From Cations to Anions and More: The Renal Labs

Janie McDaniel, MS, MLS(ASCP)SC
Yale PA Online Program

Yale SCHOOL OF MEDICINE
Physician Assistant Online

Disclosures

I have no relevant relationships with ineligible companies to disclose within the past 24 months.

(Note: Ineligible companies as those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.)

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Objectives

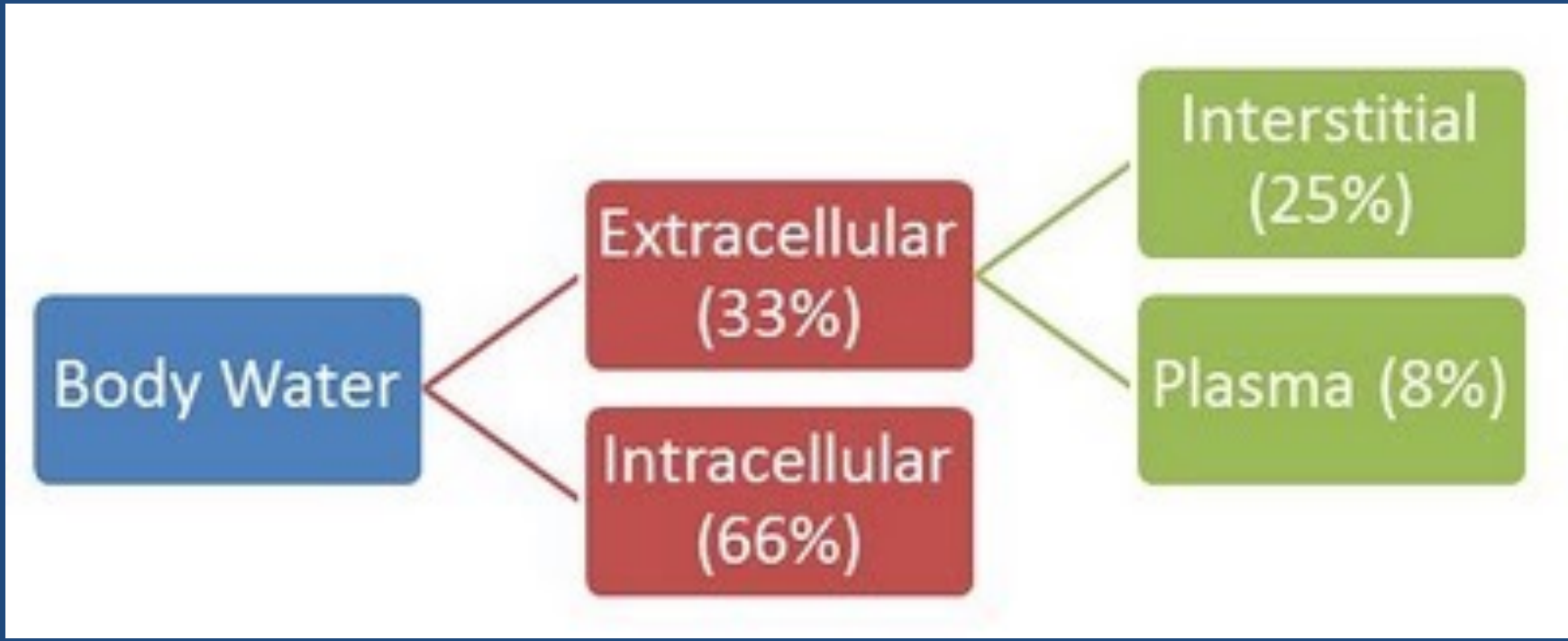
Upon completion of this educational activity, participants will be able to:

- Evaluate the basic normal physiology and pathophysiology of the common renal electrolytes and other renal labs
- Identify the disease states indicated by specific combinations of renal lab abnormalities
- Establish clinical correlation of renal laboratory values to specific patient presentations

Electrolytes

- Involved in:
  - Metabolic functions
  - Maintenance of osmotic pressure and proper hydration
  - Maintenance of pH
  - Regulation of function of heart and other muscles
  - Oxidation-reduction reactions
  - Activating enzyme systems

Body Fluid Compartments



Body Fluid Compartments

- Intracellular ~ 66% of total body volume
  - Major intracellular ions
    - K^+, Mg^{++}, $PO4^-$, proteins

- Extracellular ~ 33% of total body volume
  - Interstitial fluid and vascular fluid (blood plasma)
  - Major extracellular ions
    - Na^+, Cl^-, $HCO3^-$

Body Fluid Compartments

- Passive diffusion vs. active transport
  - Passive diffusion
    - Moves molecules down their concentration gradients
    - Substances move from area of high concentration to an area of low concentration
  - Active Transport
    - Moves molecules against their concentration gradients
    - Move from low concentration to high concentration
      - Example: sodium pump which transports sodium out of the cell and brings potassium inside

