

Revisiting Electrolytes

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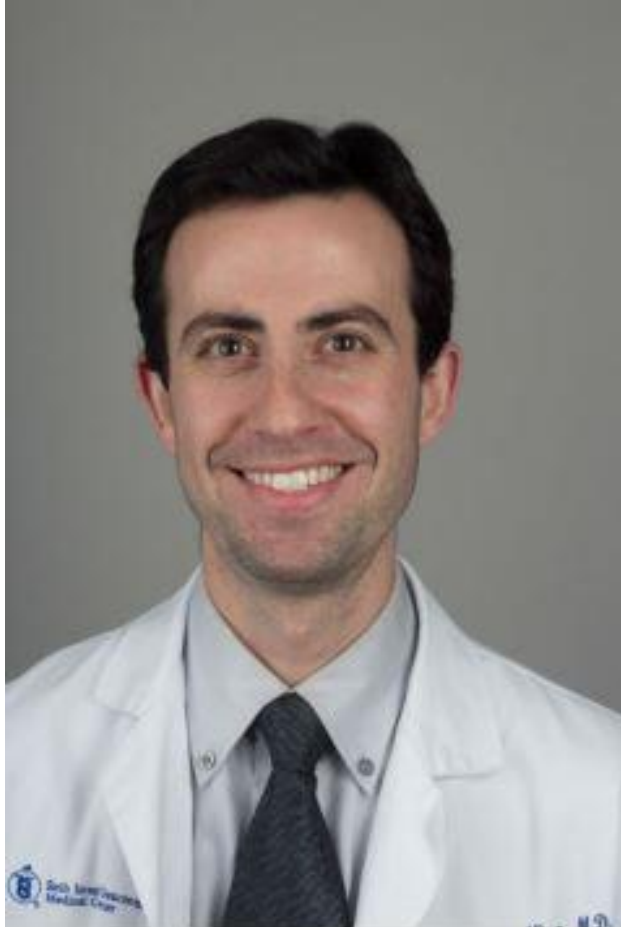
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Disclosures

None.

After this talk, you will be able to...

- ...appropriately triage electrolyte abnormalities
- ...apply the physiology of K^+ transport to the treatment of hyperkalemia
- ...utilize an organized approach to the diagnosis and treatment of **hyponatremia (Na^+)**

Case

Mr. P is a 70-year-old man with a history of insulin-dependent type 2 diabetes mellitus, brought in by his daughter due to worsening confusion and fatigue. He has been very sleepy and has not been eating very much. He stopped all of his medications, except lisinopril, for the past 1-2 weeks. Routine Chem-7, with a subsequent ABG, shows the following:

118	90	109	
7.8	14	10.8	446

ABG

pH 7.29

pCO₂ 30

pO₂ 95

Triaging abnormal electrolytes

Which electrolyte abnormality will you address **first**?

- a) Hyponatremia
- b) Hyperkalemia
- c) Acidemia (with low bicarbonate)
- d) Azotemia (high BUN and creatinine)
- e) Hyperglycemia

118	90	109	< 446
7.8	14	10.8	

ABG

pH 7.29

pCO₂ 30

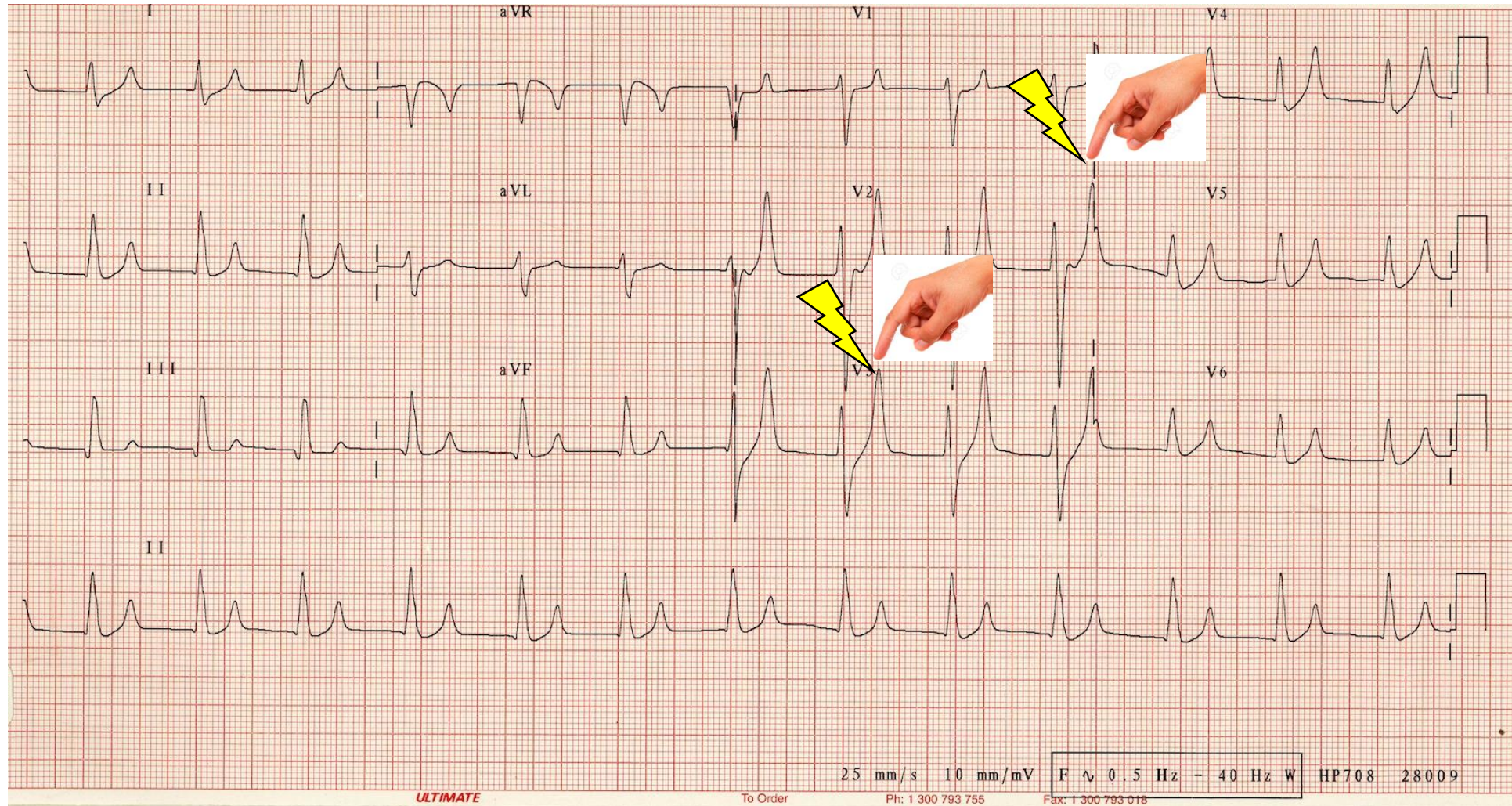
pO₂ 95

EKGs are quick, easy, and helpful

- EKG findings
 - Peaked T waves (most common)
 - Shortened QT interval
 - Progressive lengthening of PR interval and widening of QRS

Most commonly *asymptomatic* or only non-specific symptoms (fatigue, weakness)!

