RENAL METABOLIC DISORDERS
Tina Y. Ko, DO

POMA District VIII Winter Seminar
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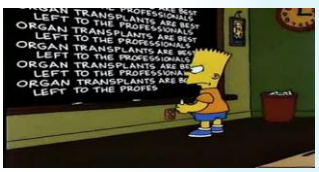
- I have no disclosures



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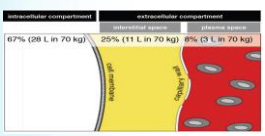
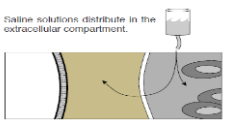
CRYSTALLOD SOLUTIONS

- Used to increase the intravascular space
- Isotonic crystalloids stay in the extracellular compartment and distribute between the interstitial and intravascular compartments– for every one liter of NS, 250 ml remain in the intravascular compartment





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Content of human plasma, 0.9% saline, Lactated Ringer's, and Plasma-Lyte A

			Balanced crystalloids	
	Human plasma	0.9% saline	Lactated Ringer's	Plasma-Lyte A©
Sodium (mEq/L)	135–145	154	130	140
Potassium (mEq/L)	4.5–5.0	0	4	5
Chloride (mEq/L)	94–111	154	109	98
Calcium (mEq/L)	2.2–2.6	0	2.7	0
Magnesium (mEq/L)	0.8–1.0	0	0	3
Bicarbonate (mEq/L)	23–27	0	0	0
Lactate (mEq/L)	1–2	0	28	0
Acetate (mEq/L)	0	0	0	27
Gluconate (mEq/L)	0	0	0	23

Figure 1.
Table 1 from Self WH, Semler MW, Wanderer JP, et al. Saline versus balanced crystalloids for intravenous fluid therapy in the emergency department: study protocol for a cluster-randomized, multiple-crossover trial. *Trials*. 2017;18:178. doi:10.1186/s13063-017-1923-6.

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Normal saline-induced hyperchloremic metabolic acidosis

- When you give your patient NS (**h**yperchloremic solution) you are increasing the chloride significantly and it is the chloride anion that is causing the acidosis
- When you give NaCl it combines with water:
  - NaCl + H2O → HCl + NaOH.
- The strong acid (HCl) and the strong base (NaOH) should cancel each other out with no effect on pH
- HOWEVER because the normal concentrations of Na and Cl in the serum are 140 and 100 respectively, adding saline (154 meq Na and 154 meq Cl) cause the chloride to increase more than the sodium.
- This increase in chloride tips the acid-base balance toward HCl thus causing a non anion gap metabolic acidosis

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H., Jonathan P. Wanderer, M.D., Jesse M. Ehrenfeld, M.D., M.P.H., Li Wang, M.S., Daniel W. Byrne, M.S., Joanna L. Stollings, Pharm.D., Avinash B. Kumar, M.D., Christopher G. Hughes, M.D., Antonio Hernandez, M.D., Oscar D. Guillamondegui, M.D., M.P.H., Addison K. May, M.D., Liza Weavind, M.B., B.Ch., Jonathan D. Casey, M.D., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SMART Investigators and the Pragmatic Critical Care Research Group*

N Engl J Med 2018;378:829-39.
DOI: 10.1056/NEJMoa1711584

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SMART (Isotonic Solutions and Major Adverse Renal Events Trial)

- Randomized multiple-crossover trial in 5 ICU at an academic center
- Assigned 15,802 adults to either normal saline or balanced crystalloids (lactated ringer's solution or plasma-lyte A).
- Primary outcomes – major adverse kidney event within 30 days, a composite of death from any cause, new renal replacement therapy, or persistence of renal dysfunction which were all censored at hospital discharge or 30 days, whichever occurred first
- 7942 pt in the balanced crystalloids group, 1139 (14.3%) had a major adverse kidney event as compared with 1211 of 7860 patients (15.4%) in the saline group (marginal odds ratio, 0.91; 95% confidence interval; p= 0.04).
- In hospital mortality at 30 days was 10.3% in the balanced-crystalloids and 11.1% in the saline group (p = 0.006).
- Incidence of new RRT was 2.5% and 2.9% respectively (p = 0.08)
- Incidence of persistent renal dysfunction was 6.4% and 6.6% (p = 0.6)
- CONCLUSIONS:
  - Among critically ill adults the use of balanced crystalloids for intravenous fluid administration resulted in lower rate of the composite outcome of death for any cause, new RRT, or persistent renal dysfunction that use of saline

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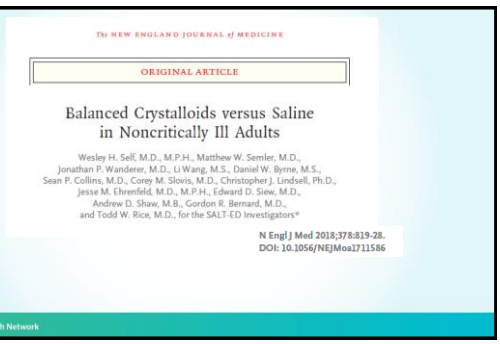

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Noncritically Ill Adults

Wesley H. Self, M.D., M.P.H., Matthew W. Semler, M.D., Jonathan P. Wanderer, M.D., Li Wang, M.S., Daniel W. Byrne, M.S., Sean P. Collins, M.D., Corey M. Slovis, M.D., Christopher J. Lindsell, Ph.D., Jesse M. Ehrenfeld, M.D., M.P.H., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SALT-ED Investigators*

N Engl J Med 2018;378:819-28.
DOI: 10.1056/NEJMoa1711586

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SMART-EM trial

- Single center, pragmatic, multiple-crossover trial comparing balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A) with saline among adults in the emergency department and were subsequently hospitalized outside an ICU. The type of crystalloid that was administered in the emergency department was assigned to each patient on the basis of calendar month, with the entire emergency department crossing over between balanced crystalloids and saline monthly during the 16-month trial.
- The primary outcome was hospital-free days (days alive after discharge before day 28). Secondary outcomes included major adverse kidney events within 30 days — a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction — all censored at hospital discharge or 30 days, whichever occurred first.
- A total of 13,347 patients were enrolled. Median crystalloid volume administered in the emergency department of 1079 ml and 88.3% of the patients exclusively receiving the assigned crystalloid.
- The number of hospital-free days did not differ between the balanced-crystalloids and saline groups (median, 25 days in each group; adjusted odds ratio with balanced crystalloids, 0.98; 95% confidence interval; P=0.41).
- Balanced crystalloids resulted in a lower incidence of major adverse kidney events within 30 days than saline (4.7% vs. 5.6%; adjusted odds ratio, 0.82; 95% CI: P=0.01).
- CONCLUSIONS
- Among noncritically ill adults treated with intravenous fluids in the emergency department, there was no difference in hospital-free days between treatment with balanced crystalloids and treatment with saline.

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So, does the type of fluid matter?