Osmolality

- Osmolality = particle concentration
  - Determines distribution of water between intra- and extra-cellular compartments

$$\text{Osmolality} = 2(Na^+) + \text{Glucose}/18 + \text{BUN}/2.8$$

Normal = 275-295 mOsm/kg

- Osmolal Gap
  - measured serum osmo – calculated serum osmo
  - If osmolal gap > 10, think poisoning

ELECTROLYTES

Lab Order for "Electrolytes"

Na^+, K^+, Cl^- , CO_2

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Sodium (Na^+)

- Normal Range = 135 – 145 meq/l
- Major extracellular cation
  - Responsible for maintenance of normal water distribution and osmotic pressure
  - Readily obtained in diet
  - Excreted primarily by the kidneys (controlled by adrenocortical hormones)
- Hyponatremia
  - Decreased serum sodium concentration
- Hypernatremia
  - Increased serum sodium concentration

	Excess (hypernatremia)	Deficit (Hyponatremia)
Causes	Chronic diarrhea	Excess hypotonic IV fluid
	No access to H_20 or decreased thirst	Excess ADH secretion
	High solute loads (tube feeds)	Excess H2O intake Tap water enemas NG irrigation with H20
	Diabetes insipidus	Psychogenic polydipsia
	Diabetes mellitus	
	Increased respiratory rates	
Signs and symptoms	Due to water deficit and increased osmolality	Due to water excess and decreased osmolality
	Cells shrink Confusion, lethargy, Muscle weakness, convulsions	Cells swell Confusion, lethargy, Nausea, coma
Treatment	Prevention	Don't treat unless <130meq/l
	Increase free water intake	Fluid restriction
	Treat slowly	Don't usually give hypertonic fluid

Correcting Na^+ for Hyperglycemia

- Factitious hyponatremia in hyperglycemia
- Correction: For every 100 mg/dL glucose over 100 mg/dL, add 1.6 meq/L to sodium
- Example:
  - Sodium = 133 meq/L
  - Glucose = 402 mg/dL
  - Corrected Na^+ = 1.6 x 3 = 4.8 meq/L
  - 133 + 5 = 138 meq/L (corrected value)

Potassium (K^+)

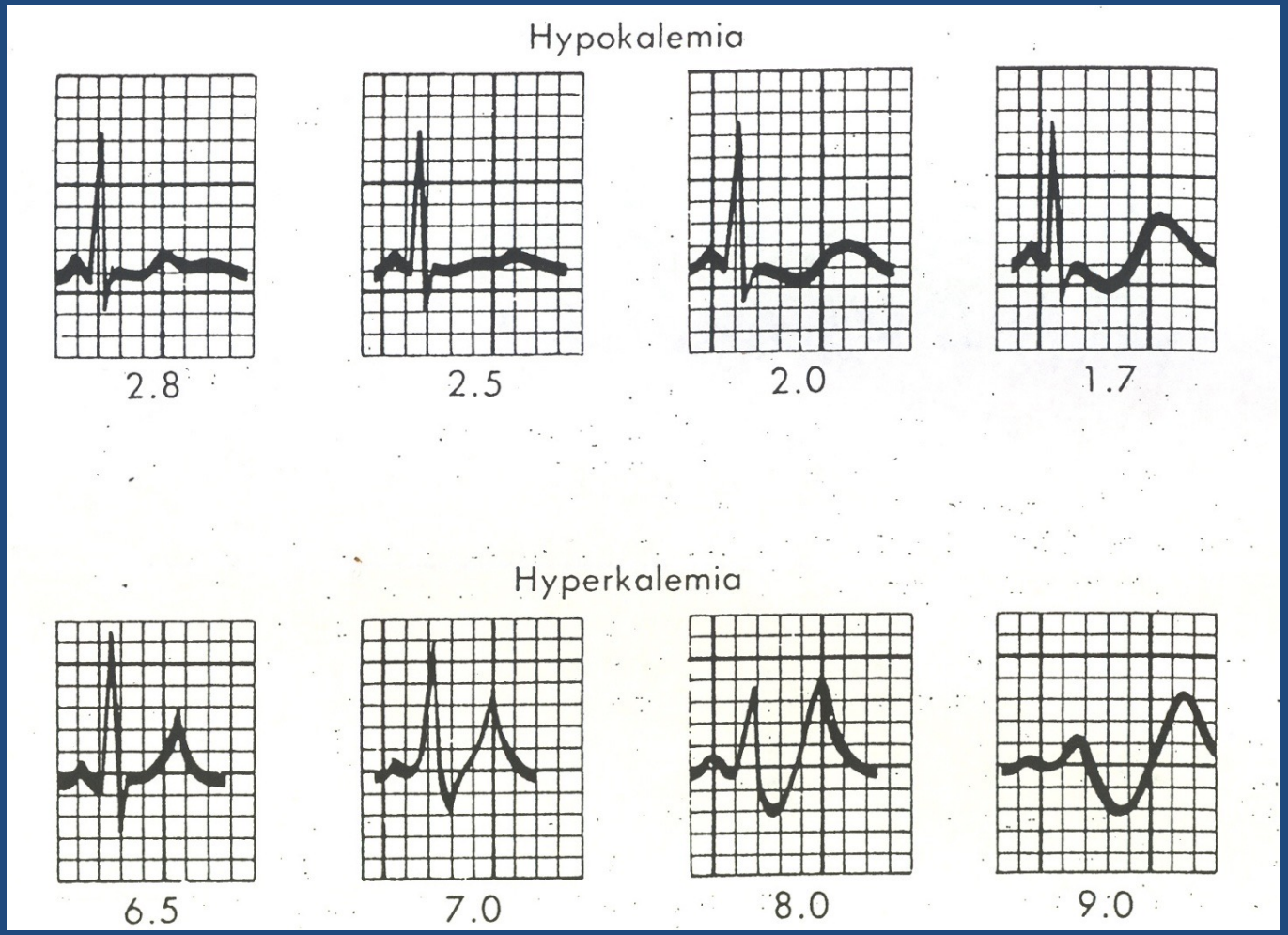
- Normal range = 3.5-5.0 meq/l
  - Major intracellular cation
  - RBC membranes have low permeability to K^+, so K^+ usually shifts out of RBCs slowly
  - Generally, K^+ readily obtained in the diet
  - Excreted in the kidneys without a threshold
    - Protective mechanism to prevent elevated K^+ which is toxic (increased muscular irritability, changes in respiration, and cardiac rhythm)
    - Low K^+ also toxic
  - Due to effect of low or high K^+ on cardiac function, assays frequently ordered STAT