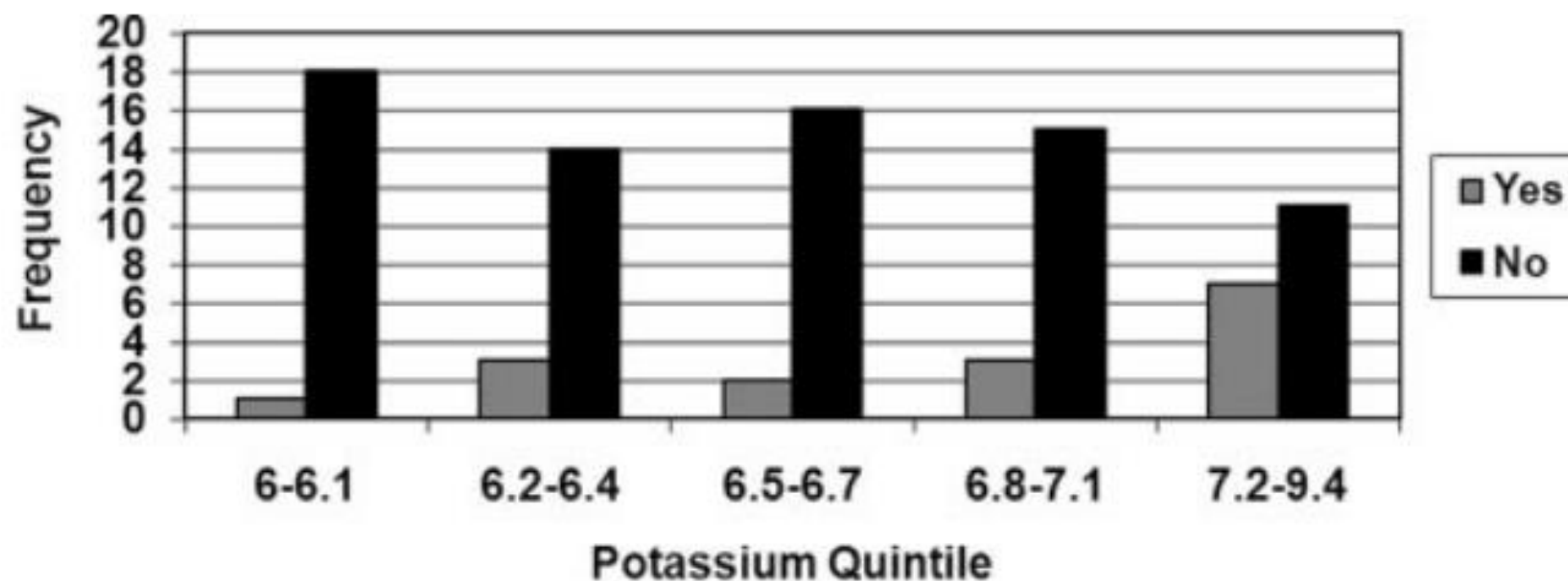
Physiology of hyperkalemia



Retrospective Review of the Frequency of ECG Changes in Hyperkalemia

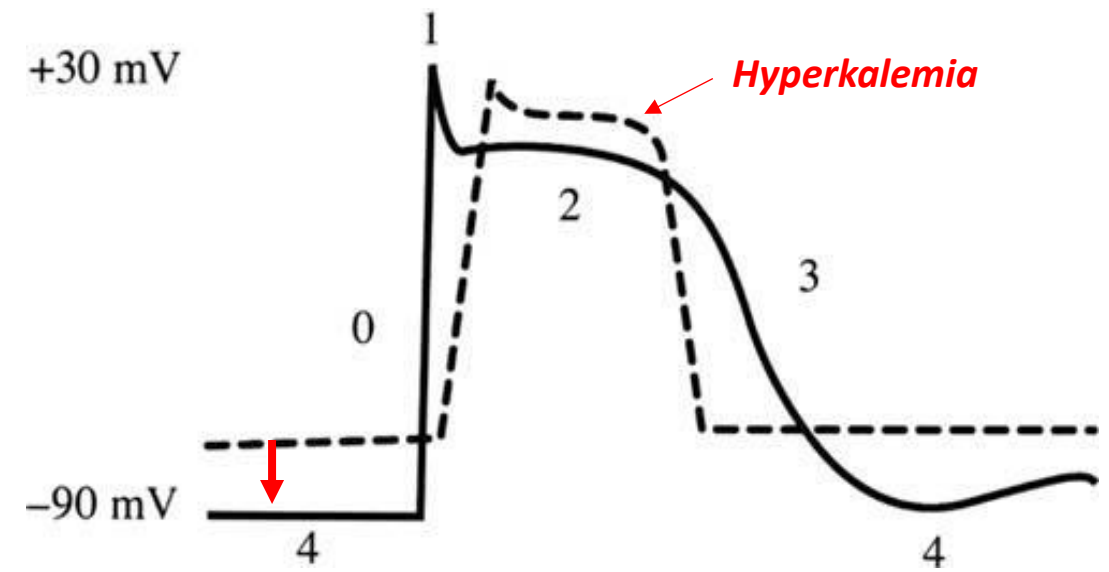
Brian T. Montague, Jason R. Ouellette, and Gregory K. Buller

Department of Medicine, Yale University School of Medicine, New Haven, and Saint Mary's Hospital, Waterbury, Connecticut



Why do we give calcium?

