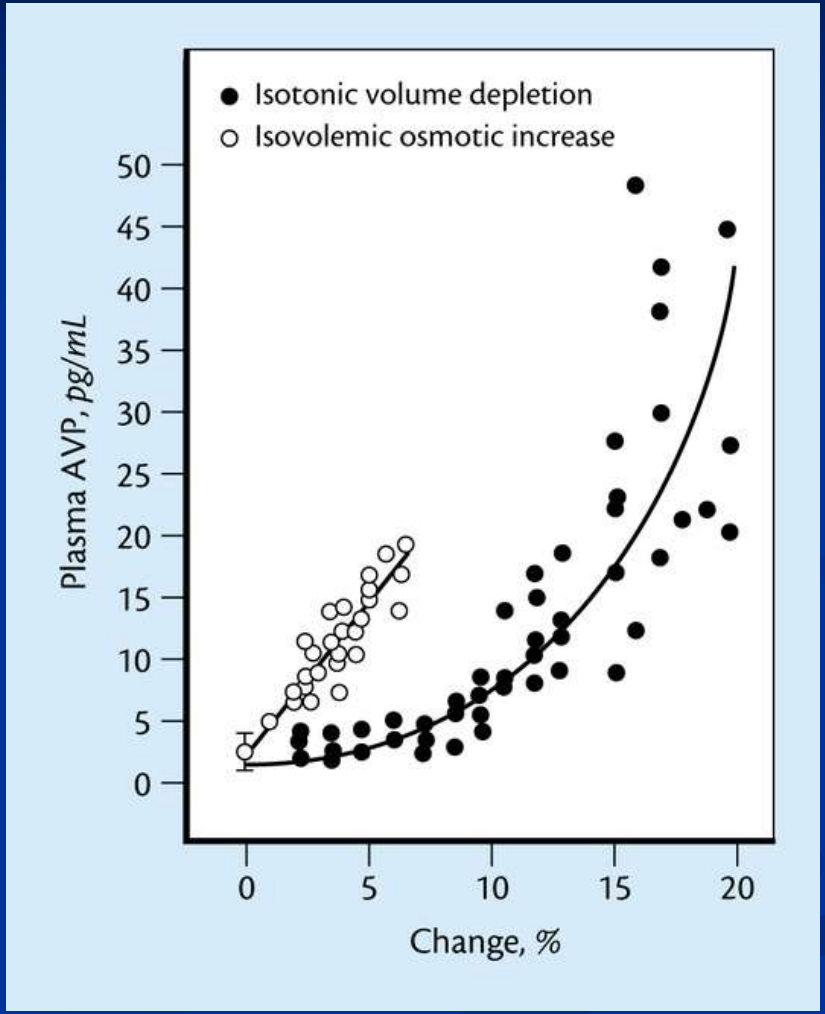
http://www.as.miami.edu/chemistry/2086/Chap26/Chapter%2026-NEW_part2.htm



http://www.medscape.com

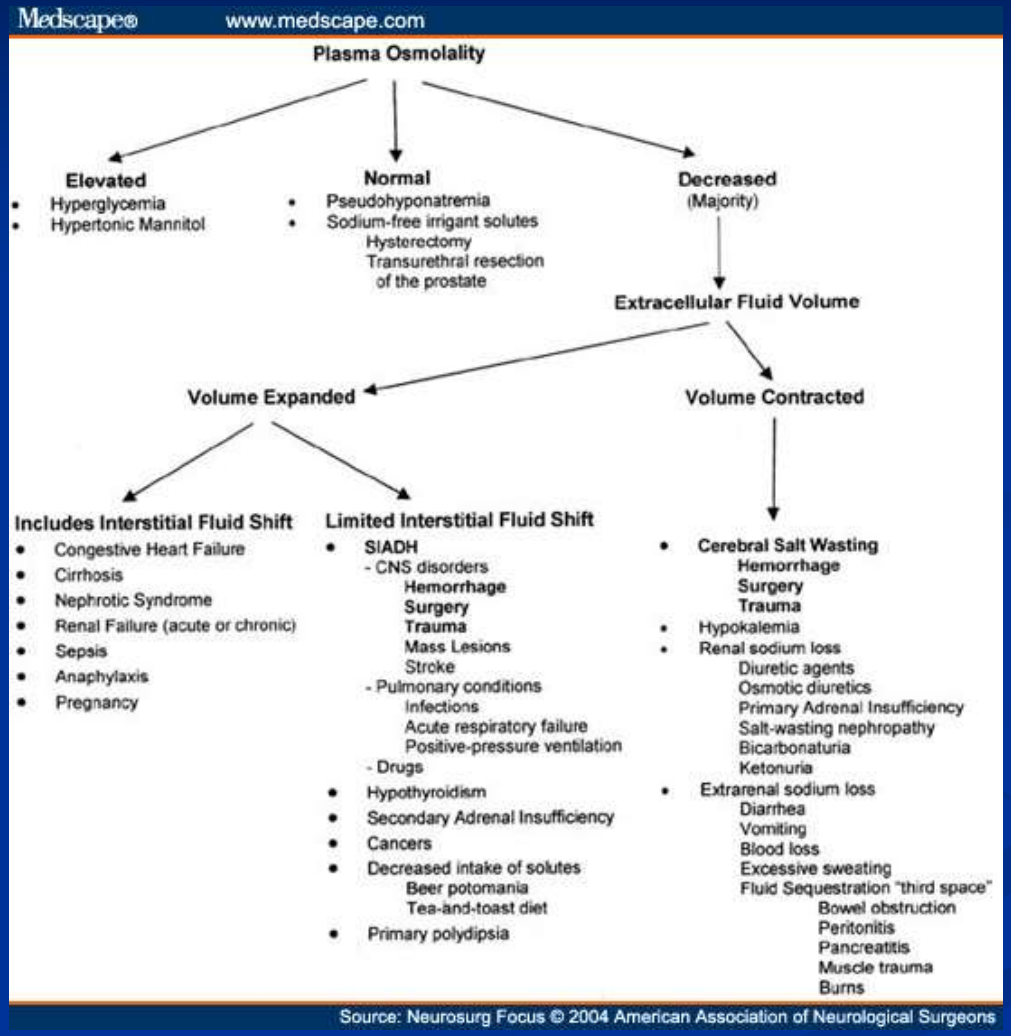
Antidiuretic Hormone: Non-osmotic Stimulation

