TH9- Demystifying the Basic Metabolic Panel

Thursday, March 22
1:30 PM- 5:00 PM

Session Description
This interactive, case-based session will engage participants in problem solving commonly reported electrolyte abnormalities encountered in LTC. The cornerstones of understanding altered physiology, astute clinical assessment, and application of logical diagnostic and therapeutic strategies will be highlighted.

Learning Objectives
Interpret the BMP accurately, Diagnose and manage hyponatremia and hypernatremia.
Identify causes work up and treatment of hyperkalemia and hypokalemia and acid base imbalance.
Describe the differential diagnosis of hypercalcemia and hypocalcemia and appropriate management.

Presenter(s): T. S. Dharmarajan, MD; Meenakshi Patel, MD, MMM, CMD; Naushira Pandya, MD, CMD

Presenter(s) Disclosures: All speakers have reported they have no relevant financial relationships to disclose.
Demystifying the Basic Metabolic Panel

Dr. Meenakshi Patel Clinical Associate Professor, Wright State University

Speaker Disclosures

Dr. Patel has no relevant financial relationship for this topic.

Dr. Pandya has no relevant financial relationship for this topic.

Dr. Dhamarajan has no relevant financial relationship for this topic.

Learning Objectives

By the end of the session, participants will be able to:

• Interpret the BMP accurately, Diagnose and manage hyponatremia and hypernatremia.
• Identify causes work up and treatment of hyperkalemia and hypokalemia and acid base imbalance.
• Describe the differential diagnosis of hypercalcemia and hypocalcemia and appropriate management.

Incidence and Prevalence

• Prospective observational study aged ≥65 years admitted with a fragility fracture to a university hospital between 7th January and 4th April 2013
• Point prevalence of hyponatremia
  • At admission was 13.4%
  • 12.6% more developed hyponatremia during admission.
  • Hypovolemic hyponatremia was predominant (70%).
  • 73% of cases were multi-factorial in etiology

DOI: 10.21276/aimdr.2017.3.2.ME5

HYPONATREMIA

Scope of electrolyte disorders in the elderly

246 of 526 elderly hospitalized had hyponatremia
136 (56.6%) females
Diuretics were found to be the most common cause of hyponatremia: 82 (34.2%) patients, of whom 28 (33.6%) were hypovolemic and 54 (66.4%) hypervolemic.
Other potential causes of hyponatremia included:
- Respiratory infection (n=37, 15.1%)
- Infection (n=4, 1.6%)
- Syndrome of inappropriate antidiuretic hormone (SIADH) (n=10, 4.1%)
- Malignancy (8.3%)
- Use sodium and (n=10, 4.1%) and congestive heart failure (n=22, 9.1%)
- Diabetes mellitus (13.7%) and hypertension (27.8%) were the most common co-morbidities associated with hyponatremia

Severe neurological manifestations were detected only in 25 (10.4%)
The majority were asymptomatic or had minor symptoms pertaining to hyponatremia.
Seventeen (7.1%) patients with moderate (n=12) and severe (n=5) hyponatremia succumbed.

DOI: 10.21276/aimdr.2017.3.2.ME5
Demystifying the Basic Metabolic Panel - Patel

Case: Hyponatremia
- Mr. PH is an 84 y.o. WM with a H/O HTN, CHF, Lung carcinoma and seizures admitted to the ICU for exacerbation of CHF and hypoxia.
- He was successfully diuresed and lost 20 lbs in the hospital - transferred to your facility after 4 days.
- Meds:
  - Depakote, Furosemide, Metazalone, Lisinopril, ASA, and Levetiracetam in addition to a multitude of vitamin supplements.

Case: Hyponatremia
- In the hospital his sodium went down to 127 and he was started in NaCl tabs 1 gm tid.
- What are your orders when you admit the patient to your rehab unit?
- What do you need to think about?
- What is the appropriate course of action?
- When is it appropriate to use NaCl tabs?

Signs and symptoms of hyponatremia
- Mild chronic hyponatremia may appear to be asymptomatic.
- May still have serious consequences in the elderly; 21.3% increase in falls vs. 5.35% with normal Na levels.
- Alterations in gait and attention.
- Se Na levels <125 mEq/L maybe accompanied by lethargy, fatigue, anorexia, nausea, and muscle cramps.
- With worsening hyponatremia, CNS sx predominate (confusion to coma to seizures).
- Increased risk of death in severely symptomatic patients with se Na <110 mEq/L who also have underlying disease with cachexia.

Risk Factors for Hyponatremia in the Elderly

<table>
<thead>
<tr>
<th>RISK FACTORS</th>
<th>EXAMPLES</th>
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<tbody>
<tr>
<td>Physiologic changes of normal aging</td>
<td>No conservation, RA activity, renal water excretion, GFR, AVP, ANP (5 fold)</td>
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<tr>
<td>Diseases accompanied by SIADH</td>
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<tr>
<td>Increased water intake</td>
<td>Oral, IV fluids,</td>
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<tr>
<td>Decreased Na intake</td>
<td>Low Na diet, tube feeding</td>
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<tr>
<td>Increased Na loss</td>
<td>Renal disease</td>
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<tr>
<td>Gastrointestinal tract</td>
<td>Nausea, vomiting, diarrhea, gastric suctioning</td>
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<tr>
<td>Central salt wasting</td>
<td>Hyperosmolar intravascular shift</td>
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<td>Age &gt;80y</td>
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Diseases/disorders associated with hyponatremia in elderly