- The main concern with isotonic saline is felt to be related to the high Chloride concentration relative to the plasma Chloride concentration. The excessive Chloride concentration:
  - May decrease renal perfusion by causing renal vasoconstriction and reductions in renal blood flow and thus leading to acute kidney injury.
  - It also causes a dilutional non-anion-gap metabolic acidosis and may also cause inflammation, hypertension, all of which have the potential to increase mortality.
- What is the relative precautions of balanced crystalloids?
  - The relative hypotonicity of the balanced crystalloids (276 mOsm) may increase intracranial pressure so need to be cautious when treating traumatic brain injury and in patients who are hyperkalemic, hypercalcemic, liver failure
- Recent data suggest that the use of balanced solutions was associated with a lower rate of major adverse renal events and death in hypovolemic patients as compared with isotonic saline. This difference, while meager, may still warrant its use since the cost difference between the two solutions is minimal. The effects on morbidity and mortality may be more important in septic patients in which the use of large volume resuscitation is often required.
- The case for balanced crystalloids is growing BUT….

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DYSNATREMIAS – hyponatremia and hypernatremia

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HYPONATREMIA

- Low serum sodium < 136 mEq
  - *Increased free water retention*
  - Urinary sodium loss
- Signs and symptoms:
  - Neurologic – nausea, vomiting, weakness, confusion, forgetfulness, disorientation, obtundation, noncardiogenic pulmonary edema, headache, falls, seizure, coma, decorticate posturing, dysgeusia

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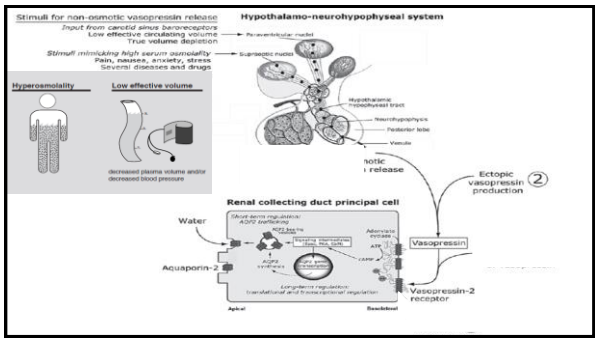

ADH release

- *Physiologic release*:
  - **Increased serum osm** where the increased ADH leads to retention of free water to "hydrate" the patient (thereby producing a CONCENTRATED urine)
  - **Decreased BP/perfusion** where the increased ADH leads to preservation of the intravascular volume and some degree of vasoconstriction

- *NON-physiologic release*:
  - **Increased hypothalamic production of ADH**:
    - Neuro-psychiatric d/o
      - Infections like meningitis, encephilitis
      - SAH, SDH, CVA
      - Traumatic brain injury
    - Drugs
    - Lung disease
      - PNA
      - TB
      - Lung abscess, empyema
    - Perioperative associated with the stress response to pain
  - **Ectopic (non-hypothalamus) production of ADH:**
    - CA like small cell, bronchogenic
    - Hodgkin's, leukemia
    - Pulmonary TB
  - **Exogenous administration of ADH:**
    - Vasopressin, desmopressin
    - oxytocin

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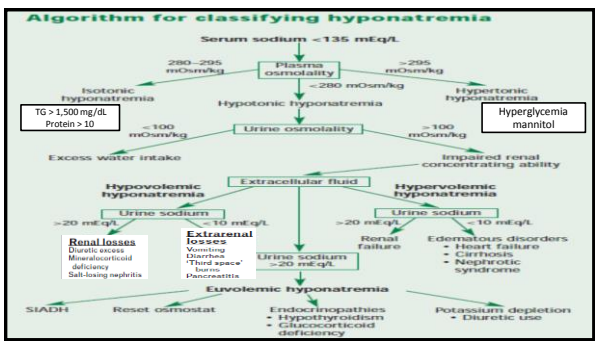

Evaluation of hyponatremia

- Step 1: Is renal failure present? What is the serum osm, urine osm, urine sodium.
- Step 2: Are there signs of ECFV depletion?
  - History of nausea, vomiting or other source of depletion with water ingestion. Is the urine sodium low (<20)?

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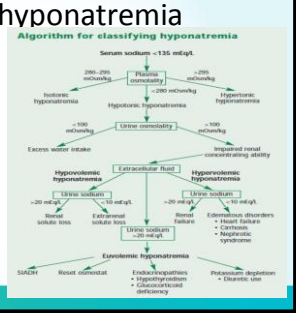
Evaluation of hyponatremia

- Step 3: Are there signs of ECFV overload?
  - Careful history and physical: signs of CHF with increased JVP, rales, effusions, ascites, S3, edema
  - Cirrhosis with edema and ascites
  - Nephrotic syndrome: check urine protein
  - Is urine sodium low? Due to decreased effective circulating volume leading to increased sodium retention by the kidney



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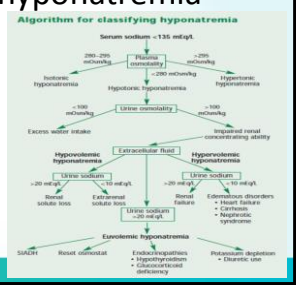
Evaluation of hyponatremia

- Step 4: Is the patient taking thiazide diuretics?
- Step 5: Is there a condition or drug capable of producing SIADH?
- Step 6: Is there evidence of thyroid or adrenal insufficiency?
- Step 7: Elderly/poor solute intake? Leads to lower medullary solute concentration gradient and less ability to concentrate the urine.
  - 24 hr total solute excretion < 600 mOsm/24 hr



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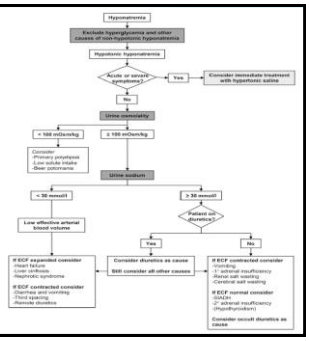
Diagnostic Algorithm for hyponatremia
European guideline



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DIAGNOSIS SIADH

Essential features

Decreased effective osmolality (<275 mOsm/kg of water)
Urinary osmolality >100 mOsm/kg of water during hypotonicity
Clinical euvolemia
No clinical signs of volume depletion of extracellular fluid
No orthostasis, tachycardia, decreased skin turgor, or dry mucous membranes
No clinical signs of excessive volume of extracellular fluid
No edema or ascites
Urinary sodium >40 mmol/liter with normal dietary salt intake
Normal thyroid and adrenal function
No recent use of diuretic agents

Supplemental features

Plasma uric acid <4 mg/dl
Blood urea nitrogen <10 mg/dl
Fractional sodium excretion >1%; fractional urea excretion >55%
Failure to correct hyponatremia after 0.9% saline infusion
Correction of hyponatremia through fluid restriction
Abnormal result on test of water load (<80% excretion of 20 ml of water per kilogram of body weight over a period of 4 hours), or inadequate urinary dilution (<100 mOsm/kg of water)
Elevated plasma AVP levels, despite the presence of hypotonicity and clinical euvolemia

? Feurea >12%
Copeptin (marker that is higher in hypo or hypervoemic hyponatermia than SIADH)