- ADH
  - More sensitive to osmolality
  - More robust response to volume after 10% loss of volume



http://www.springerimages.com/Images/MedicineAndPublicHealth/2-ADK0101-01-01-011

Hyponatremia classification



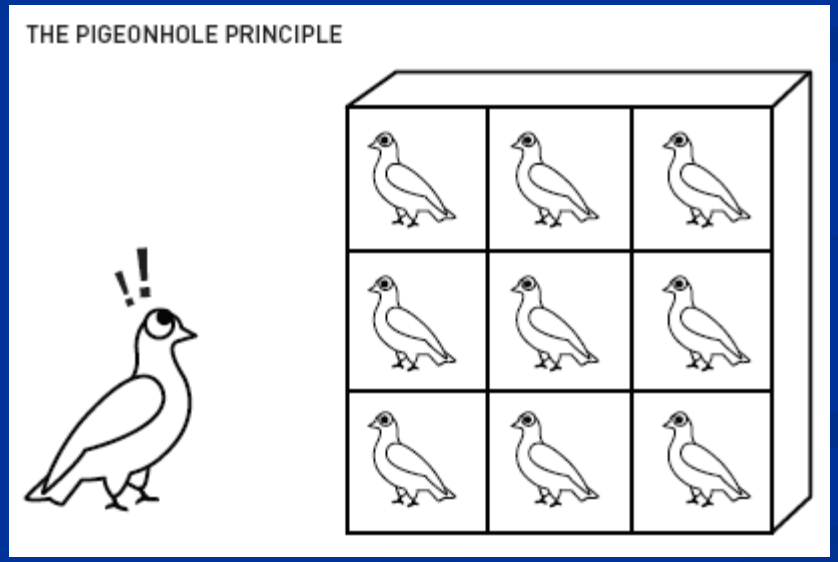
http://www.medscape.com

Hyponatremia classification

- Hypovolemic: loss of Na from renal/GI/other source and intake of free water during states of high ADH
- Euvolemic: Inability to excrete daily free water load
- Hypervolemic: High total Na but decreased effective blood volume. Inability to excrete free water load due to proximal tubule Na avidity and low GFR (low flow to diluting segment)

Hyponatremia classification

- Edema = hypervolemic
- No edema + orthostasis = hypovolemia
- Everything else is difficult to pigeonhole



Hyponatremia classification

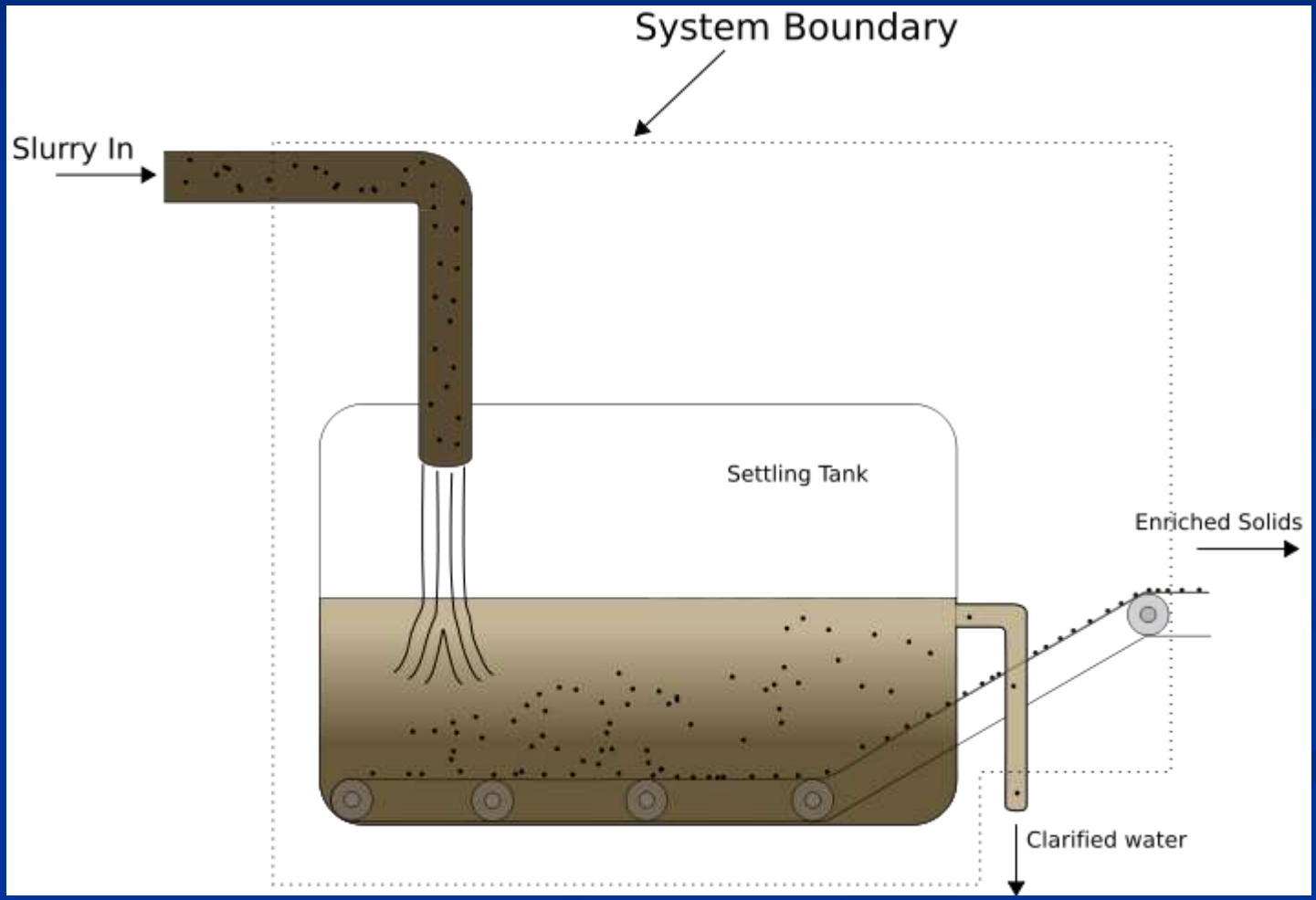
"*Physical Exam is nearly useless in deciding if someone is euvolemic or slightly hypovolemic. The urinary sodium gives much more accurate assessment of physiologic perceived volume than your exam ever can.*" –David H. Ellison, Former Division Chief Nephrology at OHSU