Potassium (K^+)

- K^+ is responsible for resting membrane potential of cells
- Hyperkalemia
  - Makes resting potential less negative. Nerve and muscle depolarize more easily. May not be able to repolarize normally, causing muscle weakness and cardiac arrhythmia
- Hypokalemia
  - Hyperpolarizes membrane potential making it more difficult to reach threshold and create an action potential, causing muscle weakness and cardiac arrhythmia

	Excess (hyperkalemia)	Deficit (hypokalemia)
Causes	Increased intake: Accidental IV bolus Salt substitute in children Administration of old blood	Decreased intake: NPO Anorexia
	Decreased excretion: Oliguric renal failure ↓ aldosterone secretion	Increased excretion: Diuretics ↑ aldosterone (' s) diarrhea/vomiting/NG suction
	Shift from body cells: Crushing injuries Acidosis chemotherapy	Shift into cells: Alkalosis
Signs and symptoms	Due to decrease (less negative) in resting potential: Muscle weakness Ascending paralysis Cardiac arrhythmias	Due to increased resting Potential (more negative): Muscle weakness Paralytic ileus Cardiac arrhythmias
Treatment	Dialysis	K^+ rich foods/fluids
	Kayexalate	Oral/IV KCl
	Insulin/glucose	
	Correct acidosis	Correct alkalosis

EKG Manifestations of K^+ Abnormalities



Correcting K^+ for Hyperglycemia

- Factitious hyperkalemia in hyperglycemia
- Correction: For every 0.1 decrease in pH, subtract 0.6 mEq/L from the measured potassium value
- Example:
  - Potassium = 5.0 mEq/L
  - pH = 6.94
  - Corrected K^+ = 2.0 mEq/L
  - 5.0 – (5 x 0.6) = 2.0 mEq/L (corrected value)

Chloride (Cl^-)

- Normal range = 95-110 meq/l
- Major extracellular anion
  - Helps maintain proper water distribution and osmotic pressure, important in anion-cation balance
  - Slightly decreased after a meal due to formation of gastric HCl.
  - Readily obtained in the diet and excreted by the kidneys and feces.
- Hypochloridemia = low serum chloride
  - Ex. prolonged vomiting
- Hyperchloridemia = high serum chloride
  - Ex. dehydration

Carbon Dioxide (CO_2)

- Normal range 22-30 meq/l
- Second extracellular anion
  - Most of the CO_2 in the blood is in the form of bicarbonate (HCO_3^-)

Total CO_2 =
bicarbonate , carbonate , carbamino compounds
+ physically dissolved, anhydrous CO_2
+ carbonic acid

Carbon Dioxide (CO_2)

- Hypocapnia = decreased total CO_2
  - respiratory alkalosis
  - metabolic acidosis
- Hypercapnia = increased total CO_2
  - respiratory acidosis
  - metabolic alkalosis

Anion Gap

- Used to detect altered concentrations of ions other than Na, K, Cl, and HCO_3
- Anion gap is the difference between measured anions and measured cations

Anion Gap =

$Na - (Cl + CO_2) = 8\text{-}16$ meq/l

- Decreased gap = hypoalbuminemia or increase in unmeasured cation
  - Can also signify analytical error
- Increased gap = retention of 1 or more unmeasured anions

OTHER ELECTROLYTES

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Calcium (Ca^{++})

- Normal = 8.4-10.2 mg/dL
- Necessary in bone structure, blood coagulation, contraction of muscles and transmission of nerve impulses.
    - Vitamin D is necessary for absorption of calcium in intestine
    - Calcium stored in bone; parathyroid hormone causes Ca^{++} in bone to go into solution and into serum if intake is decreased.