Table 1 Causes of the syndrome of inappropriate antidiuretic hormone secretion

Malignant diseases	Pulmonary disorders	Disorders of the central nervous system	Drugs	Other causes
Carcinoma	Infections	Infection	Drugs that stimulate release of AVP or enhance its action	Hereditary (gain-of-function mutations in the vasopressin V2 receptor)
Lung	Bacterial pneumonia	Encephalitis	Chlorpropramide	
Small-cell	Viral pneumonia	Meningitis	SSRIs	Transient or endurance exercise
Mesothelioma	Pulmonary abscess	Brain abscess	Tricyclic antidepressants	
Oropharynx	Tuberculosis	Rocky Mountain spotted fever	Clofibrate	General anesthesia
Gastrointestinal tract	Aspergillosis	AIDS	Carbamazepine	Nausea
Stomach	Asthma	Bleeding and masses	Vincristine	Pain
Duodenum	Cystic fibrosis	Subdural hematoma	Nicotine	Stress
Pancreas	Respiratory failure associated with positive-pressure breathing	Subarachnoid hemorrhage	Narcotics	
Genitourinary tract		Cerebrovascular accident	Antipsychotic drugs	
Ureter		Brain tumors	Ifosfamide	
Bladder		Head trauma	Cyclophosphamide	
Prostate		Hydrocephalus	Nonsteroidal antiinflammatory drugs	
Endometrium		Cavernous sinus thrombosis	(3,4-methylenedioxymeth amphetamine (MDMA ('ecstasy')	
Endocrine		Other	AVP analogues	
Thymoma		Multiple sclerosis	Desmopressin	
Lymphomas		Guillain–Barré syndrome	Oxytocin	
Sarcomas		Shy–Drager syndrome	Vasopressin	
Ewing's sarcoma		Delirium tremens		
		Acute intermittent porphyria		

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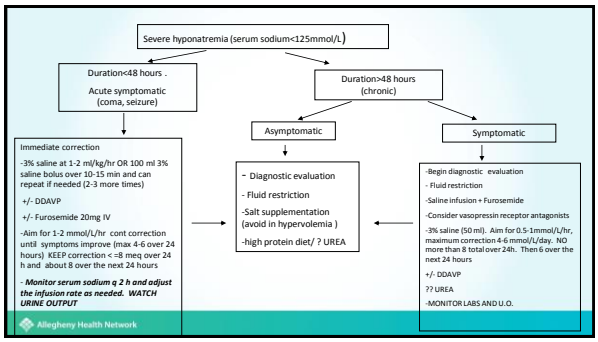

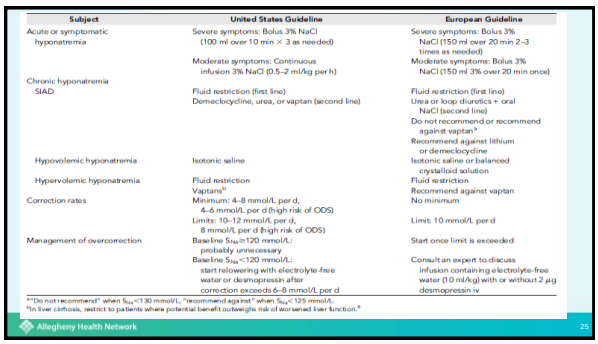

Subject	United States Guideline	European Guideline
Acute or symptomatic hyponatremia	Severe symptoms: Bolus 3% NaCl (100 ml over 10 min × 3 as needed) Moderate symptoms: Continuous infusion 3% NaCl (0.5–2 ml/kg per h)	Severe symptoms: Bolus 3% NaCl (150 ml over 20 min 2–3 times as needed) Moderate symptoms: Bolus 3% NaCl (150 ml 3% over 20 min once)
Chronic hyponatremia SIAD	Fluid restriction (first line) Demeclocycline, urea, or vaptan (second line)	Fluid restriction (first line) Urea or loop diuretics + oral NaCl (second line) Do not recommend or recommend against vaptan* Recommend against lithium or demeclocycline
Hypovolemic hyponatremia	Isotonic saline	Isotonic saline or balanced crystalloid solution
Hypervolemic hyponatremia	Fluid restriction Vaptans†	Fluid restriction Recommend against vaptan
Correction rates	Minimum: 4–8 mmol/L per d, 4–6 mmol/L per d (high risk of ODS) Limits: 10–12 mmol/L per d, 8 mmol/L per d (high risk of ODS)	No minimum Limit: 10 mmol/L per d
Management of overcorrection	Baseline S_{Na}≥120 mmol/L: probably unnecessary Baseline S_{Na}<120 mmol/L: start relowering with electrolyte-free water or desmopressin after correction exceeds 6–8 mmol/L per d	Start once limit is exceeded Consult an expert to discuss infusion containing electrolyte-free water (10 ml/kg) with or without 2 μg desmopressin iv

**"Do not recommend" when S_{Na}<130 mmol/L, "recommend against" when S_{Na}<125 mmol/L.
†In liver cirrhosis, restrict to patients where potential benefit outweighs risk of worsened liver function.*

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Treatment of symptomatic non-emergent hyponatremia

- Calculate the amount of sodium needed to bring the serum sodium up by only 4 to 6 mEq/ liter in a 24 h period (usually enough to reverse symptoms without over shoot):
  - Na deficit: 0.6 x wt (in kg) (desired sNa – present sNa)
- Example: a 60kg woman (use 0.5 instead of 0.6) with a serum sodium of 110 and lethargy and no evidence of volume depletion or CHF**; want to correct no more than 6 mEq/l in first 24 hr. Correction to 116.
  - 0.5 x 60 x (116 – 110) = 180 mEq
  - 1 liter of 3% saline contains 513 mEq salt; therefore 350 ml of 3% saline over next 24 hr. Order would read 3% saline at 15 ml/hr for 24 hr with frequent repeat serum sodium levels
- ** patients with volume depletion will correct with normal saline as soon as volume stimulation of ADH is shut off
- **Patients with active CHF and severe symptomatic hyponatremia are better treated with AVP antagonists

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Hyponatremia correction equations:

Source	Step 1	Step 2	Example of Rate (ml/hr)
Traditional[2]	Na required = TBW × ([Na]$_d$ − [Na]$_s$)	Volume (liter) = $\frac{\text{Na required (mmol)}}{513\ \text{mmol/liter}}$	82
Adrogué and Madias[3]	$\Delta[Na]_s$ (with 1 liter) = $\frac{[Na]_{inf} - [Na]_s}{TBW + 1}$	Volume (liter) = $\frac{\text{Desired } \Delta[Na]_s}{\Delta[Na]_s \text{(with 1 liter)}}$	107
Barsoum and Levine[39]	$\Delta[Na]_s = \frac{(V_{inf})([Na]_{inf} - (V_u)([E]_{urine} - (\Delta V)[Na]_s}{TBW + \Delta V}$	Volume (liter) = $\frac{\text{Desired } \Delta[Na]_s}{\Delta[Na]_s \text{ (with 1 liter)}}$	107
Nguyen and Kurtz[40]		Volume (liter) = $\frac{TBW \times \left(1 - \frac{[Na]_s + 23.8}{[Na]_d + 23.8}\right) + V_{input} - \frac{[E]_{input} \times V_{input}}{[E]_{urine}}}{\frac{[E]_{inf}}{[E]_{urine}} - 1}$	90
Janicic and Verbalis[9]		Rate (ml/hr) is the goal rate of [Na]$_s$ rise (mmol/liter/hr) per kg of body weight	70

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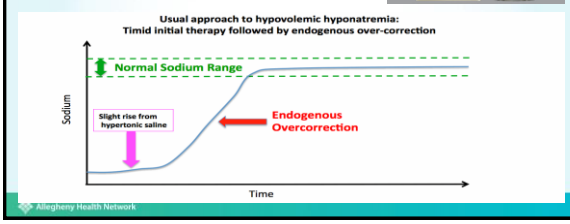
Why DDAVP????



