Electrolyte Abnormalities in Neonates

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Electrolyte Abnormalities
- Sodium/Water Balance
- Hyponatremia/Hypernatremia
- Hypokalemia/Hyperkalemia

Sodium and Water Homeostasis
- Sodium
  - Tight regulation
  - RAA system
  - Sympathetic NS
  - Atrial Natriuretic Peptide
  - Brain Natriuretic Peptide
  - Closely correlated ECV
  - Vascular volume
  - Serum water
- Water
  - ADH
  - Osm – 1-2% change
  - Baroreceptors
  - Osmolarity and effective perfusion
Sodium/Water Balance

- Transition from fetal physiology
  - Late term fetus
  - High $F_{Na}$
  - Transition – to low $F_{Na}$
    - Most species during 1st day
    - Fetal foal - before birth
- Sodium conserving mode
  - Na requirement for growth
  - Bone growth
  - ↑ body mass
  - Increase in interstitial space
  - Milk diet
  - Fresh milk is sodium poor
    - 9-15 mEq/l

Sodium/Water Balance
Sodium Overload

- Sodium containing intravenous fluids
  - 6-7 mEq Na/kg/day
  - Mare’s milk – 1.8 mEq Na/kg/day
  - 3-4 X normal Na
- Sodium overloading
  - Expansion of the extracellular fluid space
  - Sodium fractional excretion will remain low
  - Difficulty dealing with volume loading

Hyponatremia
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<th>Cl</th>
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- Usg = 1.011
- UpH = 5
- Upro +
- Uglu neg
- WBC – 0
- RBC – 0
- Casts – 0
- Epith cells – 1 clump, few other
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- pH 7.29
- Pco2 41.8
- BE -11
- Tco2 18
- SID 29

Hyponatremia

- Spurious hyponatremia
- Dilutional hyponatremia
- Depletional hyponatremia
- Redistribution hyponatremia

Spurious Hyponatremia

- Normal plasma sodium concentration
- Laboratory reports a low concentration
  - Presence of interfering substances
    - Lipids or large proteins
    - Artificially dilutes sample
    - Not with modern assay techniques
  - Mistakes in sampling
    - Venipuncture site distal to a low Na drip
    - Sample is taken from a catheter drip
    - Infusion of a low Na solution
    - Insufficient dead space clearing
Dilutional Hyponatremia

- Lack of balance
  - Fluid intake/urine output
- Loss of integrity of the urinary system
  - Ruptured bladder
  - Ruptured/necrotic urachus
  - Fenestrated ureters
- Renal failure
  - Low GFR
  - Na wasting

Dilutional Hyponatremia

- Failed/delayed renal transition fetal to neonatal physiology
  - Low GFR
- Water overload
  - Management mistakes
    - Dilute milk replacer
    - Excessive water enemas (retained)
    - Fluid therapy errors (Na wasting renal syndromes)
  - Syndrome of inappropriate antidiuresis (SIA)
  - Appropriate antidiuresis
    - Decreased arterial volume

Dilutional Hyponatremia

- Most common form hyponatremia in neonates
- Only occurs with intake of hyponatremic fluid
  - Fresh milk
  - Hyponatremic rehydration formulas
    - Dextrose in water or half strength saline
  - Not with isotonic Na containing fluids
    - Normisol-R, Lactated Ringers, Plasmalyte
    - Less marked on milk replacer than fresh milk
Hyponatremia

Syndrome of Inappropriate Antidiuresis (SIAD)

- SIADH
  - Syndrome of Inappropriate Antidiuretic Hormone Secretion
- Hyponatremia secondary to
  - Inappropriate reabsorption of water from urine
- Diagnosis
  - High urine osmolarity
  - Hyposmolar hyponatremia - plasma
  - Normal renal function
  - Normal adrenal function
  - Euvolemia
  - Can have excessive renal sodium excretion
    - Often absent in the neonate
    - Low sodium intake

- Clinical syndrome
  - Sudden decrease in urine output
  - High urine specific gravity
  - Weight gain
    - 10-15% of body weight overnight
  - No edema
  - Decreasing plasma sodium concentration
  - ADH increased
    - No osmotic stimulus
    - No hypovolemic stimulus