Calcium (Ca^{++})

- Imbalances due to effects on threshold potential of nerve and muscle cells.
  - Hypocalcemia decreases the threshold, resulting in hyperexcitability (twitching, tetany)
  - Hypercalcemia increases the threshold, resulting in neuromuscular depression (hyporeflexia).

Calcium (Ca^{++})

- Total Calcium
  - 50% bound to albumin
    - must look at calcium in relation to albumin
  - 3% complexed with phosphorus
  - 47% free – ionized

- Formula for calculating corrected calcium:

$(Ca^{++} - Alb) + 4 =$ corrected total calcium

Phosphorus (PO_4)

- Normal Range = 2.6-5.4 mg/dL
- Also necessary in bone-building process
- Obtained in nearly all foods we eat; excess excreted in urine or feces
- Phosphate is important in the regulation of cellular enzymes and is a substrate for ATP synthesis
- Phosphate deficiency is characterized by symptoms of generalized cellular energy deficiency

Phosphorus (PO_4)

- Hyperphosphatemia is associated with vascular calcification in patients with CKD and ESRD
- Ca and PO_4 are reciprocals of each other; when one is elevated, the other goes down.
- Ca and PO_4 are used as diagnostic tools in parathyroid diseases:
  - Hyperparathyroidism = Ca ↑, PO_4 ↓
    - Adenoma
  - Hypoparathyroidism (primary) = Ca ↓, PO_4 ↑
    - Removal of or damage to parathyroid gland
  - Hyperparathyroidism (secondary) = Ca ↓, PO_4 ↑
    - Renal failure

Magnesium (Mg^{++})

- Normal range = 1.6-2.6 mg/dL
- Magnesium imbalances present similarly to those of calcium
- Mg^{++} "rides with" Ca^{++}
- Magnesium inhibits release of acetylcholine at the neuromuscular junction.
  - Hypermagnesemia depresses neuromuscular excitability (hyporeflexia)
  - Hypomagnesemia increases excitability (twitching)

KIDNEY FUNCTION TESTS: A BRIEF OVERVIEW

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Blood Urea Nitrogen (BUN)

- Normal range = 5-20 mg/dL
- BUN reflects renal function and impaired glomerular filtration
  - Filtration falls below half the normal rate = BUN elevated
  - Urea not excreted in urine, is reabsorbed into the blood stream
  - ↑ with age, and may be ↑ after hemorrhage into the intestine or with obstruction of urine flow, even though kidneys are OK
- Levels slightly above normal should be considered a sign of diminished renal function until proven otherwise
- Urea produced from breakdown of dietary protein
  - BUN may be if ↑ patient is on a high protein diet

Creatinine

- Normal range = 0.5-1.2 mg/dL based on age and muscle mass
- Often reported as eGFR
- Creatinine levels reflect glomerular filtration
- End product of creatine metabolism (found in skeletal muscle)
- Creatinine generated is proportional to muscle mass
- Blood flow and urine production affect creatinine much less than BUN
- BUN elevated and creatinine normal = non-renal cause

BUN/Creatinine ratio

- Normal ratio = 10:1 to 20:1
- Increased in prerenal and postrenal causes to > 20:1
  - Increased tubular reabsorption of urea due to stagnant flow of urine (postrenal)
  - Increased tubular reabsorption of urea due to decreased GFR with unchanged secretion of creatinine into tubules (prerenal)
- Ratio < 15:1 in intrarenal (acute tubular necrosis)
  - Intrarenal affects both BUN and Creatinine

URINE PROTEIN (ALBUMIN) TESTING

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Urine Protein/Albumin

- Normal urine proteins = albumin and low molecular weight serum globulins
  - Healthy individuals excrete small amounts
  - 80-100 mg/day of protein; < 10 mg/day albumin
- Proteinuria = renal loss of protein
  - >150 mg protein excreted in 24 hrs = proteinuria
  - >500 mg/day (kidney damage)
- Albuminuria = abnormal excretion of albumin
  - 30-300 mg/day (diabetic nephropathy; glomerular disease; hypertension)

Urine Dipstick Testing

- Multitest dipstick for protein
  - Sensitive only to albumin, but do not detect low levels of albumin
  - Insensitive to presence of low molecular weight proteins
  - Rated as negative, trace, +1, +2, +3, +4
- Albumin specific dipstick
  - Detect lower concentration of albumin