In the absence of edema, a low urinary sodium is indicative of volume depletion and is much more sensitive than various exam maneuvers to estimate volume status.

Treatment

- In all cases free water excretion, not Na addition, is the goal
- The mechanism to achieve that varies based on the volume status

Hyponatremia Treatment :
How I visualize people as a nephrologist
Input – Output = Accumulation



http://en.wikipedia.org/wiki/File:Mass_bal_clarifier.svg

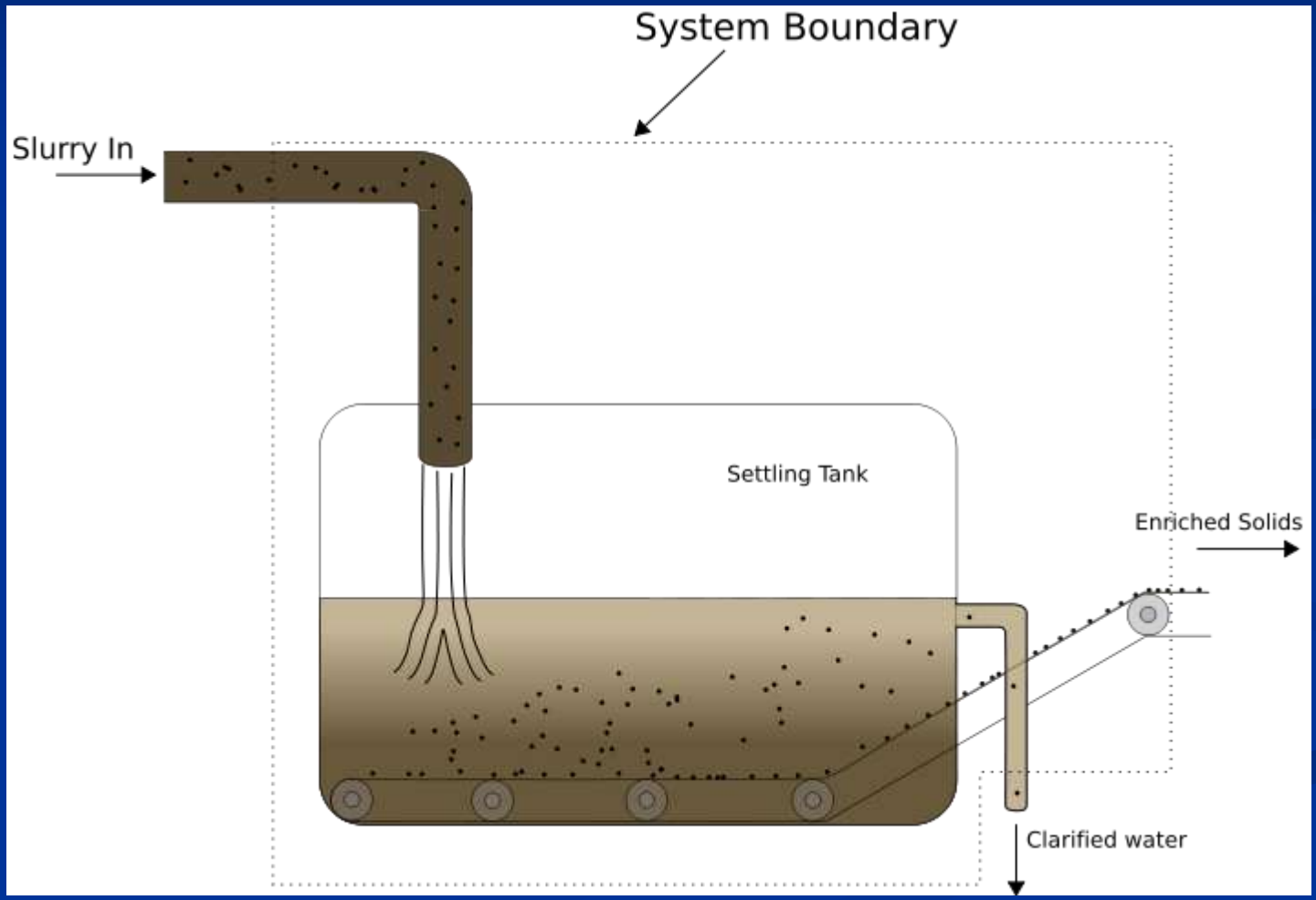
Hypovolemic Hyponatremia

- The problem: low volume sets off ADH and water retention
- The solution: addition of Na load will shut off non-osmotic stimulus for ADH and allow free water excretion

Hypovolemic Hyponatremia Case

- A 59 y/o male presents with 6 days of profuse diarrhea and has only been able to take in one bottle of gatorade a day. He is found to have a BP of 100/50 which drops to 80/40 when he stands with a pulse of 120. He has no edema on exam. On laboratory examination he is found to have a serum Na of 129, a urine Na of 10 and a urine osmolality of 600.