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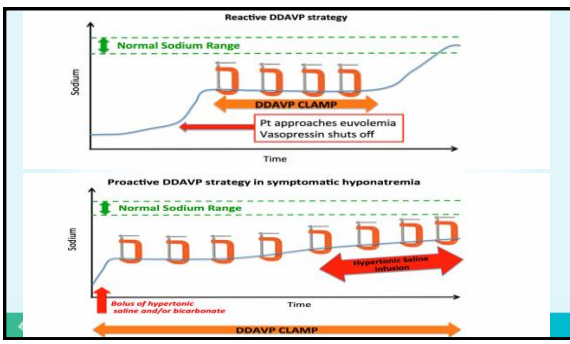

PROACTIVE or responsive DDAVP?

- Patients with reversible cause of hyponatremia who are likely to develop a water diuresis
- Pt at risk for osmotic demyelination:
  - Very low serum sodium at the start (≤105 mmol/L)
  - Concomitant hypokalemia
  - Cirrhosis
  - Malnutrition
  - Advanced liver disease
- DDAVP (with the 3% at 15-30 ml/hour) 1-2 mcg of desmopressin (DDAVP) IV or SQ every 6-8 hours -- "DDAVP clamp" it prevents the body from autocorrecting the sodium and allows for a well-regulated, slow rise in sodium. Also need to restrict free water intake

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Who should not get DDAVP?

- If the cause of hypotnatremia is UNLIKELY to be rapidly reversible (those who are unlikely to develop a water diuresis) such as:
  - Edematous pt (Heart failure or cirrhosis). Desmopressin (DDAVP) may increase the amount of hypertonic saline required to achieve the desired increase in serum sodium concentration and the likelihood of overly rapid correction is low in these patients. In such patients, it may be better to give FUROSEMIDE with the hypertonic saline to prevent hypervolemia
- In patients with recurrent hyponatremia that is caused by a chronic SIADH secretion.

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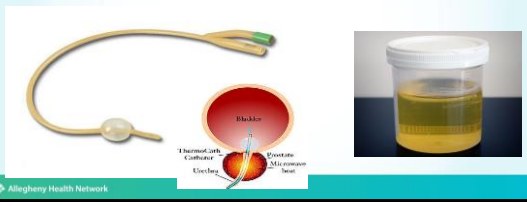
When treating severe hyponatremia don't forget!!!



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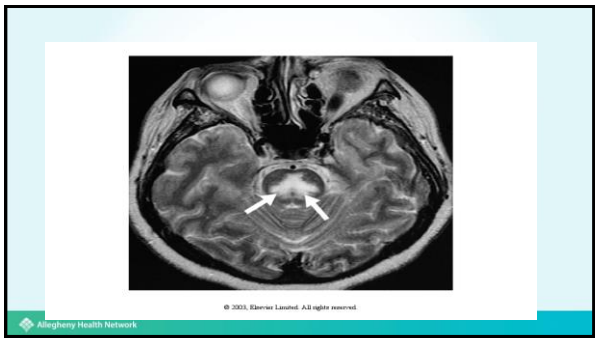
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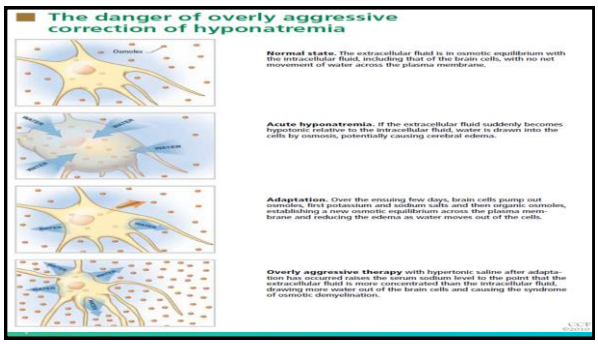
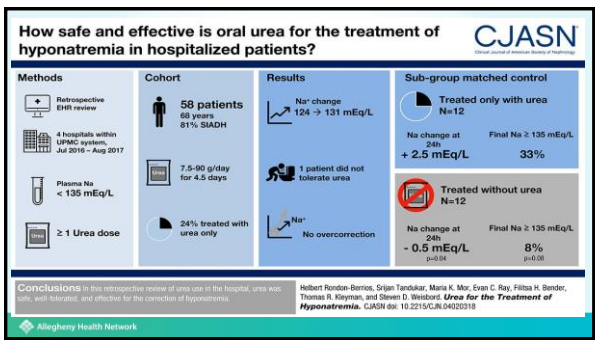

The danger of overly aggressive correction of hyponatremia
Normal state. The extracellular fluid is in osmotic equilibrium with the intracellular fluid, including that of the brain cells, with no net movement of water across the plasma membrane.
Acute hyponatremia. If the extracellular fluid suddenly becomes hypotonic relative to the intracellular fluid, water is drawn into the cells by osmosis, potentially causing cerebral edema.
Adaptation. Over the ensuing few days, brain cells pump out osmoles, first potassium and sodium salts and then organic osmoles, establishing a new osmotic equilibrium across the plasma membrane and reducing the edema as water moves out of the cells.
Overly aggressive therapy with hypertonic saline after adaptation has occurred raises the serum sodium level to the point that the extracellular fluid is more concentrated than the intracellular fluid, drawing more water out of the brain cells and causing the syndrome of osmotic demyelination.


How safe and effective is oral urea for the treatment of hyponatremia in hospitalized patients?
CJASN
Methods
Retrospective EHR review
4 hospitals within UPMC system, Jul 2016 – Aug 2017
Plasma Na < 135 mEq/L
≥ 1 Urea dose
Cohort
58 patients
68 years
81% SIADH
7.5-90 g/day for 4.5 days
24% treated with urea only
Results
Na+ change 124 → 131 mEq/L
1 patient did not tolerate urea
Na+ No overcorrection
Sub-group matched control
Treated only with urea N=12
Na change at 24h + 2.5 mEq/L
Final Na ≥ 135 mEq/L 33%
Treated without urea N=12
Na change at 24h - 0.5 mEq/L p=0.04
Final Na ≥ 135 mEq/L 8% p=0.08
Conclusions In this retrospective review of urea use in the hospital, urea was safe, well-tolerated, and effective for the correction of hyponatremia.
Helbert Rondon-Berrios, Srijan Tandukar, Maria K. Mor, Evan C. Ray, Filitsa H. Bender, Thomas R. Kleyman, and Steven D. Weisbord. Urea for the Treatment of Hyponatremia. CJASN doi: 10.2215/CJN.04020318
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Efficacy and Tolerance of Urea Compared with Vaptans for Long-Term Treatment of Patients with SIADH

Alain Sougarat,*† Michel Coffernils,* Bruno Couturier,‡ Fabrice Gankam-Kengne,† and Guy Decaux†

Clin J Am Soc Nephrol 7: 742–747, 2012.