24 Hour Urine Protein

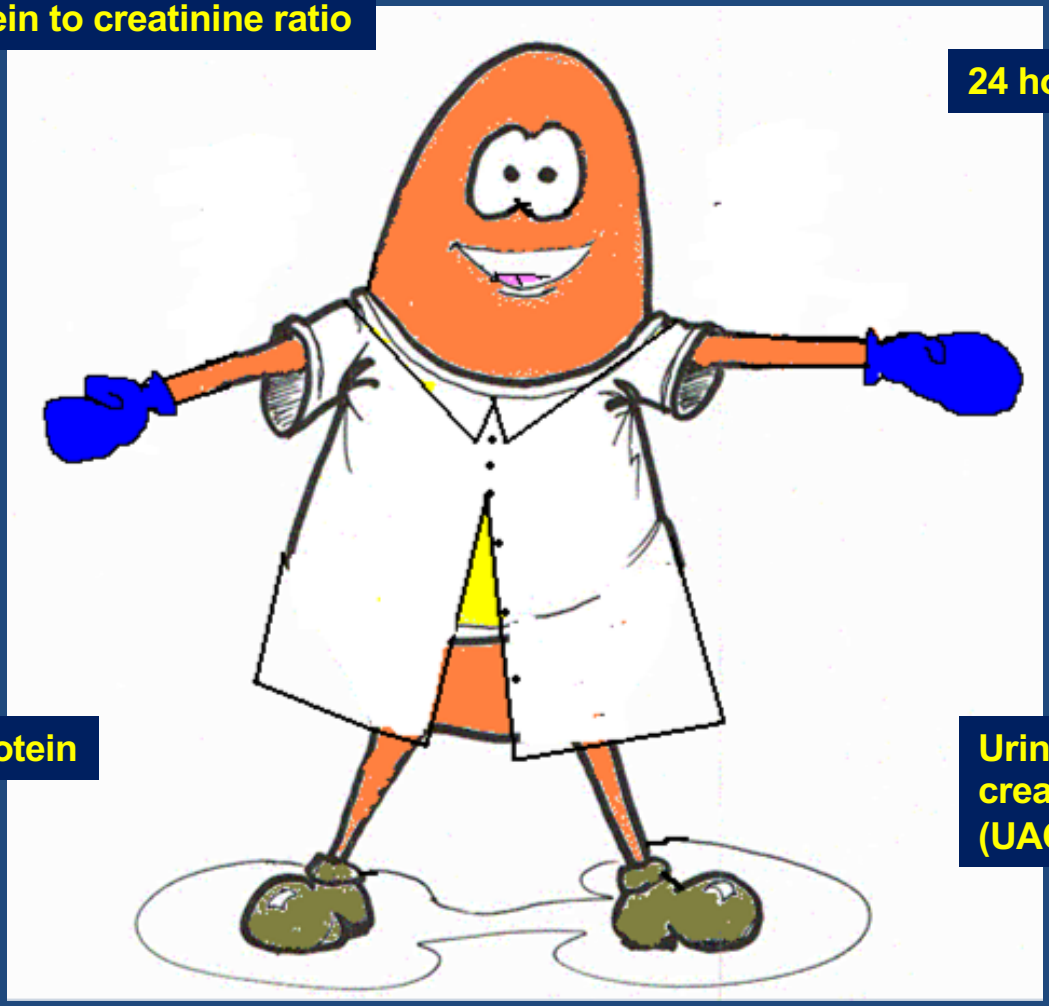
- 24 hour urine protein measurement
  - Collection
    - First morning urine eliminated
    - All following voids are saved in a container kept on ice
    - Test ends after next morning first void is collected
  - Measures all proteins
  - Normal range = 80 – 100 mg/day

Urine Protein:Creatinine Ratio (PCR)
Urine Albumin:Creatinine Ratio (ACR)

- Ratio of protein (or albumin) to creatinine in an untimed urine sample is convenient and is unaffected by variation in urine concentration
- Protein (or albumin) excretion is standardized to creatinine excretion
- Measured on random urine sample. Ratio can be correlated to amount of protein in a 24 hr urine sample
  - ratio of 2.5 = 2.5 grams protein expected in 24 hrs.

Urine protein to creatinine ratio

24 hour urine



Urinary protein

Urine albumin to creatinine ratio (UACR)

Special Thanks to Scott and White of Temple TX for use of their kidney comic

Urine Albumin:Creatinine Ratio

- Detects urinary excretion of albumin that is below the detection capability of standard urine dipsticks, but above the upper limit of normal for healthy individuals
- Identifies patients at risk for diabetic nephropathy
- Screening test of choice:
  - Urine albumin to creatinine ratio (ACR)
  - Ratio between 30 and 300 mg/g establishes presence of moderately increased albuminuria
  - 2 of 3 consecutive samples over 3-month period
  - Results affected by NSAIDS and ACE inhibitors

KDIGO Clinical Practice Guidelines for Chronic Kidney Disease

- Adult patients without risk for kidney disease
  - Standard dipstick - if 1+ (30 mg/dL), then PCR
  - If PCR > 200 mg protein/gm creatinine – evaluate for kidney disease

- Adult patient at risk for kidney disease
  - Initial screen with albumin specific dipstick, if positive, screen with ACR
  - ACR > 30 mg albumin/gm creatinine in two consecutive samples in 3 months, evaluate for CKD

CASE STUDIES

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Case 1

- Sodium- 150 mEq/L
- Potassium- 4.0 mEq/L
- Chloride- 110 mEq/L
- HCO_3- 24 mEq/L
- BUN- 18 mg/dL
- Creatinine- 1.8 mg/dL

- So what is abnormal?
- Since the patient is hypernatremic, what is their volume status?
- What is their BUN:Creatinine ratio?