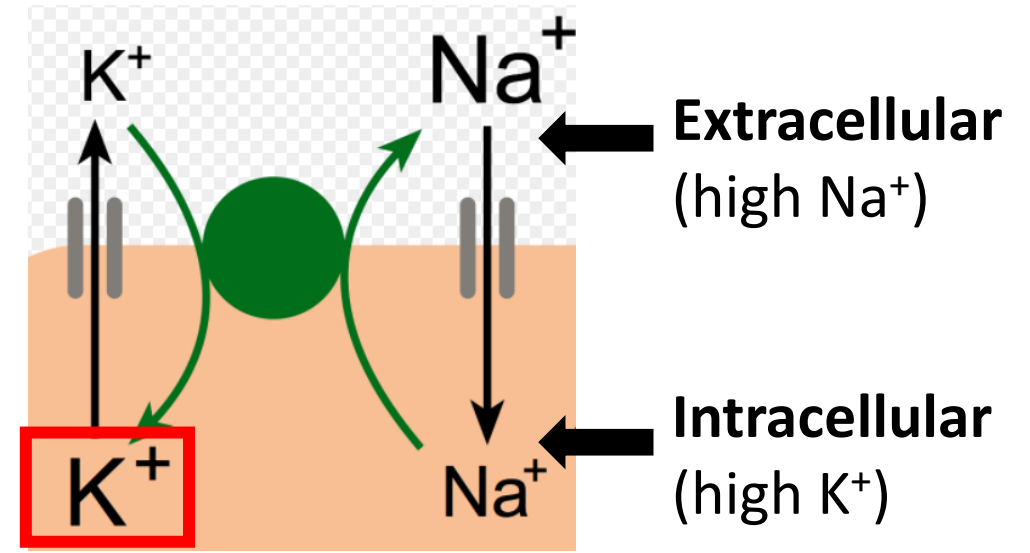
- Membrane stabilization!
 - Shift of the resting potential back toward normal (more negative)
 - Improvement of myocyte excitability
- Infusion works within minutes, but lasts only 1 hour
- No role in *cellular shift* of K^+ from the blood and back into cells



Physiology of hyperkalemia

“Why is there too much K^+ in the blood?”*

- 1) Increased K^+ release from cells
 - Shift to the extracellular space
 - Cell lysis (*in vivo*)
- 2) Decreased urinary K^+ excretion via the filtrate (+ increased intake)



Hyperkalemia is often multifactorial and dependent on the clinical scenario!

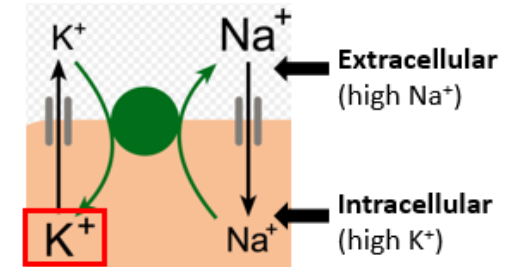
* Pseudohyperkalemia (*in vitro*) - tourniquet use, clot formation in EDTA-based collection tubes

Cellular shift physiology

Insulin and/or catecholamine release



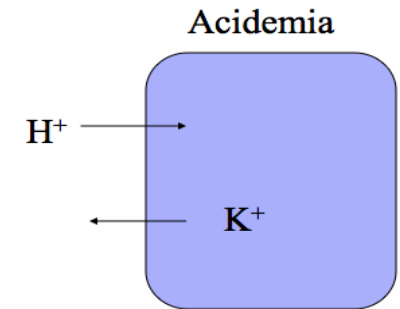
Increased activity of the $\text{Na}^+\text{-K}^+$ ATPase (more K^+ into the cell)



Metabolic acidosis



$\text{H}^+\text{-K}^+$ exchange moves more K^+ out of the cell



Hemolysis
(both in vivo and in vitro)



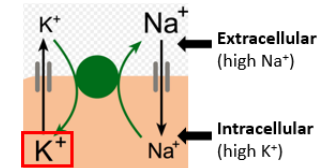
Cell lysis and release of intracellular contents within the body OR in the blood collection tube (pseudohyperkalemia)

HyperK⁺ therapies harness normal physiology!

IV insulin +/- dextrose
Albuterol (β-agonist)



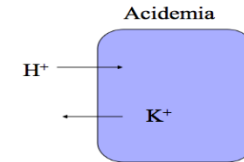
Increased activity of the Na⁺-K⁺ ATPase
(more K⁺ into the cell)



Bicarbonate infusion



H⁺-K⁺ exchange moves
more K⁺ **into** the cell



K⁺ excretion



Sodium polystyrene sulfonate (SPS, Kayexalate)
Patiromer (Veltassa)
Sodium zirconium cyclosilicate (Lokelma)
Loop diuretics



January 2015

A New Era for the Treatment of Hyperkalemia?

Julie R. Ingelfinger, M.D.

Patiromer (Weir et al.)

- *Veltassa*
- Non-absorbable spherical beads (powder mixed with water)
- Binds K^+ in the *colon*
- Exchanges K^+ for Ca^{++} (but doesn't absorb either one)
- Gradual decrease in K^+ , so its performance in an acute situation is unclear (used for 12 weeks)

Sodium zirconium cyclosilicate (SZC) (Packham et al.)

- *Lokelma*
- Crystalline lattice structure that preferentially traps K^+ ; Na^+ -based
- Insoluble (remains in *small intestine*)
- Traps 10x amount of K^+ vs. SPS (in vitro)
- Short study – only 14 days, but longer-term use now supported by additional double-blind studies

Back to our case...

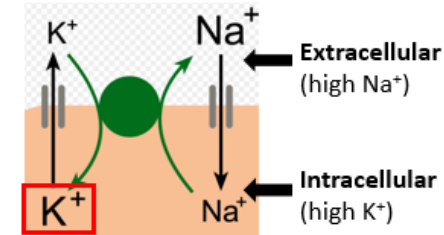
Pertinent case details:

- History of insulin-dependent t2DM, hypertension
- Continues to take lisinopril

118	90	109	446
7.8	14	10.8	

Intra → Extracellular shift

- Insulin deficiency
- Hyperglycemia
- Metabolic acidosis
- Pseudohyperkalemia?