Hypovolemic Hyponatremia : Enriched Solids = isotonic diarrhea Slurry In = hypotonic gatorade



http://en.wikipedia.org/wiki/File:Mass_bal_clarifier.svg

Tonicity of Fluids

Also all fluid is more or less hypotonic other than normal saline and chicken broth because of sugar content

Hypovolemic Hyponatremia Treatment

- Low Urine Na tells us patient has high renin-AII-aldosterone activity
- Exam tells us pt is hypovolemic
- Patient is given 2L of NS
- This shuts off non-osmotic stimulus for ADH
- Pt has low serum osmolality so will have no ADH and put out dilute water rich urine to return to normal serum osmolality

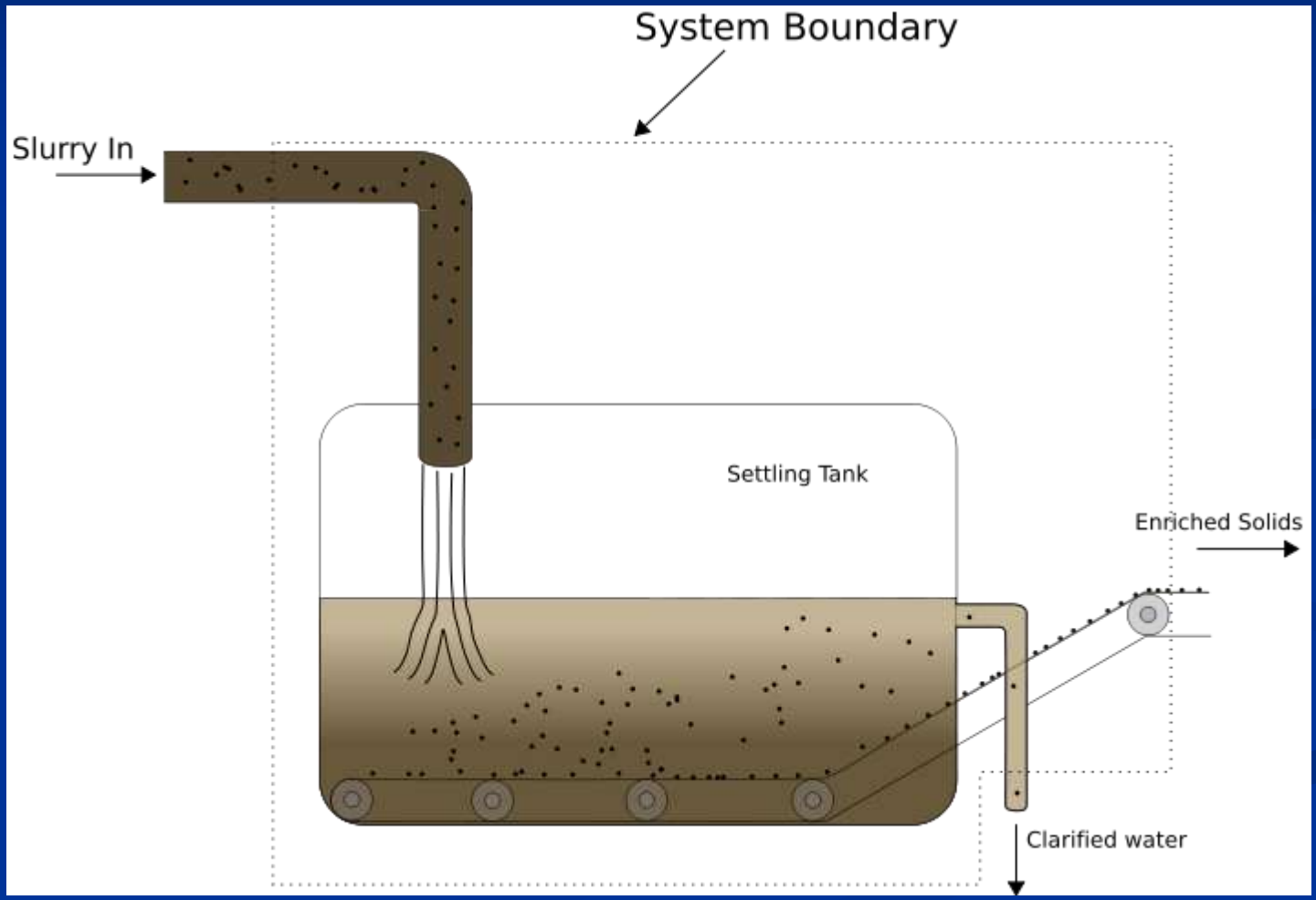
Hypervolemic Hyponatremia

- The problem: low GFR results in low urine flow to diluting segment of the nephron
- The solution: loop diuretics to increase flow through the loop of henle

Hypervolemic Hyponatremia

- A 59 y/o man with a h/o CHF presents with increasing edema and SOB. On exam he has a BP of 100/50 which drops to 80/40 when he stands with a pulse of 120. He has crackles in his lung bases bilaterally and 3+ edema. On laboratory examination he is found to have a serum Na of 129, a urine Na of 10 and a urine osmolality of 600.