Case 1

- The approach to hypernatremia begins with an assessment of the patient's volume status. Typically, a normal serum bicarbonate and BUN/creatinine ratio suggest euvolemia

- The patient may be euvolemic because the person is able to compensate for the hypernatremia by increasing his water intake (hypernatremia is a potent stimulus of thirst)

- The patient has a urine output of 4L/day

- The patient also has polyuria, defined as more than 3 L urine output per day. The pathologic diuresis may be secondary to solute diuresis (glucose, urea, etc) or water diuresis (poor response to ADH due to central or nephrogenic diabetes insipidus)

Case 1 - additional labs

- Serum Osm- 295
- Urine Osm- 204
- Urine sodium- 30
- Serum glucose- 90 mg/dL
- Serum calcium – 9.0 mg/dL

Case 1

- This patient has a normal glucose and BUN, and his urine osmolality of 204 mosm/L with 4 liters urine output suggests that he is ingesting 816 mosm/day
  - This is a normal amount of daily solute intake (600 to 900)
- So, this is a water diuresis
- The diagnosis is diabetes insipidus: either from nephrogenic (kidney is to blame) or neurogenic (hypothalamus/pituitary is to blame)
- Since there is evidence of acute or chronic kidney disease, common causes of nephrogenic DI with kidney damage include: hypercalcemia or lithium toxicity
- Calcium is normal

Case 1 - Diagnosis

- This is a 25-year-old with bipolar disorder on chronic lithium therapy
- Lithium is a commonly used drug that is nephrotoxic and leads to nephrogenic diabetes insipidus

Case 2

- Sodium- 136 mEq/L
- Potassium- 5.3 mEq/L
- Chloride- 100 mEq/L
- HCO_3- 11 mEq/L
- BUN- 56 mg/dL
- Creatinine- 1.8 mg/dL

- So what is abnormal?

- The low serum bicarbonate suggests a metabolic acidosis. The first step is to determine if there is an anion gap present

Case 2

- The anion gap is defined
  - Sodium – (Chloride + Bicarbonate)
  - In this case: 136 - (100 + 11) = 25
- A normal gap is 8-12, so this patient has an elevated anion gap metabolic acidosis
- Causes of an elevated gap include:
  - Glycols (ethylene and propylene), L-lactate, Methanol, Aspirin, Renal failure, and Ketoacidosis (MUDPILES)

Case 2

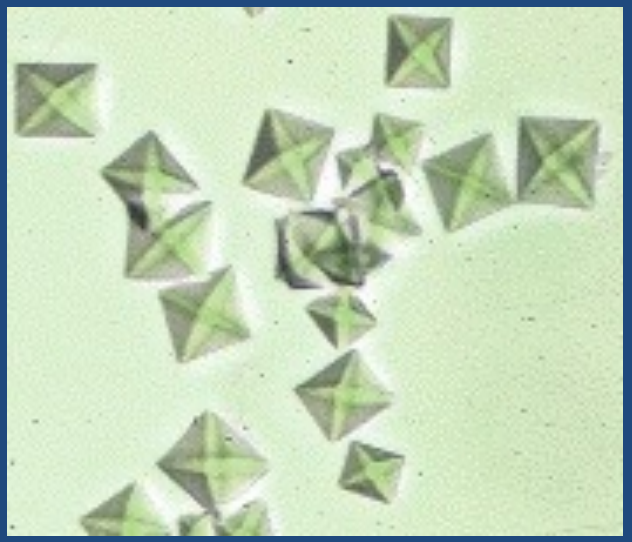
- Next is to find out what the patients' starting bicarbonate is to see if there is a secondary metabolic disorder

- The change in anion gap is defined as: patient gap – normal gap. In this case: 25 – 10 = 15

- This is added to the patient's bicarbonate to determine the starting bicarbonate (before the anion gap acidosis)
  - For this case: 15 + 11 = 26. Since 26 is within the normal range of 22-28, there is no secondary metabolic process

Case 2 - additional labs

- Serum Osm- 315
- Serum glucose- 72 mg/dL
- CPK - 25 IU/L
- Urine crystals



Case 2

- The *lab-measured* osmolality is 315. The *calculated* osmolality is 295
- The osmolar gap is > 10 suggesting the presence of a low molecular weight alcohol (ethanol, propylene glycol, methanol or ethylene glycol)
  - Ethanol (drinking alcohol) is safe to consume ☺
  - Propylene glycol is a solvent used in industrial applications, including antifreeze, but it is rarely toxic in humans because it is converted into pyruvic, lactic, and acetic acids
  - Methanol ingestion results in blurry vision (formic acid)
  - Ethylene glycol leads to crystalluria
    - oxalic acid → calcium-oxalate stones

Case 2 - Diagnosis

- The presence of urinary calcium oxalate crystals confirms the diagnosis as ethylene glycol toxicity
  - Crystals lead to micro-obstruction of the tubules and can cause acute kidney injury

- 35-year-old male with altered mental status, found at home next to empty jug of anti-freeze

Case 3

- 65 y/o male; 1 week history of nausea, vomiting, general malaise
- History of uncontrolled hypertension, Type 2 diabetes mellitus, diabetic nephropathy, retinopathy, neuropathy
- Meds: levothyroxine, metoclopramide 3x/d, subcutaneous insulin regimen 2x/d
- PE: BP 160/99, diabetic retinopathy, diminished sensation bilaterally below knees

Lee M. *Basic Skills in Interpreting Laboratory Data*. 6th ed. Bethesda, MD: American Society of Health-System Pharmacists; 2017.