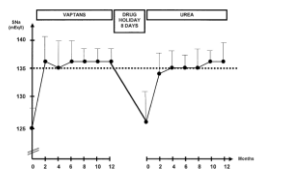

Figure 1. | Serum sodium (PNa) values during treatment with vaptans and urea. Each point is the mean value of serum sodium for the 12 patients (mean ± SD).

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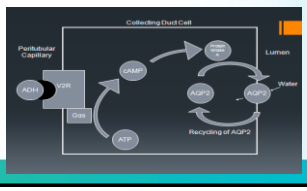
Table 3. Vasopressin-Receptor Antagonists.*

Drug	Dose of Drug	Vasopressin Receptor	Route of Administration	Urinary Volume	Urinary Osmolality
Conivaptan (Vaprisol, Astellas Pharma)†	20–40 mg daily	V_{1A} and V_2	Intravenous	Increased	Decreased
Tolvaptan (Otsuka)	15–60 mg daily	V_2	Oral	Increased	Decreased
Lixivaptan (CardioKine)	100–200 mg	V_2	Oral	Increased	Decreased
Satavaptan (Sanofi-Aventis)	12.5–50 mg	V_2	Oral	Increased	Decreased



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Appropriate uses for VAPTANS

- Hyponatremia from syndrome of inappropriate antidiuretic hormone secretion
- Malignancy, especially small cell lung cancers
- Cirrhosis
- Pulmonary disorders
- Medications, when chronic use is required
- Nausea or pain, when chronic and intractable
- Idiopathic
- Hyponatremia from heart failure
- Non-severe hyponatremia
- Hyponatremia that is not amenable to correction with fluid restriction or other therapies

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HYPERNATREMIA

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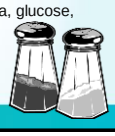
Hypernatremia

- Reason for water loss or sodium gain:
  - Increased insensible losses (fever, tachypnea); sweat losses; diarrhea; renal water loss (>3L/24hr); administration of hypertonic sodium
- Reason for inadequate water intake:
  - Impaired thirst; altered mental status; primary neurological disorder (stroke, infection, tumor); no access to water
- Is polyuria present:
  - Urine Osm >300 mOsm/L (osmotic diuresis): urea, glucose, mannitol, saline
  - Urine Osm <150 mOsm/L (diabetes insipidus):
    - Response to vasopressin:
      - No response: nephrogenic DI
      - Urine Osm increases to >300 mOsm/L: central DI



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Hypernatremia: treatment

- **<u>If volume depleted/ hypotensive, begin correction with isotonic saline</u>**
- Aim to correct the sodium by about 0.5 to 1 mEq/L/hr
- slowly correct over 36 to 72 hrs to avoid cerebral edema
- Calculate the water deficit:
  - TBW x (measured Na – desired Na)/ desired Na
  - Example: a 70kg man has a serum sodium of 170 and you desire to correct to 160 over the next 12 hrs:
  - deficit= 0.6 x 70 x (170-160)/160 = 2.6L
  - Add to this any ongoing insensible (0.5 to 1L/day depending on fever) or urinary or GI losses

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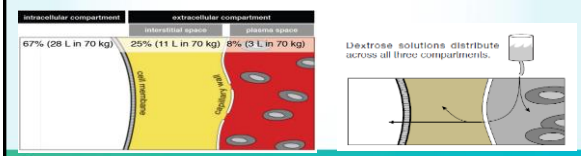
DEXTROSE and WATER SOLUTIONS

- D5 W, will deliver water according to the natural distribution of body water
- If it is D5 normal saline it will distribute according to normal saline
- 2/3 of the fluid moves intracellularly
- 8% (or 80 ml of every 1000ml) remains in the intravascular space



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POTASSIUM – hyperkalemia and hypokalemia

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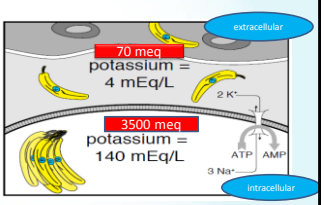
POTASSIUM HOMEOSTASIS

- Total content 3500 mmol
- 98% INTRACELLULAR
- 2% in the extracelluar compartment
- Average diet contain about 100 mmol potassium
- 90-95% is renal excreted



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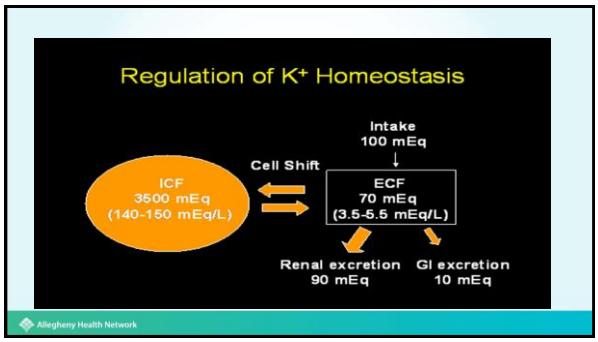
Regulation of K+ Homeostasis
Intake
100 mEq
Cell Shift
ICF
3500 mEq
(140-150 mEq/L)
ECF
70 mEq
(3.5-5.5 mEq/L)
Renal excretion
90 mEq
GI excretion
10 mEq
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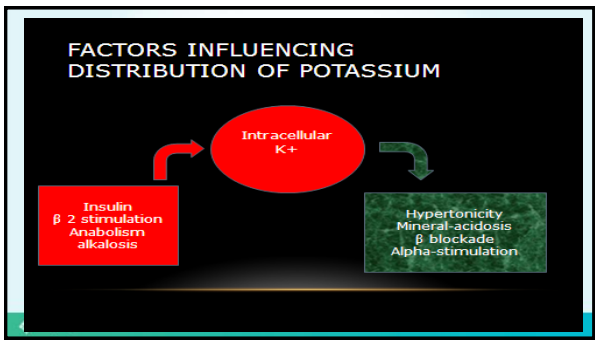
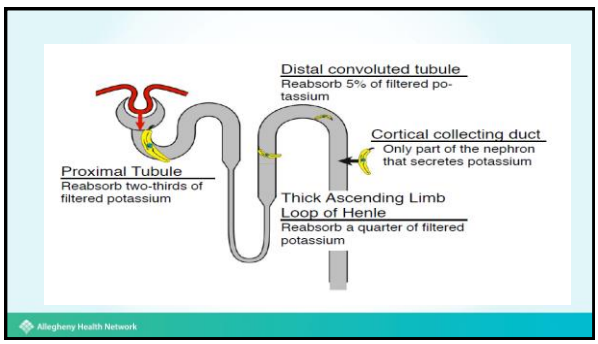

FACTORS INFLUENCING
DISTRIBUTION OF POTASSIUM
Intracellular
K+
Insulin
β 2 stimulation
Anabolism
alkalosis
Hypertonicity
Mineral-acidosis
β blockade
Alpha-stimulation


Distal convoluted tubule
Reabsorb 5% of filtered po-
tassium
Cortical collecting duct
Only part of the nephron
that secretes potassium
Proximal Tubule
Reabsorb two-thirds of
filtered potassium
Thick Ascending Limb
Loop of Henle
Reabsorb a quarter of filtered
potassium
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Determinants of CCD K^+ Secretion

- Mineralocorticoid activity
- Distal delivery of Na^+
- Luminal flow rate

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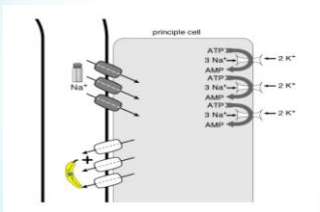
Mineralocorticoid activity



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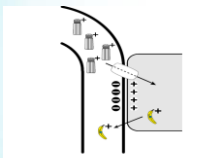
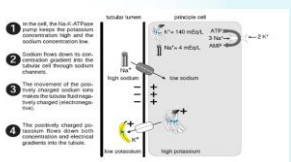
Distal sodium delivery



Increased delivery of sodium increases sodium resorption to enhance the electrical gradient.