Hypervolemic Hyponatremia :
Clarified water = low volume concentrated urine
Slurry In = normal intake



http://en.wikipedia.org/wiki/File:Mass_bal_clarifier.svg

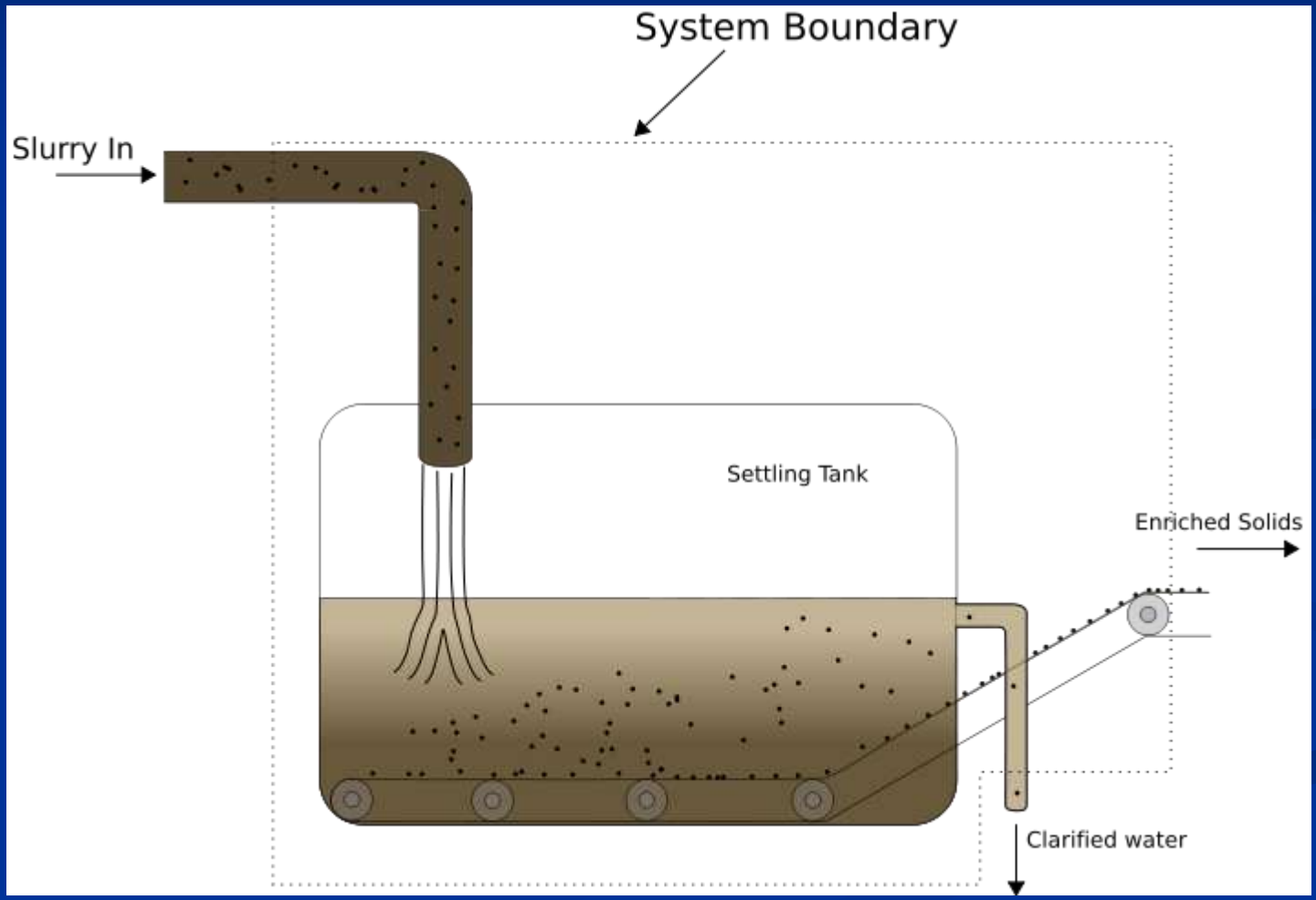
Hypervolemic Hyponatremia Treatment

- Increase urinary flow
  - Loop diuretics to increase flow to diluting segment
  - For low EF, ionotropes will fix this by increasing GFR

Euvolemic Hyponatremia

- The problem: inability to excrete the daily free water load
  - Large free water intake – 10+ L/day
  - Reduced free water excretion in the urine typically from SIADH

Euvolemic Hyponatremia :
Clarified water = low volume concentrated urine
Slurry In = normal intake



http://en.wikipedia.org/wiki/File:Mass_bal_clarifier.svg

Free water accumulation in euvolemic hyponatremia

- Imbalance caused by same input/output as hypervolemic hyponatremia but caused by ADH mechanism rather than low GFR

Euvolemic Hyponatremia Treatment

- Limit Free Water intake
- Increase Free Water excretion
  - Demeclocycline
  - Vasopressin antagonists akaVaptans
  - Hypertonic saline
  - Ure-Na
  - SGLT2i

Goals of Treatment

- Asymptomatic:
  - slow, <10 mEq/L per day
  - Usually can be done via restriction alone
- Symptomatic: confusion/seizures
  - Quick correction of 6 mEq/L
  - 6 mEq/L is enough to correct symptoms regardless of starting level

Hyponatremia Treatment

Box 2. Teaching Points for Managing Profound Hyponatremia

- Prompt correction by enough to improve symptoms and reduce the risk of seizures
  - ◊ 4-6 mEq/L is enough correction regardless of the severity of the hyponatremia
  - ◊ Correct hyponatremia rapidly in the first few hours and then slow down
- Limited correction to prevent neurologic injury (osmotic demyelination syndrome)
  - ◊ <10 mEq/L in a 24-hour period
  - ◊ <18 mEq/L in a 48-hour period
  - ◊ Stay well below these limits in patients at high risk of osmotic demyelination
- Anticipate and manage reversible causes of hyponatremia
  - ◊ Administration of desmopressin every 6-8 hours with hypertonic saline solution is an effective strategy to control the rate of correction
  - ◊ Water intake and hypotonic intravenous fluids (including those containing medications) must be restricted in hyponatremic patients treated with desmopressin

Note: No conversion necessary for sodium in mEq/L and mmol/L.