Decreased urinary excretion (↓GFR)

- Renal failure (AKI)
 - volume depletion
 - obstruction
- Medication effect (ACE-i)

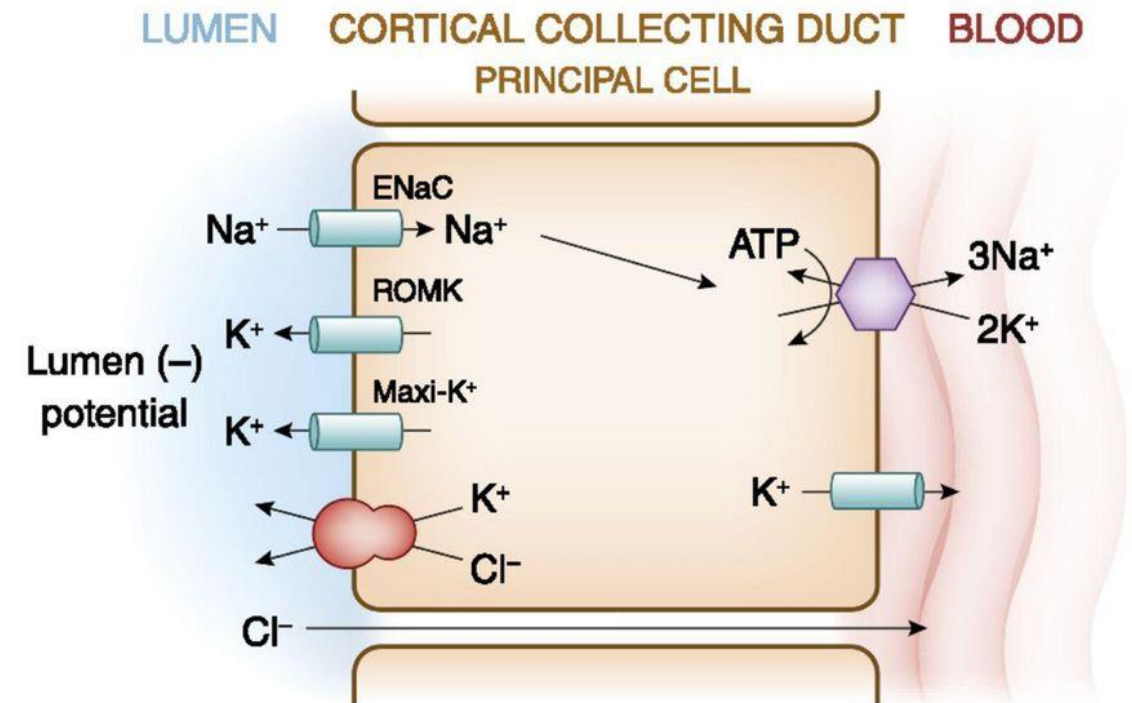


K⁺ and the cortical collecting duct

Decreased urinary excretion (↓CCD)

- Medication effect on ENaC
 - Amiloride
 - Trimethoprim
 - Pentamidine
 - Spironolactone
- Adrenal effects (MR)
 - Heparin
 - Addison's disease
 - *Hyporeninemic hypoaldosteronism*

The cell that is responsible for K⁺ secretion in the initial collecting duct and the cortical collecting duct is the principal cell.



Biff F. Palmer CJASN 2015;10:1050-1060

Type 4 RTA (hyporeninemic hypoaldosteronism)

- Hyperkalemia is more significant than the GFR would predict
- *Mild* non-gap metabolic acidosis, with normal urinary acidification
- Mild CKD
- Typically presents with an underlying tubulointerstitial disease
 - Diabetes mellitus
 - NSAIDs
 - SLE
 - Myeloma/amyloid
 - HIV

Case (continued)

- 2g of IV calcium gluconate (administered over 30 minutes)
 - 10 units of IV insulin
 - 2L of 0.9% (normal) saline – increased distal Na⁺ delivery to CCD!
 - Sodium zirconium cyclosilicate 10g x1
-
- Sent to your ICU with documentation of a stable EKG.
 - Urine output initially recorded as 10cc over the first 6 hours, but now picking up to 20cc/hr with a single dose of IV furosemide.

Case (continued)

- Repeat electrolytes (8pm):

118	93	90	< 88
5.5	17	8.5	

- Prior studies (2pm):

118	90	109	< 446
7.8	14	10.8	

Signing out

It is now the end of your shift and you're signing out to your colleague. Before you leave, you notice that the urine output has dropped once again while on 0.9% saline at 100 cc/hr. Labs are checked and the **serum Na⁺ is now 115 mEq/L (from 118)**. Clinically, the patient is increasingly disoriented.

What advice will you give to your colleague?

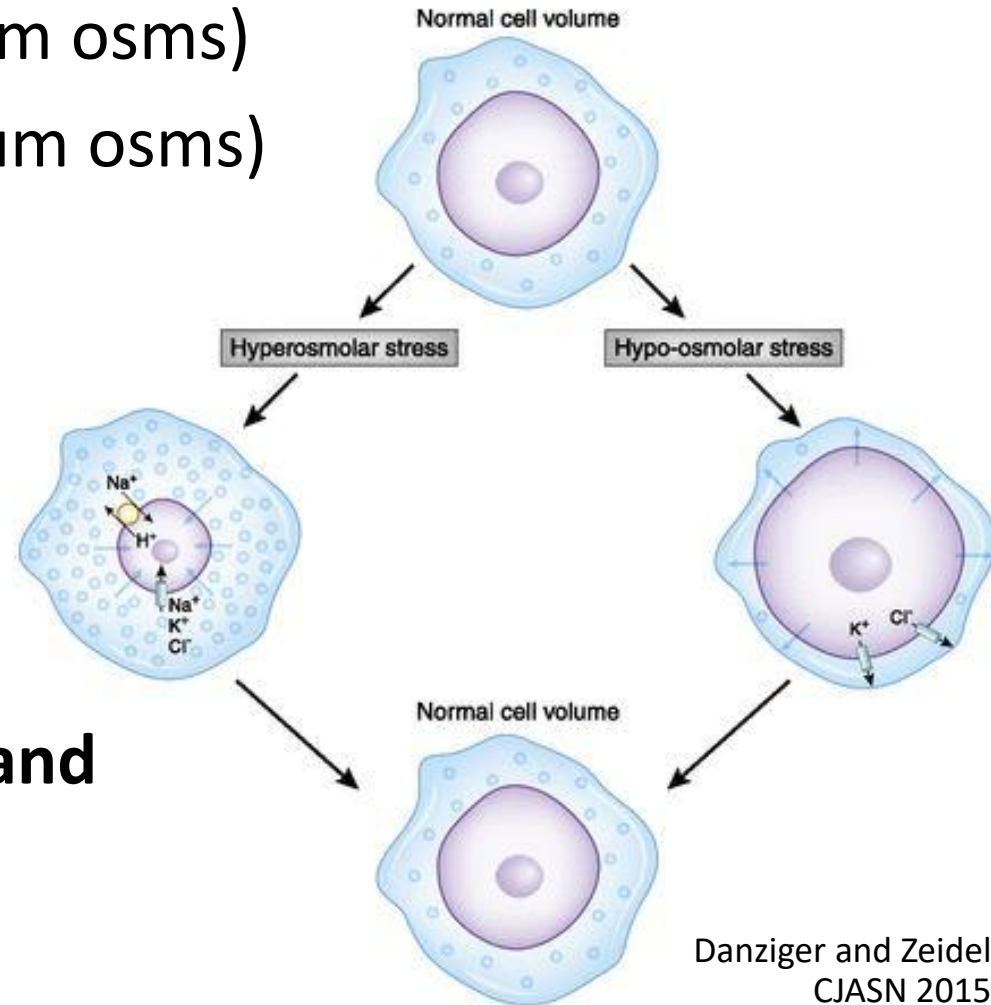
- a) Switch fluids to D5W
- b) Switch the fluids to a bolus of 3% saline (100cc)
- c) Continue to give 0.9% saline. He may still be volume depleted.
- d) Check a urine osmolality before giving more IV fluids
- e) Start salt tabs instead of IV fluids
- f) Just call Renal. They're nice and they will tell you what to do.