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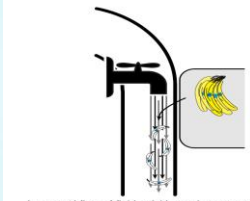
Luminal flow rate



Increased flow of fluid quickly washes away secreted potassium to maintain the concentration gradient.

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HYPERKALEMIA

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HYPERKALEMIA

- Exact incidence and prevalence of hyperkalemia is unknown
  - 1-10% of hospitalized patients
  - Up to 11% of patients on ACE inhibitors at VA outpatient clinic
  - As high as 40-50% in CKD patients
  - 1-24% in heart failure patients
- The most common predisposing factor is CKD. Other co-morbid conditions:
  - Heart failure
  - DM2
  - Advanced age
  - Use of RAAS inhibitors

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Causes of hyperkalemia

- Pseudohyperkalemia
- Excess intake
- Cell shifts
- Impaired renal excretion

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Pseudohyperkalemia

- Hemolysis during Venopuncture
- Excessive blood-sample clotting
- Hereditary spherocytosis
- Increased WBC and platelet count
- Familial hyperkalemia

- Suspect by history OR can find a lower potassium concentration in plasma versus serum:
  - ***Serum*** is made up of non-clotting proteins, glucose, nutrients, electrolytes, hormones, antigens, antibodies and other particles.
  - ***plasma*** components are same as that of serum, except for fibrinogens and clotting factors that are absent in serum.
  - serum = plasma after removal of clotting factors'
  - Potassium is released from leukocytes and platelets when a blood sample is allowed to clot in vitro…. Usually the ***serum*** potassium is about ***0.1-0.4 meq/L > than*** measured in the ***plasma***, in which the clotting is prevented by drawing the blood into a heparinized tube….

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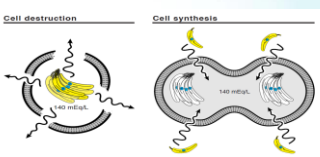
CELL SHIFTS

- Cell injury
  - Rhabdomyolysis
  - Tumor lysis
  - Massive hemolysis
  - Ischemia
- Toxins/Drugs:
  - Digoxin
  - Succinylcholine
- DKA and NKHS



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Impaired renal excretion

- Primary decrease in mineralocorticoid activity:
  - NSAIDS
  - Beta blockers
  - Cyclosporine and tacrolimus
  - Ace inhibitors and ARBs
  - Ketoconazole
  - Spironolactone
- Primary decrease in distal sodium delivery:
  - Oliguric AKI
  - Acute GN
- Abnormal cortical collecting duct:
  - Drugs
  - Tubulointerstitial nephritis
  - Urinary obstruction

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WHY is hyperkalemia important?

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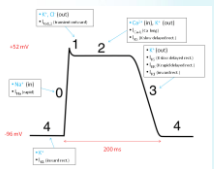
Manifestations of hyperkalemia

- Ascending muscle weakness
- Flaccid Paralysis
- Cardiac conduction abnormalities:
  - Right and left BBB
  - bifascicular block
  - Advanced AV block
- Cardiac arrhythmias:
  - Sinus bradycardia
  - Sinus arrest
  - Slow idioventricular rhythms
  - Ventricular tachycardia and fibrillation
  - ***Asystole***
- EKG changes



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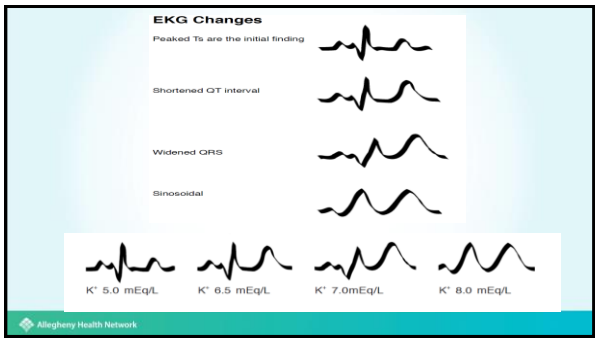
EKG Changes
Peaked Ts are the initial finding
Shortened QT interval
Widened QRS
Sinosoidal
K+ 5.0 mEq/L
K+ 6.5 mEq/L
K+ 7.0mEq/L
K+ 8.0 mEq/L
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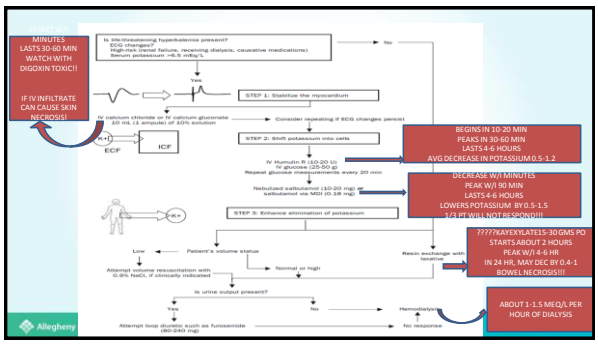
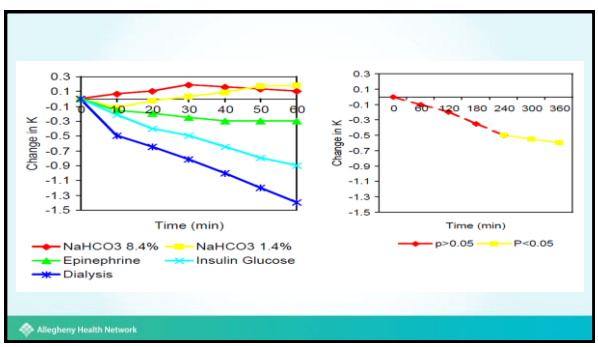

MINUTES
LASTS 30-60 MIN
WATCH WITH DIGOXIN TOXIC!!
IF IV INFILTRATE CAN CAUSE SKIN NECROSIS!
BEGINS IN 10-20 MIN
PEAKS IN 30-60 MIN
LASTS 4-6 HOURS
AVG DECREASE IN POTASSIUM 0.5-1.2
DECREASE W/I MINUTES
PEAK W/I 90 MIN
LASTS 4-6 HOURS
LOWERS POTASSIUM BY 0.5-1.5
1/3 PT WILL NOT RESPOND!!!
?????KAYEXYLATE15-30 GMS PO
STARTS ABOUT 2 HOURS
PEAK W/I 4-6 HR
IN 24 HR, MAY DEC BY 0.4-1
BOWEL NECROSIS!!!
ABOUT 1-1.5 MEQ/L PER HOUR OF DIALYSIS
STEP 1: Stabilize the myocardium
STEP 2: Shift potassium into cells
STEP 3: Enhance elimination of potassium
ECF
ICF
Allegheny


Change in K
Time (min)
NaHCO3 8.4%
NaHCO3 1.4%
Epinephrine
Insulin Glucose
Dialysis
p>0.05
P<0.05
Allegheny Health Network

HOWEVER……..