Box 3. Correction Goals for Severe Chronic Hyponatremia

Rule of Sixes:

- Six-a-day makes sense for safety
- Six in six hours for severe sxs and *stop*

Explanation:

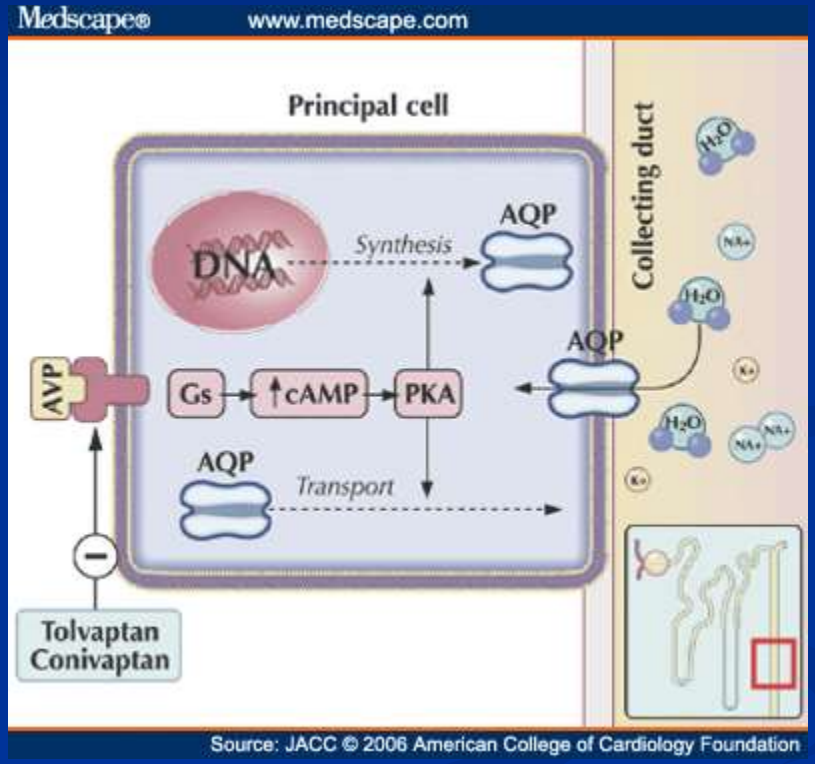
For all patients with chronic hyponatremia, the goal is 6 mEq/L during the initial 24 hours. For those with severe symptoms (seizure, severe delirium, and unresponsiveness), the goal is preloaded in the first six hours, postponing subsequent efforts to increase serum sodium level until the next day.

Abbreviation: sx, symptom.

Sterns RH, Hix JK, Silver S. Treating profound hyponatremia: a strategy for controlled correction. Am J Kidney Dis. **2010** Oct;56(4):774-9.

Increased Free Water Excretion

- Both demeclocycline and vaptans inhibit ADH activity in collecting ducts
- ADH activity results in insertion of aquaporins to membrane and water reabsorption from the urine