Dysnatremias are WATER problems

- Hyponatremia = too **much** water (low serum osms)
- Hypernatremia = too **little** water (high serum osms)

*Serum Na^+ represents a concentration,
not a volume status!*

- Dysnatremias represent changes in serum **osmolality** and, in turn, neuronal **cell size** and **resting membrane potential**



The 4-step approach to hyponatremia*

- ☒ **Step 1** – *Confirm the diagnosis (serum osmolality)*
- ☒ **Step 2** – *Determine volume status (physical exam)*
- ☒ **Step 3** – *Measure the urine osmolality and urine sodium (ADH/RAAS status)*
- ☒ **Step 4** – *Consider the appropriate treatment/work-up*

*impaired kidney function complicates this algorithm!

The 4-step approach to hyponatremia

Step 1 – Confirm the diagnosis

Is it REALLY a hypo-osmolar state? (i.e., does the serum Na⁺ truly reflect a low serum osmolality?)

$$\text{Calculated plasma Osm} = 2 \times \text{SNa} + \text{glucose}/18 + \text{BUN}/2.8$$

Lab test = ***serum osmolality***

- If it's high or normal, rule out...
 - Severe hypertriglyceridemia or hyperproteinemia = lab artifact
 - *Dilutional hyponatremia* from hyperglycemia (correct serum Na⁺ for elevated glucose)

The 4-step approach to hyponatremia

Step 2 – Determine volume status

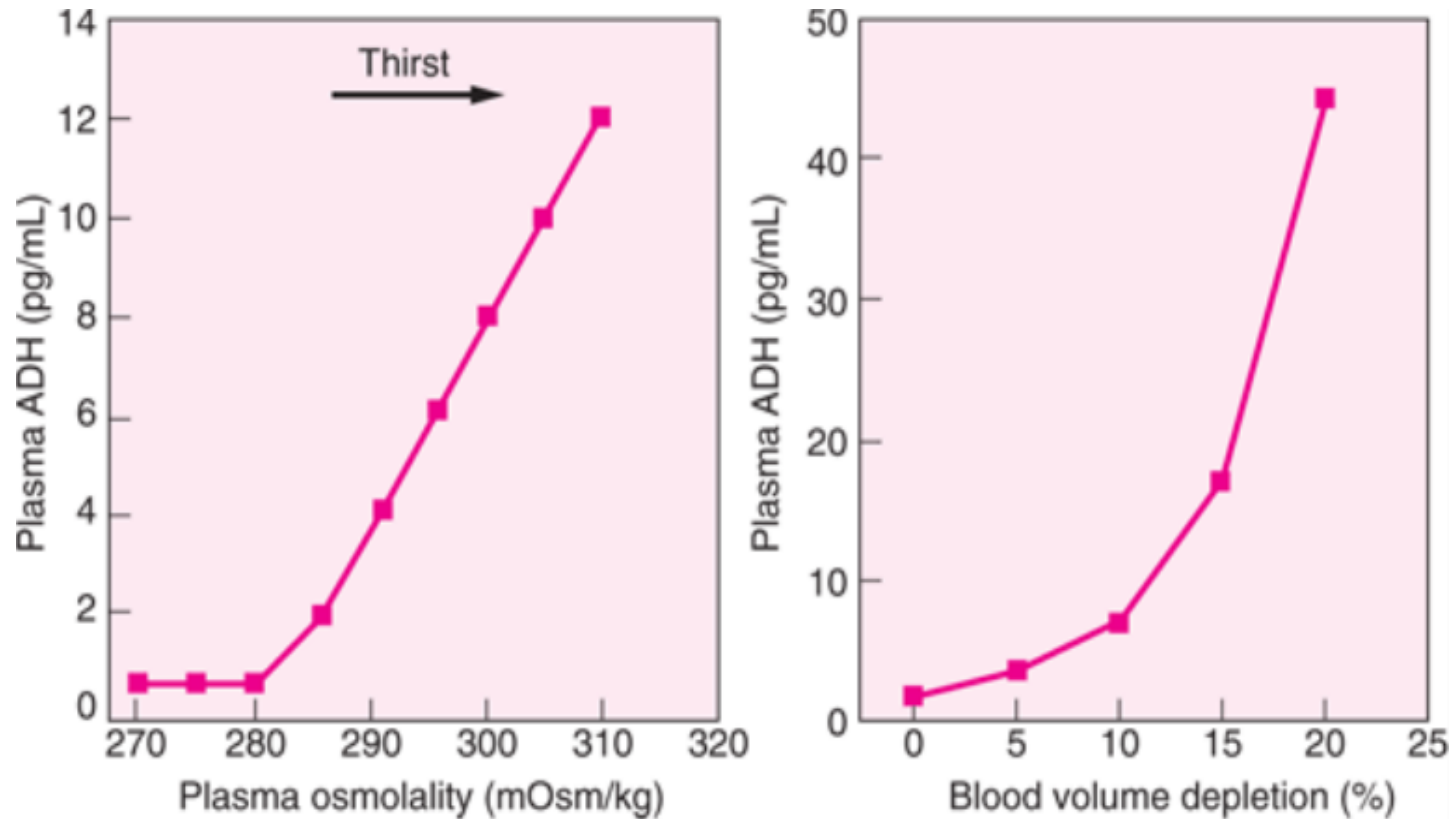
Why is ADH on?