Case 3 - labs

- Sodium - 146 mEq/L
- Potassium - 4.7 mEq/L
- Chloride – 104 mEq/L
- CO_2 – 15 mmol/L
- BUN – 92 mg/dL
- Creatinine – 3.2 mg/dL
- Glucose – 181 mg/dL
- Calcium – 7.5 mg/dL
- Phosphate – 9.1 mg/dL
- Albumin – 3.3 g/dL
- Uric acid – 8.9 mg/dL

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Case 3

- Over next several days:
  - Finger numbness, tingling, burning of extremities
  - Increasing confusion and fatigue
  - Positive Chvostek and Trousseau signs

- Repeated labs:
  - Calcium – 6.1 mg/dL
  - Phosphate – 10.4 mg/dL
  - PTH – 280 pg/mL (N: 10-65 pg/mL)

Lee M. *Basic Skills in Interpreting Laboratory Data.* 6th ed. Bethesda, MD: American Society of Health-System Pharmacists; 2017.

Case 3

- Three lab abnormalities related to calcium-phosphate metabolism:
  - Hypocalcemia (patient has classic signs & symptoms)
  - Hyperphosphatemia
  - Hyperparathyroidism

- CKD is associated with these labs which are responsible for developing renal osteodystrophy

- Patient was asymptomatic due to slow disease progression allowing body to compensate (PTH)

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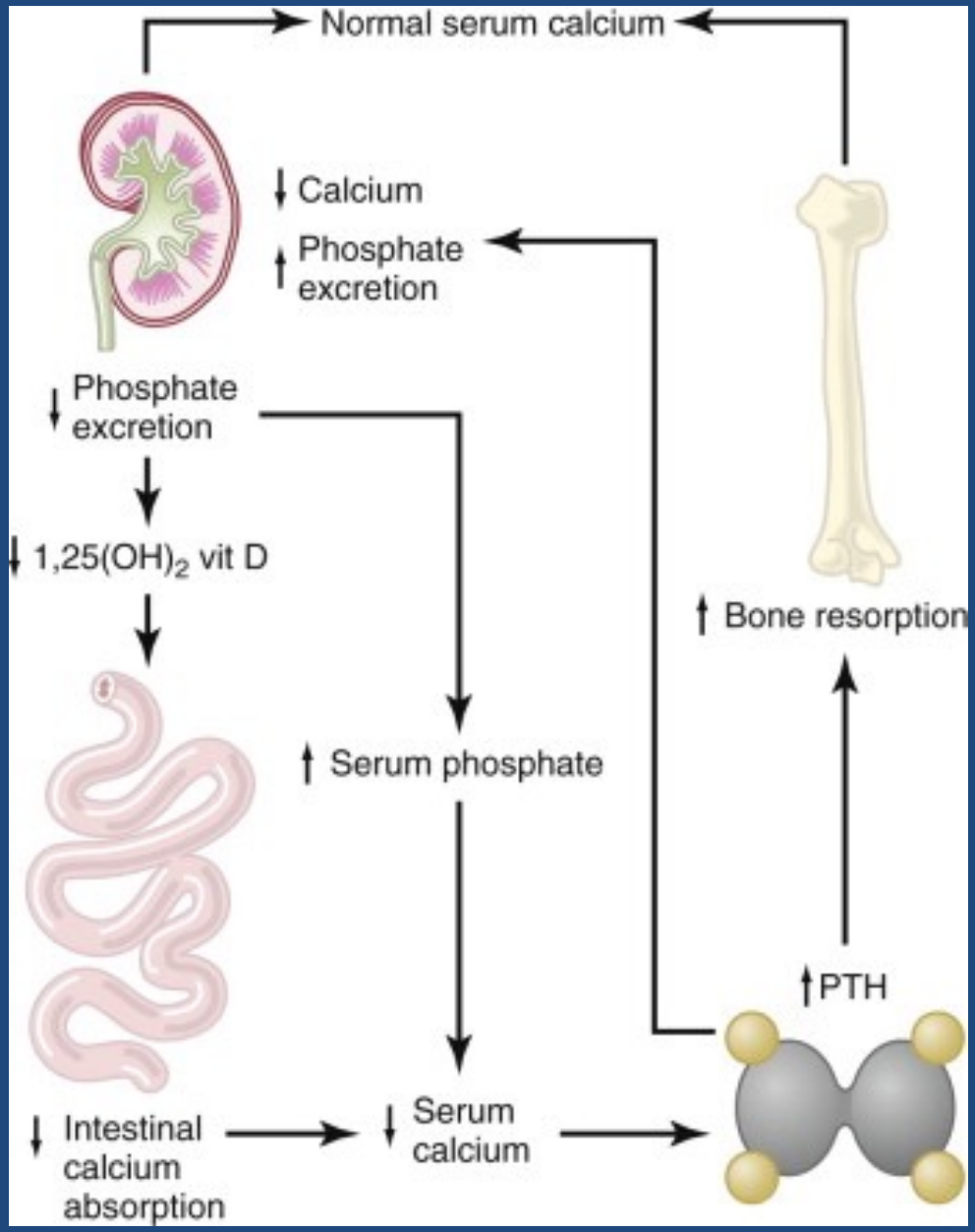