- 60% of patients with serum potassium of >6 meq/L did not have any EKG changes!! Acker CG, Johnson JP, Palevsky PM: *Hyperkalemia in hospitalized patients: Causes, adequacy of treatment, and results of an attempt to improve physician compliance with published therapy guidelines*. Arch Intern Med 158: 917–924, 1998
- V fib occasionally may occur WITHOUT antecedent peaked T-waves or QRS prolongation
- Rare case reports of patients with normal EKG with K >9!! Himad K. Khattak MD, Shahram Khalid MD: *Recurrent life-threatening hyperkalemia without typical electrocardiographic changes*. Journal of Electrocardiology, 2014-01-01, Volume 47, Issue 1, Pages 95-97

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SO…….

- If there are EKG changes emergent therapy should be initiated.
- Should also consider emergent therapy with potassium >6.5 mEq/L even in the ABSENCE of EKG changes because of the significant risk of rapid development of such changes
- CLOSE monitoring key!!!!

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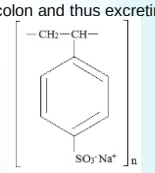
Kayexalate (sodium polystyrene sulfonate)

- Is a cation-exchange resin that was approved in 1958 as a treatment for hyperkalemia
- Kayexalate, Kionex, SPS
- Works by exchanging sodium for potassium in the colon and thus excreting potassium from the body.
- Usual dose:
  - Oral: 15 g 1 to 4 times daily.
  - Rectal: 30 to 50 g every 6 hours



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What is the evidence for Kayexalate (sodium polystyrene)?

- Flinn RB et al. *Treatment of the oliguric patient with a new sodium-exchange resin and sorbitol; a preliminary report*. NEJM. 1961;264:111.
  - Population: 10 patients with severe oliguria
  - Intervention: Sorbitol + a cation exchange resin (+ a low potassium diet)
  - Control: Sorbitol alone (+ a no potassium diet)
  - Outcome: Decreased potassium level at 5 days
  - Findings: All patients in both groups had decreased serum potassium levels at 5 days. There is no statistical analysis performed to tell us that one treatment is better than another but it doesn't appear that way. In spite of this, the authors argue for the use of the cation exchange resin.
- Scherr L et al. *Management of hyperkalemia with a cation-exchange resin*. NEJM. 1961;264:115.
  - Population: 32 patients with acute or chronic renal failure.
  - Intervention: Oral (or rectal) cation exchange resin and a low potassium diet
  - Control: None
  - Outcome: Serum potassium 24 hours post-administration
  - Findings: Scherr and colleagues found a decrease in serum potassium by 1.0 mEq on average.
- Gruy-Kapral C et al. *Effect of single dose resin-cathartic therapy on serum potassium concentration in patients with end-stage renal disease*. J Am Nephrol 1998; 9(10): 1924-30.
  - Population: 6 patients with renal failure
  - Intervention: Single dose of a cation exchange resin + sorbitol
  - Control: None
  - Outcome: Serum potassium level at 12 hours
  - Findings: The authors found no difference in serum potassium levels at 12 hours.
- Cochrane Review (Mahoney 2005) that states that potassium-absorbing resins have never been found to be effective in the first hours of treatment

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Kayexalate (sodium polystyrene) complications

- Complications COLONIC NECROSIS
- A number of case reports and case series (Lillemoe 1987, Gerstman 1992, Rogers 2001, Bomback 2009) detail patients with kayexalate-associated colonic necrosis.
- FDA added a warning back in 2011 cautioning against the use of the drug for this reason.
- SO What now?

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Veltassa (Patiromer)

- Indication:
  - Treatment of Hyperkalemia.
  - NOT to be used as EMERGENCY treatment for life threatening hyperkalemia given its delayed onset of action
- May bind to many orally administered medications and should be separated from other meds 6 hours pre and 6 hours post

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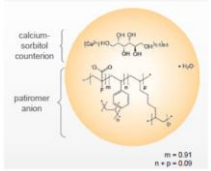
Veltassa (Patiromer)

- **Active ingredient, patiromer sorbitex calcium, consists of:**
  - Active moiety, patiromer, a non-absorbed potassium-binding polymer
  - Calcium-sorbitol counterion
- **Properties:**
  - Free-flowing powder composed of individual spherical beads
  - Exchanges calcium for potassium in the GI lumen

Chemical structure of active ingredient



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Veltassa (patiromer) – warnings and precautions

- Worsening of gastrointestinal motility
  - Avoid use of veltassa in patients with severe constipation, bowel obstruction or impaction including abnormal post-operative bowel motility disorders
  - It may be ineffective and may worsen gastrointestinal conditions
- Hypomagnesemia
  - Veltassa binds to magnesium in the colon, which can lead to hypomagnesemia.
  - It was reported as an adverse reaction in 5.3%
  - Monitor serum magnesium
- Mild to moderate hypersensitivity reaction reported in 0.3% and included edema of the lips.
- Can bind to other oral medications

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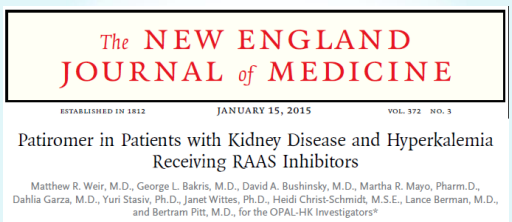
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 15, 2015 VOL. 372 NO. 3

Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

Matthew R. Weir, M.D., George L. Bakris, M.D., David A. Bushinsky, M.D., Martha R. Mayo, Pharm.D., Dahlia Garza, M.D., Yuri Stasiv, Ph.D., Janet Wittes, Ph.D., Heidi Christ-Schmidt, M.S.E., Lance Berman, M.D., and Bertram Pitt, M.D., for the OPAL-HK Investigators*

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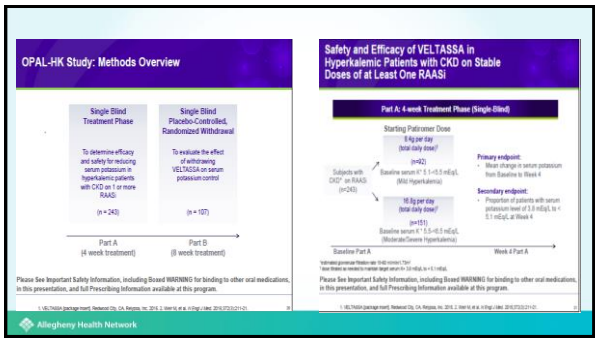
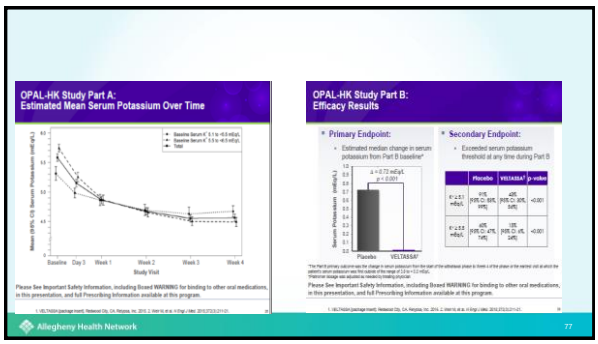
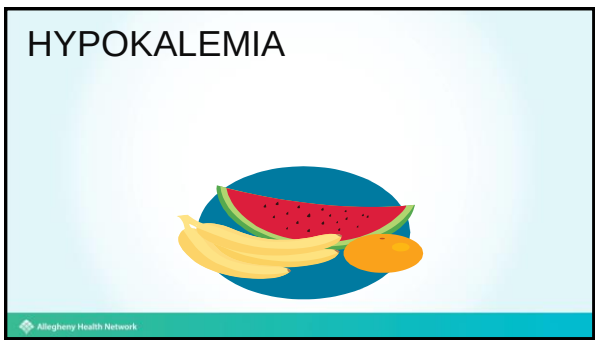