- Inappropriate vasopressin release
  - Erratic and unpredictable release vasopressin
  - Reset of the osmostat
    - Threshold for release is lowered
  - Vasopressin release not fully suppressed at low osmolality
    - But normal at higher osmolality
  - Receptor abnormality (vasopressin release normal)
    - Hypersensitive receptors
    - Receptors continue to respond
      - After vasopressin levels decrease
      - Hypovasopressinemic antidiuresis
Hyponatremia

**Syndrome of Inappropriate Antidiuresis (SIAD)**

- SIAD not SIADH
  - High urine osmolarity
  - Hyposmolar hyponatremia
  - Hypovolemia
    - Appropriate vasopressin release
    - Defense of volemia

- Nonosmotic ADH release
  - Subclinical volume depletion
    - Pain, Stress
  - Abnormal adrenal function
    - Increased ACTH
    - Stimulate ADH release
    - Cortisol deficiency
      - Reduced CO and BP
    - Non-osmotic ADH release
    - Aldosterone deficiency
      - Na wasting, reductions in ECV
    - Non-osmotic ADH release
  - Abnormal renal function

Depletional Hyponatremia

- Na loss > water
- Diarrhea
  - Excessive sodium loss in feces
  - Rehydration with Na poor fluids
    - Fresh/frozen milk
    - Fresh water
- Renal sodium wasting
  - Tubular disease
  - Use of diuretics
  - Endocrine disturbances
  - Rehydration with Na poor fluids
    - Fresh/frozen milk
    - Fresh water
Redistribution Hyponatremia

- Low sodium concentration
- Osmolarity normal
- Isosmotic hyponatremia
- Hyperosmotic hyponatremia
- Other osmotically active particles present
- Redistribute fluid from intracellular space
  - Appropriate decrease Na concentration
  - Hyperglycemia (Na, Glu in mmol/L)
    - $Na_{\text{corrected}} = Na_{\text{measured}} + \left( \frac{\text{Glu}}{100} \times 1.6 \right)$
    - 1.6 mEq/l Na decrease for 100 mg/dl glu increase
  - Iatrogenic addition of osmoles
    - Mannitol
  - Extreme hyperproteinemia
  - Secondary to sick cell syndrome

Hyponatremia

*Sick Cell Syndrome*

- Critically ill patients
  - Cellular insult
  - Loss of cell wall integrity
  - Solutes leak
    - Fluid follows
    - Dilution of extracellular sodium

Hyponatremia

*Clinical Assessment*

- Classify hyponatremia
  - Hypervolemic
  - Euvolemic
  - Hypovolemic
Hyponatremia Clinical Assessment

- Hypervolemic hyponatremia
  - Impaired water excretion
    - Ruptured bladder
    - Renal failure
    - Decreased GFR
    - Failure to dilute urine
  - Hypovolemia leading to fluid retention
    - Congestive heart failure
      - Hypovolemia – non-osmotic ADH
      - Poor renal perfusion
        - RAS
        - Increased sympathetic tone
      - Na retention and volume retention
    - ADH excess

- Hypovolemic hyponatremia
  - Splanchnic/systemic vasodilatation
    - Decreased ECV
  - Non-osmotic release of ADH
  - Increased total body water + Na
    - Water > Na
    - Edema, ascites
    - Decreased arterial volume/BP
      - Stimulate ADH secretion

- Euvolemic hyponatremia
  - Most common in human hospitalized patients
  - ADH mediated water retention
    - Increased ICF
  - Iatrogenic
    - Rx hypotonic fluids in patients
      - In the face of increased ADH secretion
  - Total body Na normal
  - No edema
    - Defines euvoletic
Hyponatremia
Clinical Assessment

- Hypovolemic hyponatremia
  - Deficit water & Na
    - Na deficit > water deficit
    - Fluid loss – renal water retention (ADH)
  - Etiology
    - Diarrhea
    - Na wasting nephropathy
    - Diuretics
    - Hemorrhage
- Appropriate ADH secretion
  - Non-osmotic release
  - Retain water because of hypovolemia
  - Further decreasing osmolarity

Cerebral Salt Wasting Syndrome
CSWS

- Hypothalamic-Renal Axis disease
- Characterized by
  - Natriuresis
    - Volume depletion
    - Followed by water retention
    - ADH induced
- Clinical findings
  - Hypovolemia
  - Hyponatremia
  - Inappropriately high urine osmolality
  - Increased urine Na (> 40 mEq/l)