From Andreoli and Carpenter's Cecil essentials of medicine, ed8, Philadelphia, 2010, Saunders.

Case 3

- Nausea and vomiting and lack of appetite caused oral calcium intake to be reduced, enhancing the hypocalcemia.

- Remember: Calcium must be corrected for low serum albumin, so:

  $(7.5 – 3.3) + 4.0 = 8.2$ mg/dL

  Although true hypocalcemia, deficit is mild

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Case 4

- 68 y/o female with diabetes mellitus, CAD, and mild CHF. Uses walker due to recent total hip replacement
- Meds: metformin, NSAIDS, lasix, Norvasc
- Referred to nephrology by primary care physician:
  - GFR = 44 ml/min
  - 24-hour urine protein = no proteinuria

Case 4

- Urine dipstick in office showed 30 – 300 mg/dL, so urine sample sent for ACR
- UACR = 288 mg/dL
  - Moderately increased albuminuria, likely to progress further
- Follow-up:
  - D/C metformin, changed to insulin
  - Stopped NSAIDS, changed to acetaminophen
  - Started ACE inhibitor

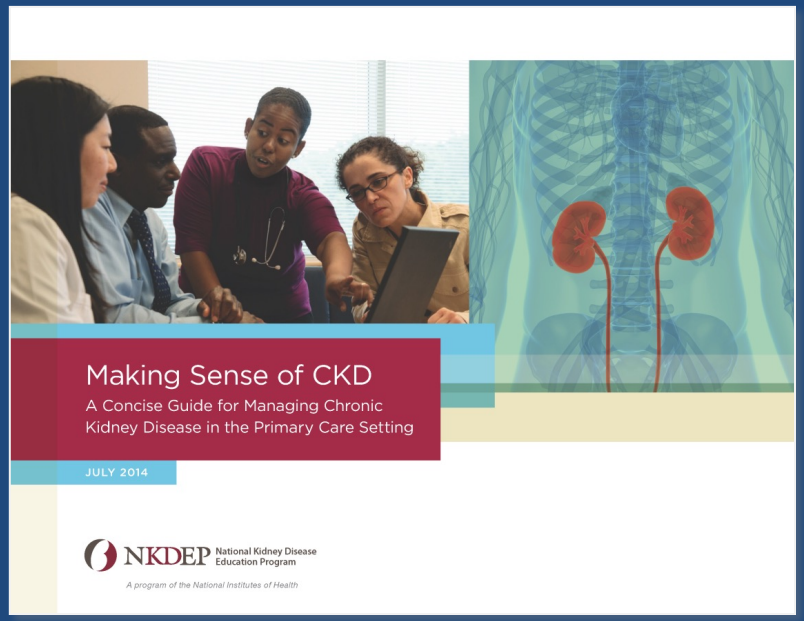
Case 4

- Reason 24-hour urine missed protein was due to incomplete collection in a functional patient (no confusion), but less functional ADLs

- Take Home Message:
  - 24-hour urine protein not best test for detecting moderately increased albuminuria
  - UACR is screening test of choice

Managing Chronic Kidney Disease in the Primary Care Setting

Numerous, sometimes conflicting CKD guidelines → challenges providing appropriate care



Making Sense of CKD

- Designed to help PCPs manage adult CKD patients
- Emphasizes key considerations for evaluating and managing CKD patients:
  - Identifying patients at highest risk for progression to kidney failure
  - Slowing progression among these high-risk patients
- Highlights useful resources:
  - Patient education materials
  - Clinical tools
  - Professional reference materials

Take Home Points

- Electrolytes are involved in all metabolic functions in the human body and understanding the interconnection is critical to patient care.
- Understanding specific combinations of renal lab abnormalities and their correlation to specific patient presentations can help identify disease states.
- The screening test of choice for identifying chronic kidney disease is the albumin/creatinine ratio.

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QUESTIONS?

Janie McDaniel, MS, MLS(ASCP)SC
Lecturer and Chair of Admissions
Yale Physician Assistant Online Program
100 Church Street South, Suite A230 | New Haven, CT 06519
Mailing: PO Box 208004 | New Haven, CT 06520-8004
336.314.7002 | F: 203.785.6391 | jane.mcdaniel@yale.edu