If serum osmolality is LOW, then ADH may be on in response to a volume-mediated cause!

- True hypovolemia
- Hypervolemia, with ineffective circulating volume

Stimuli for ADH release (Steps 1 and 2!):

Hyperosmolality and volume depletion



Volume depletion is a **very potent** stimulus for ADH release, whereas an increase in osmolality results in smaller increments of ADH once the threshold is reached

The 4-step approach to hyponatremia

Step 3 – Measure the urine osmolality and urine sodium

Urine osmolality = functional assay of ADH

- Low (<100 mOsm/L) = **Primary polydipsia**
- NOT low (>100 mOsm/L) = either appropriate or inappropriate
 - Hypovolemia or **CHF, nephrosis, cirrhosis** = appropriate
 - Euvolemia = inappropriate ADH release

***SIADH (lungs/brain/pain/nausea and vomiting),
?adrenal insufficiency, thyroid disease***

Urine sodium = functional assay of angiotensin II / RAAS

- Low (<20 mEq/L) = RAAS is ON **...supports hypovolemia**
- NOT low (>20 mEq/L) = RAAS is NOT on **...supports euvolemia**

The 4-step approach to hyponatremia

Step 4 - Consider the appropriate treatment/work-up

- Which type of IV fluids?
- Fluid restriction?
- Solute supplementation (salt or protein)?
- SIADH work-up?

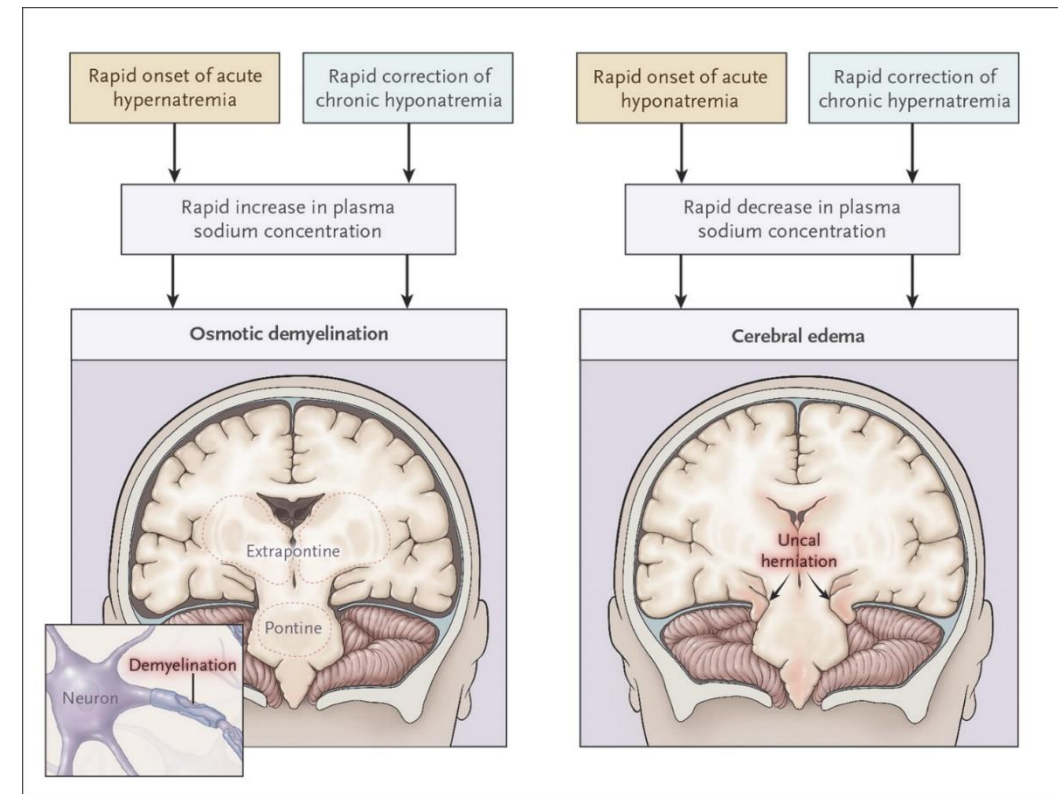
The most dangerous part of managing Na⁺/water problems is the CORRECTION

- If you did not witness the initial Na⁺ change or you aren't sure, consider the hyponatremia to be ***chronic***
- Guidelines for the correction rates of hyponatremia have become increasingly conservative over the past 2 decades (from 12 mEq/L to 6-8 mEq/L over 24 hours), though could be changing again

Managing overcorrection of hyponatremia: Who is at risk?

Risk factors for **Osmotic Demyelination Syndrome** include:

- $P_{Na} < 105 \text{ mmol/L}$
- Hypokalemia
- Malnutrition
- Alcohol use disorder
- Liver disease



Managing overcorrection of hyponatremia: Who is at risk?

- Risk factors for overly rapid correction (due to water diuresis)
 - Treatment of low dietary solute intake
 - Treatment of hypovolemia
 - Treatment of cortisol deficiency
 - Resolution of transient SIADH
 - Medications:
 - Discontinuation of thiazides
 - Initiation of vasopressin antagonists (vaptans)



What about correcting *hypernatremia*?

Is the rate of correction of hypernatremia associated with clinical outcomes?

CJASN
Clinical Journal of American Society of Nephrology

Methods and Cohort



Data from Medical Information
Mart for Intensive Care-III
(MIMIC-III)



Na >155
mmol/L



On admission
N = 122



Hospital-acquired
N = 327



Rapid correction
(>0.5 mmol/L/hr)

VS



Slow correction
(≤0.5 mmol/L/hr)

Findings



Rapid Correction



30 day mortality
25%

Slow Correction



30 day mortality
28%

NS
P=0.80



30 day mortality
44%

NS
P=0.50

30 day mortality
40%



0

cases of cerebral edema, seizures or
alteration in consciousness attributable to
rapid hypernatremia correction

Conclusions Rapid correction of hypernatremia was not associated with a higher risk for mortality, seizures, alteration of consciousness and/or cerebral edema in critically ill adults with either admission or hospital-acquired hypernatremia.