Cerebral Salt Wasting Syndrome
CSWS

- Pathogenesis????
  - Increased SNS outflow
  - Increased atrial and brain natriuretic peptides
- Traumatic intracranial injury
- Differentiate from SIADH
  - CSWS
    - Volume depletion
    - Increased urine sodium excretion
    - Before development of hyponatremia
  - SIADH
    - Euvolemic or hypervolemic
    - Low/normal urine Na (in neonate)
Hypotonic Hyponatremia
Clinical Findings
- Asymptomatic or symptomatic
- Severe
  - < 115 mEq/l – arbitrary definition
- Acute
  - < 36-48 hr
- Progressive brain edema
  - Weakness, depressed reflexes
  - Obtunded, abnormal sensorium
  - Hypothermia
  - Cheyne-Stokes respiration
  - Seizures, Coma
  - Brainstem herniation
  - Respiratory arrest

Hypotonic Hyponatremia
Brain Edema
- Abrupt hypo-osmolarity
  - Aquaporin-4 mediated
  - Water moves into brain cells
- Compensation
  - Decreased cerebral venous pooling
  - Decreased CSF volume
    - Pediatric – less relative CSF volume
- Cell volume regulatory ions
  - Na, K, Cl
  - Released within 5 min from cells
  - Can continue for 4 hours
  - Stretched cell membranes open ion channels
  - Hormone regulated cellular ion differences
    - Predisposes females to more damage

Hypotonic Hyponatremia
Brain Edema
- Reduction of cellular osmolytes
  - Polyalcohols
    - Sorbitol
    - Inositol
  - Amino acids
  - Methylamines
  - Within 2-4 days
    - Up to 50% reduction osmolytes
Hypotonic Hyponatremia
Brain Edema

- Early and late phase changes
  - Limit cellular edema
  - Limit damage
- Hypoxic ischemic encephalopathy
  - Compounds hyponatremia damage
    - Interferes with compensation
  - Cerebral edema
    - Interferes with cerebral perfusion
    - Impairs central respiratory centers

Hypotonic Hyponatremia
Chronic, severe

- Asymptomatic
  - Oligosymptomatic
    - Not treat?
  - Only for days
    - Somnolent
    - Disoriented
    - Often Rx
- Causes
  - Diuretics
  - SIADH
  - Malnourishment/liver disease
  - Diarrhea

Hypotonic Hyponatremia
Chronic, severe - treated

- Risk of cerebral myelinolysis
  - Central pontine myelinolysis
  - Initial report 12 patients – weak evidence
  - Other reports extrapontine
  - May occur in 25% cases
    - Over rapid correction
    - Other risk factors
      - Hypokalemia
      - Alcoholism in man (liver disease)
  - Experimental studies – Na 118 to 140 mEq/l
    - 48 hr – OK
    - 8 hr – 90% myelinolysis
      - Rx hypertonic saline
      - Rx ADH antagonist
### Hypotonic Hyponatremia

#### Myelinolysis - Pathogenesis

- **Osmotic reloading fails**
  - Rapid correction
  - Brain cell Na, K
    - Normal
    - High because of overshoot
  - Amino acid content low
- **Osmotic reloading**
  - Organic osmolytes take up to 5 days
  - Normal metabolic molecules
  - Parts of cellular proteins/lipids
  - External addition not speed
  - Depends on new gene expression
  - RNA transcription – protein production
  - Slowest where lesions occur
  - Blood brain barrier has role

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### Hypotonic Hyponatremia

#### Myelinolysis - Pathogenesis

- **Blood Brain Barrier**
  - Major target of cellular dehydration
  - Vascular endothelial cell
  - Astrocyte foot processes
  - Cell shrink opens cell junctions
- **Blood Brain Barrier disrupted**
  - Not protect
  - Plasma constituents have access