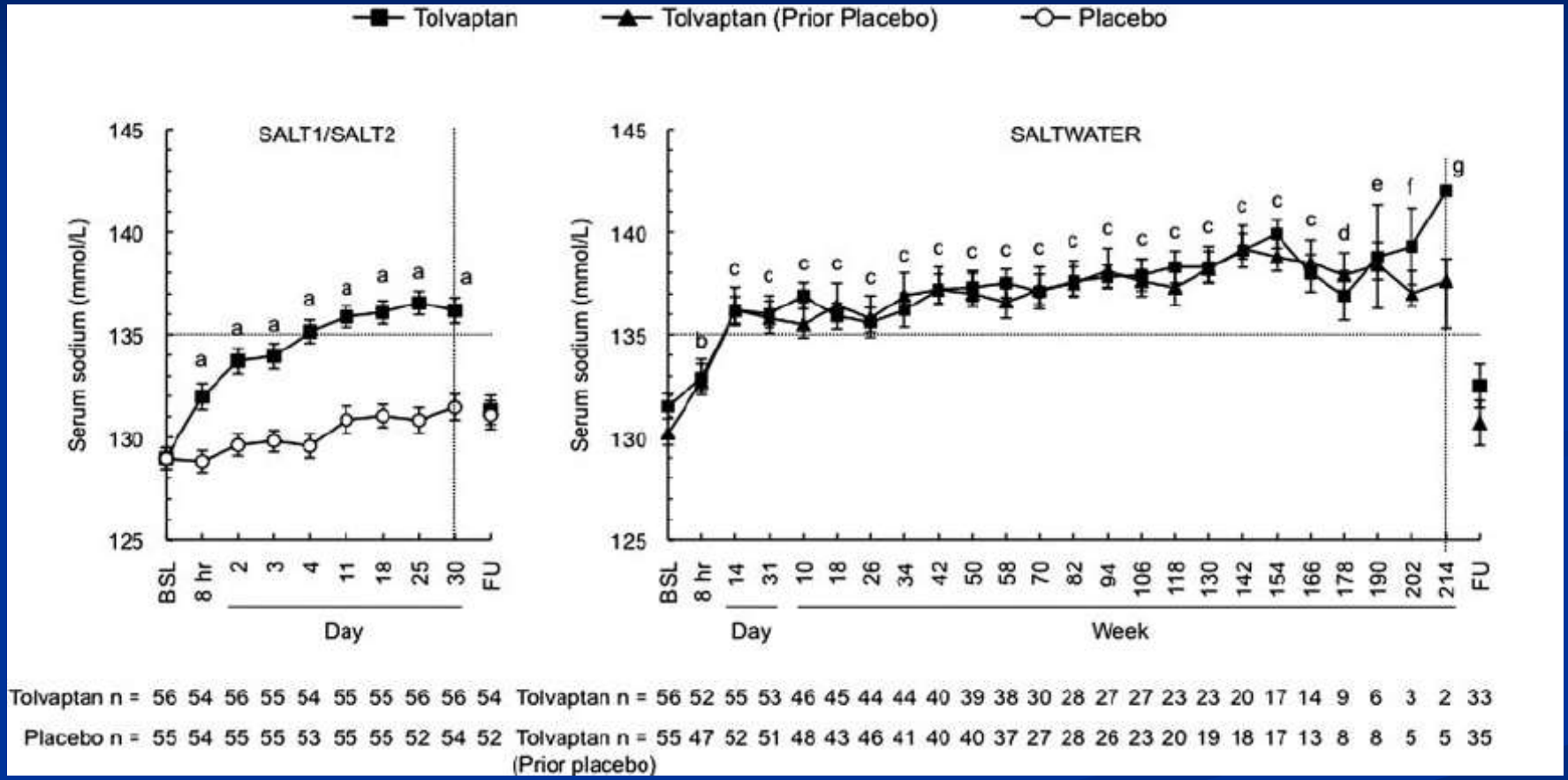
http://www.medscape.com

Increased Free Water Excretion

- SALTWATER
  - Follow up to SALT-1 and SALT-2 with 111 patients with euvolemic hyponatremia on tolvaptan 15- 60 mg daily as tolerated followed for 701 days
  - Primarily was done for safety monitoring

Berl T, Quittnat-Pelletier F, Verbalis JG, Schrier RW, Bichet DG, Ouyang J, Czerwiec FS; SALTWATER Investigators. Oral tolvaptan is safe and effective in chronic hyponatremia. J Am Soc Nephrol. 2010 Apr;21(4):705-12.

SALTWATER Results



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SALTWATER Results

- Minimal side effect profile other that increased urination/thirst
- Not compared to placebo in this study

Table 2. Investigator-assessed treatment-emergent adverse events

Parameter	Value[a]
Treated patients	111
Total exposure (patient-days)	77,369
Exposure per patient (days)	
mean	701
median	639
Total AEs (all causes; *n* [%])	105 (94.6)
Total AEs leading to discontinuation or death (all causes; *n* [%])	30 (27.0)
AEs leading to discontinuation	19 (17.1)
AEs leading to death before withdrawal	11 (9.9)
Drug-related AEs (*n* [%])	52 (46.8)
most common drug-related AEs[b]	
pollakiuria	11 (9.9)
thirst	10 (9.0)
fatigue	6 (5.4)
dry mouth	4 (3.6)
polydipsia	4 (3.6)
polyuria	4 (3.6)
hypotension	4 (3.6)
hypernatremia	4 (3.6)
dizziness	4 (3.6)
headache	4 (3.6)
peripheral edema	4 (3.6)
acute renal failure	4 (3.6)
Drug-related AEs leading to discontinuation	6 (5.4)
ventricular tachycardia	1 (0.9)
irritability	1 (0.9)
blood sodium increase	1 (0.9)
anorexia	1 (0.9)
blood creatinine increase	1 (0.9)
pruritus	1 (0.9)

AEs that started during the tolvaptan treatment phase or were continuous

Berl T, Quittnat-Pelletier F, Verbalis JG, Schrier RW, Bichet DG, Ouyang J, Czerwiec FS; SALTWATER Investigators. Oral tolvaptan is safe and effective in chronic hyponatremia. J Am Soc Nephrol. 2010 Apr;21(4):705-12.

Hypertonic Saline

- In rare cases of profound hyponatremia, 3% hypertonic saline is necessary to correct the free water excess
- If severe symptoms (i.e. seizures) can be given in 100 ml boluses which typically raise serum Na by 1.5 -2.0 mEq/L
- If less severe (i.e. confusion) can be given as gtt at ~1 ml/kg/hr
- Patients should have hourly serum Na levels drawn to avoid rapid correction and be in the ICU
- Hypertonic saline needs to be given through a central line because of sclerosing effects

Hypertonic Saline Physiology

- Unlike hypovolemic hyponatremia, patients with SIADH have a fixed urinary osmolality because the ADH stimulus is unrelated to osmolality or volume
- As the patient is euvolemic, the salt load given by hypertonic saline needs to be excreted as this is regulated by renin-AII-aldo axis
- The salt load will be excreted in a fixed amount of urine and as long as the volume given is less than the volume of urine, the patient will be in negative free water balance

Hypertonic Saline Physiology Example

- A 59 y/o male with SIADH presents with a serum Na of 106 and confusion. He has a urine Na of 40 mEq/L and urine osmolality of 308 mOSm/L. He is given a 100 ml bolus of 3% normal saline for his symptoms.