Kinsuk Chauhan, Pattharawin Pattharanitima, Niralee Patel, Aine Duffy, et al. **Rate of Correction of Hypernatremia and Health Outcomes in Critically Ill Patients.** CJASN doi: 10.2215/CJN.10640918. Visual Abstract by Michelle Lim, MBChB

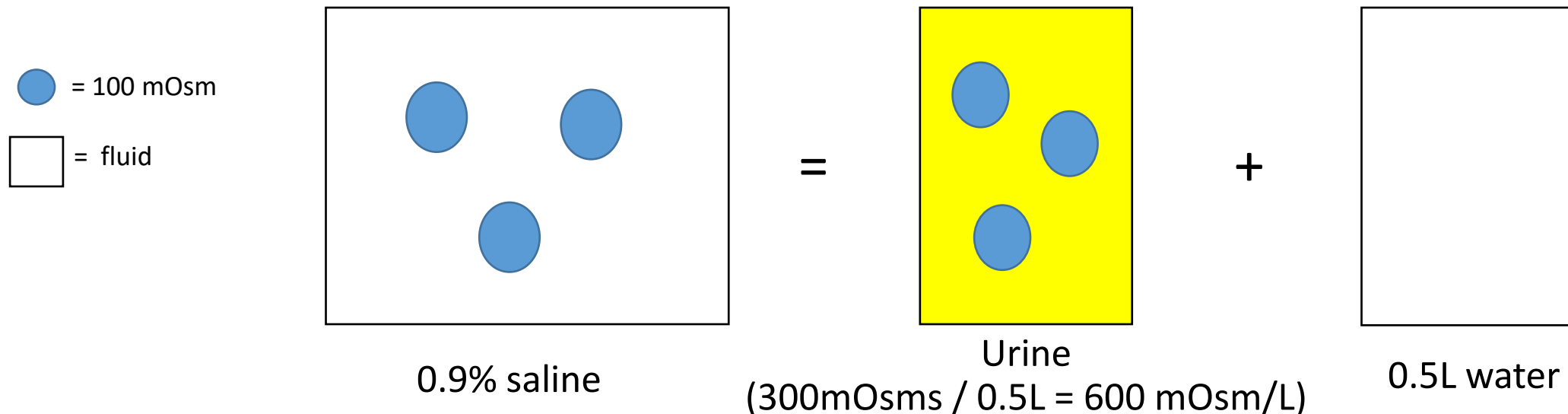
Back to our case

After applying the 4-step approach, a urine osmolality is measured at 600 mOsm/L, urine sodium is 22 mEq/L and your exam does not clearly determine if he is hypovolemic or euvolemic. You elect to give him another 2L of 0.9% saline and the serum Na^+ decreases once again to 113 mEq/L.

Why did 0.9% saline make the Na^+ worse?

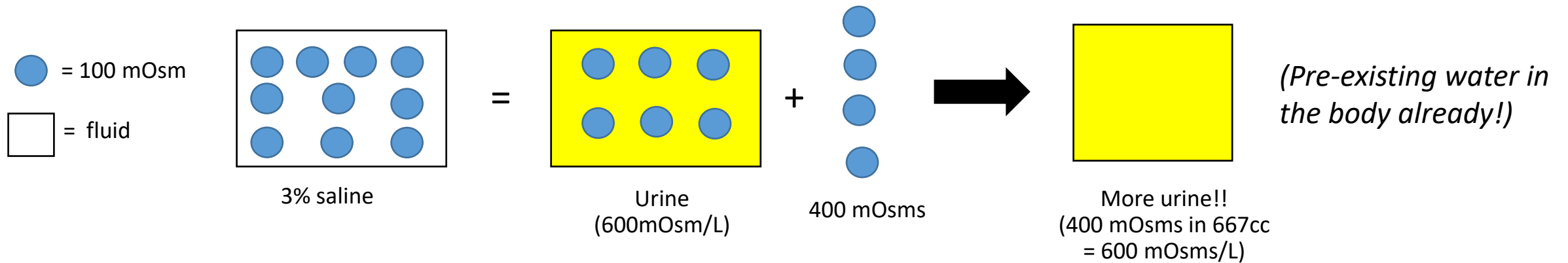
Here's the situation again:

- 1) ADH is on and the patient is euvolemic
- 2) Urine osmolality is 600 mOsm/L
- 3) 0.9% saline = ~ 300 mOsm/L ($2 \times \text{Na}^+$ of 154 mEq/L)



Why does 3% saline or salt tabs help correct hyponatremia?

- 3% saline ~ 1000 mOsm/L

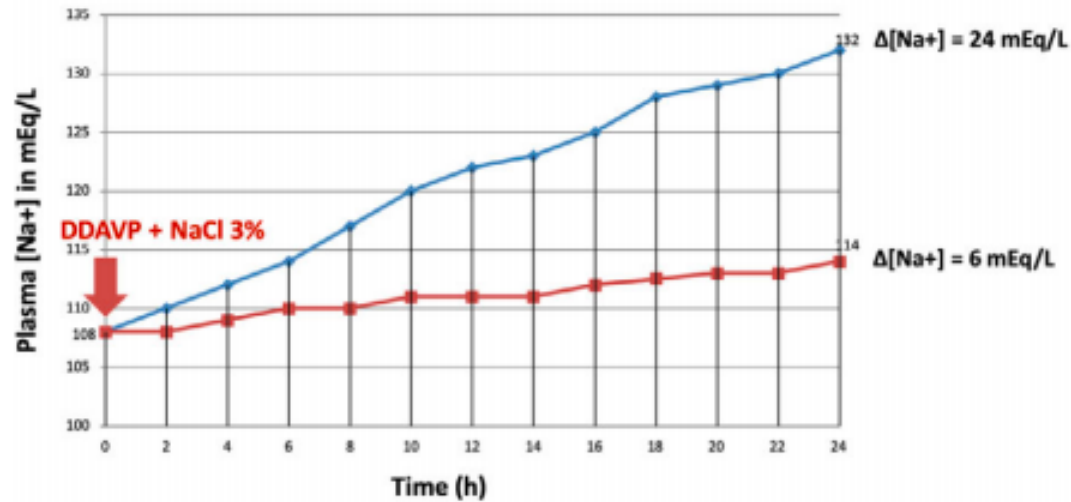


- NaCl tabs (3g TID) = 1L of 0.9% saline without the 1L of fluid
- Protein supplementation will also provide solute without extra fluid