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### Hypotonic Hyponatremia

#### Myelinolysis - Pathogenesis

- **Factors associated**
  - Overshoot hypernatremia
  - Increasing Na > 25 mEq/L 24-48 hr
  - Concurrent hypoxic event
  - Liver disease
  - Rate of Na rise
    - Less important than magnitude
  - Symptomatic hyponatremia
    - More important to treat
    - Than threat of myelinolysis
  - Signs days after Na correction
  - MRI lesions best seen 2 weeks after
Hypotonic Hyponatremia
Treatment
- Recognize cause
  - Don’t treat spurious, redistribution hyponatremia
  - Symptomatic – euvolemia/hypervolemia, with concentrated urine
- Hypertonic saline
- Furosemide – limit volume expansion
- Stop water intake
- Symptomatic – hypovolemia
  - Isotonic fluids
  - Mild symptomatic – dilute urine
  - Evaporative losses only

Hyponatremia/Hypernatremia
Osmotic Shifts

Hypotonic Hyponatremia
Treatment - Correction rate
- Acute – rapid
- Chronic
  - Increase Na < 0.5 mmol/L/hr
  - Stop once serum Na = 120-126
  - If seizures
    - Increase Na 1 – 1.5 mmol/L/hr for 1st 3 hr
    - Or until seizures stop
    - Give 1-2 ml/kg/hr 3% saline
      - If seizures severe up to 4-6 ml/kg/hr
      - Add furosemide
    - Stop when Na = 118 mEq/l
      - Goal 125 mEq/l
Hypotonic Hyponatremia
Estimate Effect of Infusate

For each liter given
Change in serum [Na] = \frac{(Infusate Na + Infusate K) - serum Na}{Total body water + 1}

Total body water
- early neonate = 0.75 \times body wt
- pediatric = 0.6 \times body wt
- adult = 0.5-0.6 \times body wt
- geriatric = 0.45-0.5 \times body wt

Hypotonic Hyponatremia
Treatment

- Vasopressin Antagonists
  - Better predictability
  - Better fine tuning
- Hyponatremia and ADH
  - Primarily disease of excess ADH
  - In face of continued hypotonic fluid intake
- Not use with hyponatremia because of
  - Renal disease
  - Volume contraction
- Oral products being tested

Hypotonic Hyponatremia
Vasopressin Antagonists

- Demeclocycline
  - Blocks at tubules
- Aquaretics
  - \text{V}_{1a} \text{ & } \text{V}_{2}
    - Conivaptan
  - \text{V}_{2}
    - Lixivaptan
    - Satavaptan
    - Tolvaptan
Hypernatremia

- Uncommon
- Deficit of water relative to Na stores
  - Water loss > Na loss
    - GI – osmotic diarrhea
    - Inosensible loss
    - Renal loss
      - Hyperglycemic hyperosmolar syndrome
      - Diabetes insipidus
        - Nephrogenic/Central
        - Medullary “washout”
      - Tubular concentration abnormality

- Lack of water intake ***
  - Must be present for hypernatremia

- Combined
  - Free water losses
  - Renal Na conservation
  - Limited water intake

- Excess Na relative to water
  - Na intake > water
    - Sodium toxicity
    - Lack of water intake must also be present
Hypernatremia

- Clinical differentiation
  - Na toxicity
    - Low urine volume
    - High USg
    - High FxNa
  - Free water loss – not renal
    - Low urine volume
    - High USg
    - Low FxNa
  - Free water loss – renal
    - High urine volume
    - Low USg
    - Low FxNa

- Hypertonic hyperosmolality - always
- Causes of hypernatremia
  - Spurious
  - Excessive free water loss
    - Pure water loss
    - Hypotonic fluid loss
  - Hyperosmotic intake
  - Iatrogenic

Spurious hypernatremia

- Sampling errors
  - Blood samples from the intravenous catheter
    - Not large enough presample
    - Sample contamination
    - with saline
Hypernatremia
Increased free water loss

- Increased insensible loss
- Increased respiratory rate
- Low humidity
- High body temperature
- External warming
  - Radiant heat
  - Hot air heat
- Increased insensible loss with limited intake
  - Hot weather
  - Neonate unable to nurse
  - Lack opportunity
  - NE

Hypernatremia
Increased free water loss

- Water loss
  - Diabetes insipidus
    - Unusual because of neonate's diet
  - $U_{osm} < R_{osm}$
- Water $>$ Na loss
  - Osmotic diuresis
    - Hyperglycemic hyperosmolar syndrome
    - Need interruption nursing/water access
    - Milk replacer with no water access
  - Glucosuria
  - Mannitol
  - Furosemide
  - Renal disease
  - Diarrhea
  - Excessive sweating