Hypertonic Saline Physiology Example

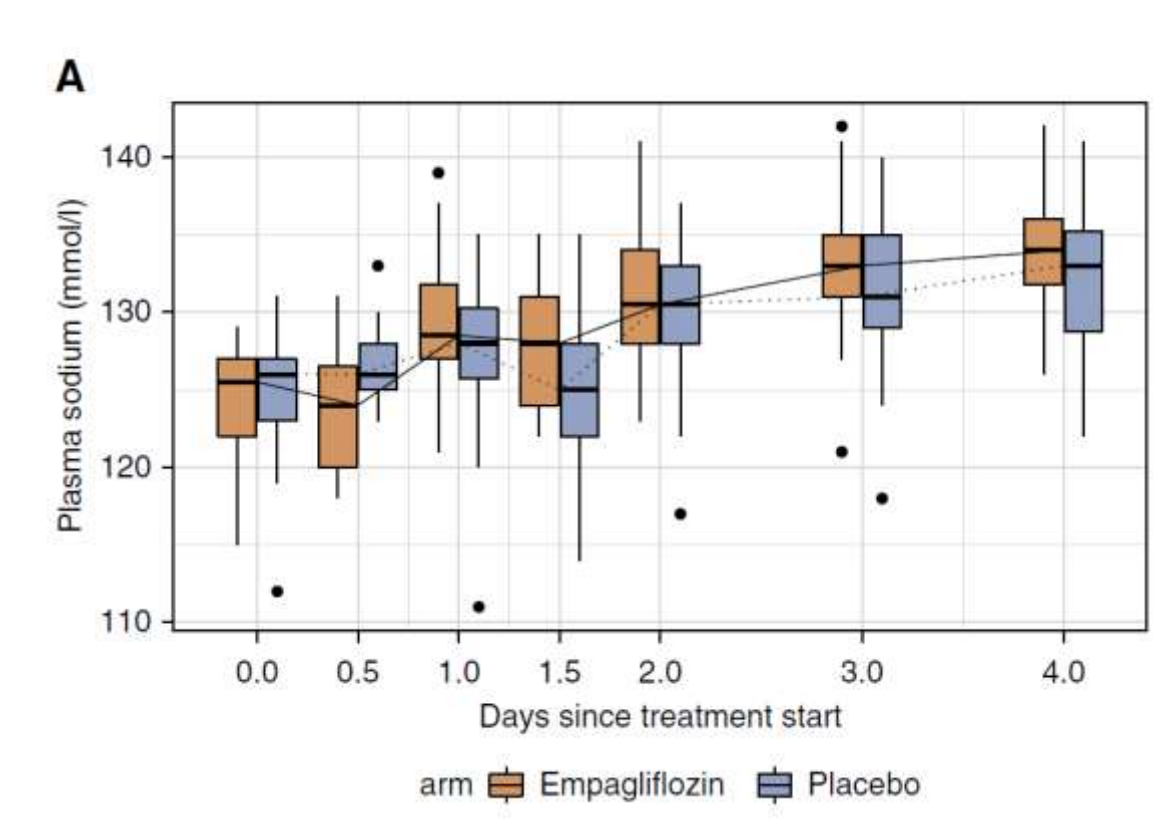
- Hypertonic saline = 924 mOsm/L
- 100 ml of hypertonic saline = 92 mOsm
- Urine excreted = 92 mOsm/ (308 mOsm/L) or ~300 ml
- Thus negative free water balance of 200 ml

Ure-Na: Osmolar Load

- 15 gm packet of Ure-Na contains 250 mOsm compared with 92 mOsms in 100 ml of hypertonic saline

https://www.ure-na.com/

SGLT2 inhibitors – Nephrology's new wonder drug



- Study of 88 patients with SIAD randomly assigned to usual care plus once daily empagliflozin 25 mg vs usual care. Na increased by 10 vs 7 in the treatment group related to osmotic diuresis from glucose

Refardt J, Imber C, Sailer CO, Jeanloz N, Potasso L, Kutz A, Widmer A, Urwyler SA, Ebrahimi F, Vogt DR, Winzeler B, Christ-Crain M. A Randomized Trial of Empagliflozin to Increase Plasma Sodium Levels in Patients with the Syndrome of Inappropriate Antidiuresis. J Am Soc Nephrol. 2020 Mar;31(3):615-624. doi: 10.1681/ASN.2019090944. Epub 2020 Feb 4. PMID: 32019783; PMCID: PMC7062212.

Avoid making things worse

- A patient presents with a serum Na of 123. Based on skin turgor and mucous membrane exam, the resident feels that the patient is hypovolemic. He proceeds to order 2L of NS fix this hypovolemic hyponatremia. The next day the patient's serum Na is 116. His urine Na is checked and is 110 mEq/L and his urine osmolality is 430 mOsms/L. What happened?

Desalination

- If the prior patient had hypovolemic hyponatremia his urine would have diluted with the saline administration
- Instead the patient had fixed urinary osmolality due to SIADH
- The addition of NS worsened his hyponatremia because the urinary osmolality > osmolality of NS

Desalination

- NS = 308 mOsm/L
- Pt given 2L so total of 616 mOsm
- Urinary osmolality was 430 mOsm/L so Na load was excreted in 616/430 or 1.4L of urine
- Thus the patient had a positive free water balance of 600 ml with the 2L of normal saline

Avoid desalination

- Prior to administering IVF on a hyponatremic patient with stable vital signs, send off urine Na and osmolality
- You can still give the IVF but
  - if the urine Na > 25 mEq/L rethink the hypovolemia
  - If the urine osmolality is >308 mOsm/L realize you may cause desalination

Summary

- Send a urine Na and urine Osm off when the patient with hyponatremia arrives
- You can still give IVF while waiting for results but it is easier to look back and adjust than try to figure out what is going on after 5 days of treatment

All the math is over!
Questions?