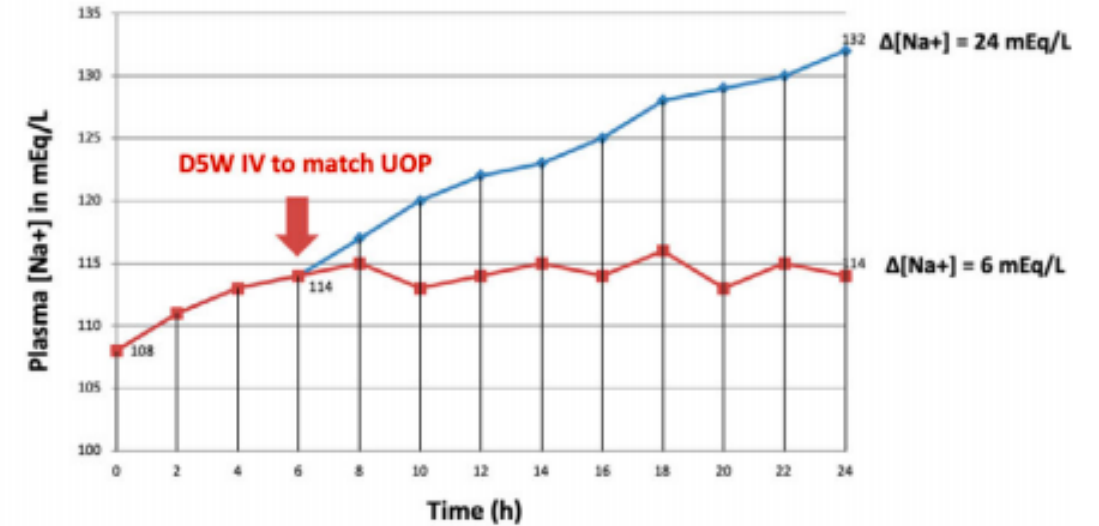
Treatment strategies in hyponatremia

Phys Reports 2019

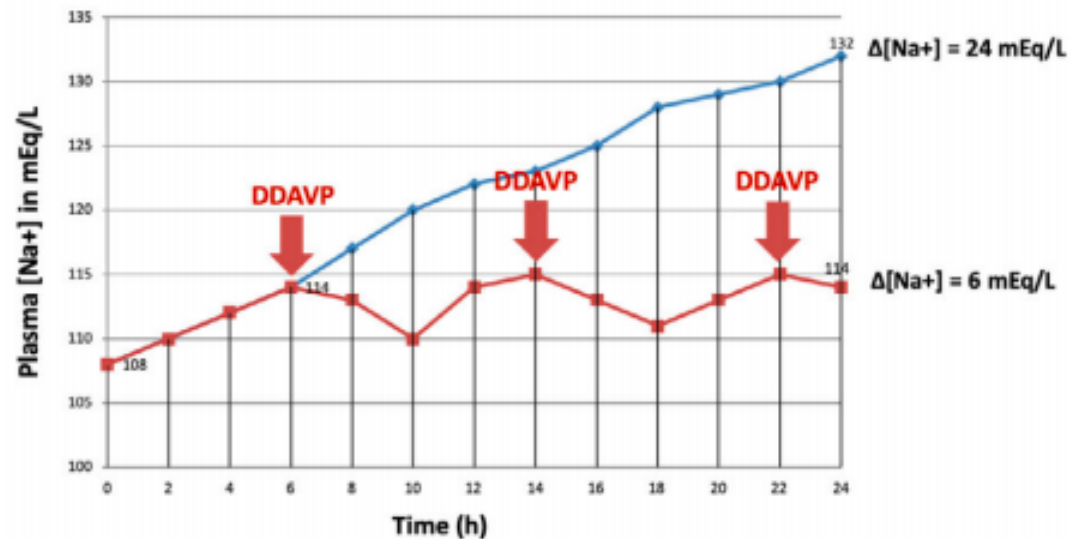
A Proactive Strategy



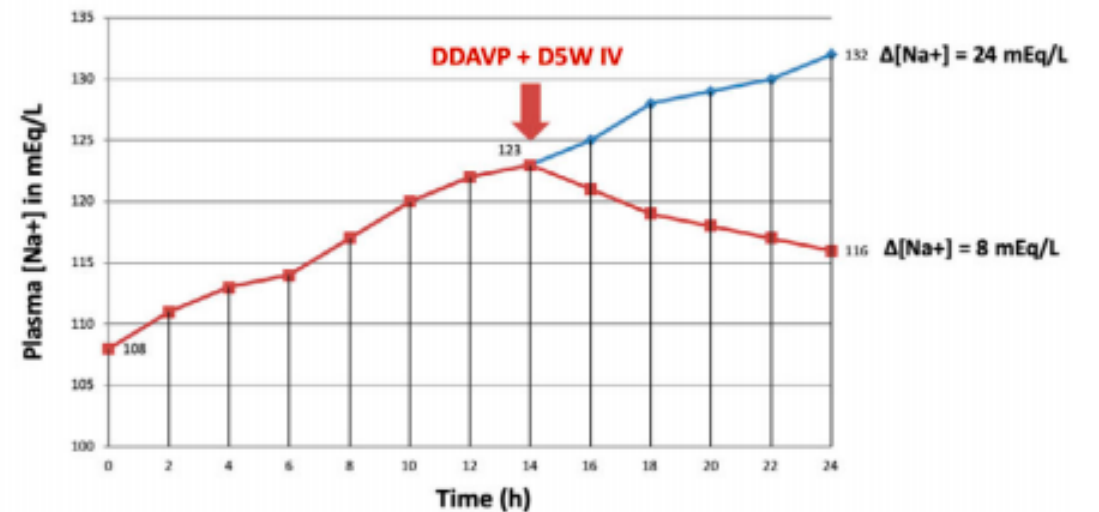
C Reactive Strategy



B Reactive Strategy



D Rescue Strategy



Take-home points

- Renal physiology is your friend! Understanding **WHY** electrolyte abnormalities occur in the clinical setting (and how they are managed) is rooted in physiology.
- Hyperkalemia – Calcium gluconate promotes membrane stabilization and should be used FIRST, but does not resolve hyperK⁺. Remember your physiology when treating.
- Hyponatremia – Troubleshoot changes in water (serum Na⁺) and consider the 4-step approach to help determine next steps. Rapid correction or rapid initial development of dysnatremias are acutely dangerous. Chronic stability is not.

After this talk, you will be able to...

- ...appropriately triage electrolyte abnormalities
- ...apply the physiology of K^+ transport to the treatment of hyperkalemia
- ...utilize an organized approach to the diagnosis and treatment of hyponatremia