Hypernatremia
Hyperosmotic Intake

- High sodium maternal milk
- Excessive sodium intake relative to free water
- Iatrogenic mishaps
  - Improperly mixed electrolyte solutions
    - Without the opportunity/ability to drink fresh water
  - Improperly mixed milk replacer
    - All powdered milk replacers are sodium rich
  - Use of hypernatremic intravenous fluids solutions
    - 5% sodium bicarbonate
    - Hypertonic saline
  - Use of saline in oxygen humidifiers
  - Hypertonic enemas (retained)
Hypernatremia
Normal defense against

- Concentrate urine
- Osmolar release ADH
- Thirst
  - Only develops if can’t get to water
  - Lack of available water – not nursing
  - Hypernatremia uncommon in neonates

Hypernatremia
Treatment

- Recognize cause
  - Eliminate/manage underlying problem
- If developed acutely (hours)
  - Can be corrected over hours (↓Na 1 mmol/hr)
  - Usually acute sodium loading
- If developed slowly (over days)
  - Intracellular accumulation organic osmolytes
  - Correct slowly to avoid cerebral cellular edema
  - ↓Na < 0.5 mmol/hr (target ↓Na 10 mmol/day)

Hypernatremia
Treatment

- If Na > 170
  - Don’t decrease < 150 for 48-72 hr
- Oral fluid therapy
  - As soon as possible
  - Na and K in milk
- Seizures during treatment
  - Common
  - From cerebral edema
  - Slow correction
Hypernatremia
Estimate Effect of Infusate

For each liter given
Change in serum [Na] = \frac{(\text{Infusate Na} + \text{Infusate K}) - \text{serum Na}}{\text{Total body water} + 1}

Total body water:
- early neonate = 0.75 X body wt
- pediatric = 0.6 X body wt
- adult = 0.5-0.6 X body wt
- geriatric = 0.45-0.5 X body wt

Hypokalemia

- Hypokalemia common in neonates
- Anabolic increase in cell mass (growth)
  - Potassium major intracellular ion
- Renal K wasting
  - Diuresis
  - Renal pathology
Hypokalemia
Stress/sepsis

- Resting muscle
  - Uses 10% of available Na⁺:K⁺ ATPase activity
- Stimulated acutely by
  - Insulin
  - Epinephrine
  - Contractile activity

Hypokalemia
Stress/sepsis

- Stress/Sepsis →↑ epinephrine
  - ↑ Na⁺:K⁺ ATPase activity
  - Significant intracellular shifts of K → hypokalemia
  - ↑ ATPase demand
    - ↑ glucose utilization/requirement
    - ↑ glucose transport into the cell resulting
    - → further shift K intracellular??

Hypokalemia
Pathogenesis

- Loss of 1% total body potassium
- Disturbs transcellular distribution
- Results in physiological changes
- Blood levels
  - Not correlate total body stores
  - Rapid drop more likely clinical signs
- Loss 100 mEq K
  - Blood level decreases by 0.3 mEq/l
  - If there are no confounders
Hypokalemia
Signs - man

- Muscle weakness
- Paralytic ileus
- Cardiac arrhythmias
  - Atrial tachycardia
  - Atrioventricular dissociation
  - Ventricular tachycardia/fibrillation
  - Flat or inverted T-waves
  - ST-segment depression
  - U-waves

- K < 2.5
  - Rhabdomyolysis with myoglobinuria
  - Acute renal failure
- K < 2.0
  - Ascending paralysis
  - Impairment of respiratory function
  - Not recognize in neonatal foals

Hypokalemia
Signs - man

- High levels of potassium in milk
  - Will support growth requirements
- Stressed/Septic neonates
  - Not tolerate oral feeding
- Neonates require significant K supplementation
  - Prolonged intravenous glucose
  - Parenteral nutrition
  - Limited or no milk feeding
- Glucocorticoid administration
  - Mineralocorticoid receptor stimulation
  - ↑ urine loss of potassium
Hypokalemia

Treatment

- Neonates
  - Milk diet – not need supplement
- Fluids only
  - If normal plasma levels – 3 mEq/kg/d
  - If hypokalemic – 6-12 mEq/kg/d or more

Hyperkalemia

- Differential diagnosis
  - Ruptured bladder
  - Urinary tract defect
  - Sick cell syndrome
  - Iatrogenic