OPAL-HK Study: Methods Overview
Single Blind Treatment Phase
To determine efficacy and safety for reducing serum potassium in hyperkalemic patients with CKD on 1 or more RAASi
(n = 243)
Single Blind Placebo-Controlled, Randomized Withdrawal
To evaluate the effect of withdrawing VELTASSA on serum potassium control
(n = 107)
Part A (4 week treatment)
Part B (8 week treatment)
Please See Important Safety Information, including Boxed WARNING for binding to other oral medications, in this presentation, and full Prescribing Information available at this program.
Allegheny Health Network
Safety and Efficacy of VELTASSA in Hyperkalemic Patients with CKD on Stable Doses of at Least One RAASi
Part A: 4-week Treatment Phase (Single-Blind)
Starting Patiromer Dose
8.4 g per day (total daily dose)†
(n=92)
Subjects with CKD* on RAASi
(n=243)
Baseline serum K+ 5.1–5.5 mEq/L (Mild Hyperkalemia)
16.8 g per day (total daily dose)†
(n=151)
Baseline serum K+ 5.5–6.5 mEq/L (Moderate/Severe Hyperkalemia)
Primary endpoint:
Mean change in serum potassium from Baseline to Week 4
Secondary endpoint:
Proportion of patients with serum potassium level of 3.8 mEq/L to < 5.1 mEq/L at Week 4
Baseline Part A
Week 4 Part A
Please See Important Safety Information, including Boxed WARNING for binding to other oral medications, in this presentation, and full Prescribing Information available at this program.


OPAL-HK Study Part A: Estimated Mean Serum Potassium Over Time
Baseline
Day 3
Week 1
Week 2
Week 3
Week 4
Study Visit
Please See Important Safety Information, including Boxed WARNING for binding to other oral medications, in this presentation, and full Prescribing Information available at this program.
Allegheny Health Network
OPAL-HK Study Part B: Efficacy Results
Primary Endpoint:
Estimated median change in serum potassium from Part B baseline*
Δ = 0.72 mEq/L
p < 0.001
Placebo
VELTASSA†
Secondary Endpoint:
Exceeded serum potassium threshold at any time during Part B
Placebo
VELTASSA† p value
Please See Important Safety Information, including Boxed WARNING for binding to other oral medications, in this presentation, and full Prescribing Information available at this program.
77


HYPOKALEMIA
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Causes of hypokalemia

- Pseudohypokalemia:
  - Uptake by metabolically active cells as in AML
- Cell shifts:
  - Alkalosis effect is small
  - Insulin
  - Increased β-adrenergic activity
    - Stress induced release of epinephrine
      - Theophylline intoxication, ritodrine, terbutaline, albuterol
  - Anabolism
    - Treatment for pernicious anemia
    - TPN
    - Rapidly growing leukemias and lymphomas
  - Hypothermia
  - Barium and chloroquine intoxication
- Inadequate intake:
  - Unusual as the only cause of hypokalemia
  - Kidney can decrease the potassium excretion to 5-15 meq/d
- GI losses
- Renal losses

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Hypokalemia – GI losses

- Urine potassium is < 20 meq/L a day
- Diarrhea is the most common cause
  - Can lose 30-50 meq/l in GI secretions
- Vomiting
  - Can lose 5-10 meq/L in vomitus
  - SO…. Most of the hypokalemia you see is ultimately RENAL loss

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Hypokalemia – Renal losses

- Urinary potassium > 20 meq/day
- No history of diarrhea
- Examples:
  - Liddle's
  - Bartter's
  - Gitelman's
  - Primary hyperaldosteronism (Conn syndrome)

Table 1- Differentiation between Bartter's and Gitelman's syndromes

	Bartter's syndrome	Gitelman's syndrome
Localisation of defect	Ascending limb of loop of Henle	Distal tubule
Age of presentation	Prenatal, during infancy, early childhood	Mostly late childhood or at adult age
Biochemical differences	Serum magnesium may be decreased, urinary excretion of calcium increased or normal	Serum magnesium decreased, urinary excretion of calcium reduced
Molecular differences	Na-K-2Cl co-transporter (NKCC2) or apical K channel (ROMK) or basolateral Cl channel (ClCNKB) in thick ascending limb of Henle	Na-Cl co-transporter in the distal tubule
Functional studies	Concentrating capacity severely impaired, GFR may be normal, decreasing or declining	Concentrating capacity normal or slightly impaired, GFR is normal

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TREATMENT

- ***estimate*** of the amount of potassium you will need:
  - (4- current K) X 100
  - example: potassium of 3.2
    - (4 – 3.2) X 100 = 80 meq

Treatment of Hypokalemia

- Address underlying cause
- Chronic treatment
  - KCl: liquid or Slow K
- Acute treatment
  - IV KCl (40-80 mEq/L at rate <20 mEq/h)
- If hypokalemia is accompanied by acidosis, treat hypokalemia before correction of acidosis

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ANION GAP DIFFERENTIAL

- M ethanol
- U remia
- D KA
- P araldahyde
- I ron, isoniazid
- L actic Acid
- E thylene glycol
- S alycylates

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Ankit Mehta, Michael Emmett. *GOLD MARK: an anion gap mnemonic for the 21st century*. The Lancet. Volume 372, Issue 9642, 13–19 September 2008

- C yanide
- I soniazid, iron
- T oluene
- E thanol

- G lycols (etheylene, propylene)
- O xoproline (ch acetaminophen use)
- L lacate
- D lacate (short bowel syndrome)

- M ethanol
- A sa
- R enal failure
- K etoacidosis (starvation, diabetic)

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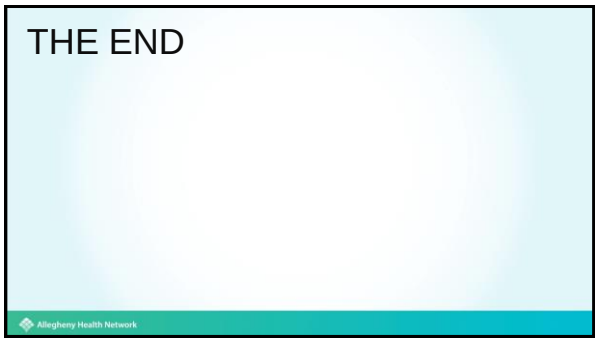
THE END
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