- Loss of integrity lower urinary tract
  - ↑K only when on a milk diet
  - Also true for ↓Na, ↓Cl
  - Receiving parenteral nutrition
    - ↑K only occur with overzealous K administration
- Sick cell syndrome
  - Suffer global cell insult
  - Perinatal hypoxic ischemic asphyxial insults
  - ↑K – 6-8 mEq/l
- Hyperglycemia – no insulin response
- Iatrogenic in the face of renal insufficiency
Hyperkalemia

Signs

- Impaired neuromuscular transmission
  - Cardiac
  - Neuromuscular paresis/paralysis
- General fatigue
- Weakness
- Paresthesia

Management of Hyperkalemia

Questions to be asked:
- Is there an emergency related to hyperkalemia?
  - If so, what is the plan for therapy?
- Is pseudohyperkalemia present?
- Did this hyperkalemia develop acutely?
  - Toxicity more related to rate of increase than level
  - Toxicity associated with acid-base status
- What role of:
  - High K intake
  - Decreased renal K excretion
  - Transcellular K shift

Management of Hyperkalemia

- ECG changes
  - Peaked T wave
    - False = depending on lead placement
  - Decrease/absence P waves
    - False = depending on lead placement
  - Prolonged PR interval
  - Widened QRS
  - Sine wave QRS
  - Asystole
- ECG not sensitive indicator of hyperkalemia
  - K > 6.0 – 46% abnormal ECG (in man)
  - K > 6.8 – 55% abnormal ECG (in man)
- Not predicable progression
Management of Hyperkalemia

- Pseudohyperkalemia
  - Sample hemolysis
  - Long, tight tourniquet (man)
  - Leukocytosis (>70,000; serum)
  - Thrombocytosis (>1,000,000; serum)
  - Measure plasma vs serum
  - If serum > 0.3 higher - pseudohyperkalemia

Management of Hyperkalemia

Urgent Therapy

- Oppose direct toxic effects
  - Ca therapy
- Promote cellular uptake K
  - Insulin (glucose)
  - β₂-agonists (albuterol)
  - NaHCO₃ - not
- Remove from body
  - Drain uroabdomen
  - Diuretics
  - Cation exchange resins

Management of Hyperkalemia

Urgent Therapy

- Calcium
  - Ca gluconate – less irritating
  - CaCl – Ca more biologically available
  - Slow IV push
    - ECG changes within 1-3 minutes
    - Lasts 30-60 minutes
Management of Hyperkalemia
Urgent Therapy

- Insulin
  - Increase Na/K pump – primarily muscle/liver
  - Increase Na/H exchanger as well – may be important
  - Onset 20 min with peak 30-60 min
  - Dose related
  - Use glucose only to prevent hypoglycemia
  - Dose – 10 units as a bolus
    - Lasts 4-6 hr
  - CRI use in neonates
  - Hypoglycemia risk – monitor

- Adrenergic Agents
  - β₂-receptor in the muscle and liver
  - Directly activate Na/K-ATPase
    - Increase cAMP
  - Albuterol
    - By insufflation or IV
    - K drop within 30 min, peak 90-120 min
    - Drop 0.6-1 mEq/l
    - Has no effect 40% dialysis patients (man)
    - Effect additive to insulin

- NaHCO₃
  - Poor response
  - Requires 4 hrs for effect
  - K decreased < 0.35 mEq/l at 6 hr

- Combined therapy
  - Insulin + β₂
    - Different mechanisms
    - In theory additive 60-100%
    - But not all respond to β₂
    - Combination – less frequent hypoglycemia
  - Insulin + NaHCO₃
    - Potentiate effect?
Management of Hyperkalemia
Direct Elimination from Body

- Gastrointestinal Route
  - Sodium polystyrene sulfonate
  - Cation exchange resin
  - 1 gm removes 0.5-1 mEq/l K
  - 4-6 hr required for full effect
- Oral, enema
  - Constipates – give with laxative
  - Minimal short term effect
  - Depends on gut perfusion

Management of Hyperkalemia
Direct Elimination from Body

- Renal
  - Na diuresis
  - Deliver Na to distal K secreting sites
  - Renal disease often attenuates effect
- Abdomen
  - Draining uroabdomen
  - Peritoneal dialysis