<table>
<thead>
<tr>
<th>CATEGORIES</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS disorders</td>
<td>Vascular, trauma and bleeding, tumor, infection</td>
</tr>
<tr>
<td>Malignancy with ectopic AVP production</td>
<td>Lung (small cell), pancreatic, pharyngeal, Hodgkins, lymphosarcoma</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>Pneumonia, TB, lung abscess, bronchiectasis</td>
</tr>
<tr>
<td>Endocrine disease</td>
<td>Hyperthyroidism, DM with hyperglycemia, adrenal insufficiency</td>
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An 82 y/o woman is admitted from a nursing home with increasing lethargy and confusion.
- H/O dementia, but is normally animated and interactive with family and staff.
- Poor appetite over the past year with significant weight loss, and currently eats very little.
- H/O HTN Two weeks ago HCTZ was added to her medications.
- Over the past few days, the nurses note some N/V, no diarrhea, fever or other complaints.
- On exam, she has some dry oral mucosa but she is not orthostatic. She is awake, but lethargic. Neuro exam is nonfocal. There is no evidence of CHF, ascites or edema.
- Labs: Na 121 (last 130 4 weeks ago), normal renal/liver function. Serum osm 200, urine osm 220, urine Na 30.
Drug-Induced Changes in Sodium and Water Regulation

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>EXAMPLES</th>
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<tbody>
<tr>
<td>Sodium retention</td>
<td>NSAIDS</td>
</tr>
<tr>
<td>Sodium loss</td>
<td>Thiazide and loop diuretics</td>
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<tr>
<td>Impaired diluting capacity</td>
<td>Thiazide diuretics</td>
</tr>
<tr>
<td>Impaired concentrating capacity</td>
<td>Lithium, demeclocycline, potassium losing diuretics</td>
</tr>
<tr>
<td>SIADH</td>
<td>CNS: Tricyclics, SSRIs and SNRIs, antiviral agents, carbamazepine, valproic acid, ACE inhibitors, Antineoplastic drugs, Chlorpropamide, Clonazepam, Nortriptyline</td>
</tr>
</tbody>
</table>

Questions- Case 2

1. What are the potential causes of hyponatremia in this patient?
2. Does her urine osm of under 300 rule out SIADH?
3. What other laboratory data is needed?
4. How might her diet be contributing to her hyponatremia?

Questions- Case 2 (cont.)

5. How is the urine Na helpful in differentiating SIADH from hypovolemia? What in this case would limit its usefulness?
6. How does water intake or relatively hypotonic fluid intake worsen hyponatremia with SIADH?
7. How would you treat this patient?

High plasma osmolality

- Hyperglycemia
- Mannitol
- IVIG with mannose retention in patients with renal failure
- Glycine irrigation in TURP: exception to rule that patients with hyperosm hyponatremia do not get into trouble; complicated by urinary retention, N/V, postsurgical state; severe hyponatremia after urological procedure should be treated acutely with saline/furosemide!

Volume Depletion

- True volume depletion due to vomiting, diarrhea, bleeding, urinary losses
- N/V also stimulate ADH release (to maintain circulating volume)
- Insensible losses (sweat) associated with loss of free water which increases plasma Na
- Adrenal Insufficiency (lack of cortisol resulting in decreased Na reabsorption plus volume depletion)
Volume Depletion: Treatment

- Carefully monitor sodium as fluids given to prevent overly rapid correction
- Goal 0.5 meq/L per hour correction
- Degree that 1 L fluid will raise plasma Na conc: Increase PNa= (infusate [Na]-PNa) / (TBW +1)
- Isotonic saline:
  - Raises plasma sodium by 1-2 meq/L for every liter of fluid infused since saline has higher Na concentration (154 meq/L) than hyponatremic plasma
  - Volume replacement removes stimulation of ADH

Thiazide Diuretics

- Elderly women at higher risk than others for hyponatremia
- Complicated picture often with some element of volume depletion as well
- Not seen as often with loop diuretics (inhibition of NaCl transport in loop of Henle prevents generation of countercurrent gradient and limits ability of ADH to induce water retention)
- May result in normal/increased urine Na, even though underlying volume depletion;
- Treatment: hold medication, sometimes fluid

CHF, Cirrhosis, Nephrotic Syndrome

- CHF/Cirrhosis:
  - Poor cardiac output or peripheral vasodilatation/poor circulating volume →
    - Decreased pressure sensed at carotid sinus baroreceptors;
    - Associated with higher mortality;
    - Degree of hyponatremia as prognostic marker
    - 21% CHF admissions with hyponatremia; 87% at discharge
- Cirrhosis
  - Incidence 35%; all with hyponatremia had ascites
- Nephrotic syndrome: usually due to renal disease rather than poor circulating volume
- Treatment: underlying disorder

Primary Polydipsia

- Psychiatric disorder, often complicated by increased thirst with antipsychotic meds
- Can occur with hypothalamic lesions (sarcoid or other infiltrative processes)
- Usually no hyponatremia unless intake over 10-15 L/day, or acute 3-4 L water load
- Urine osm below 100
- Increased problems if other ADH stimulus (N/V, anxiety)
- Treatment: hold free water intake; classically may have very rapid correction!

Low Dietary Solute Intake

- Elders who may have underlying malnourishment (“tea and toast” diets) with diet poor in solutes (Na/K)
- Beer drinkers (high water intake, low protein)
- Normally excrete 600-900 mosmol/kg solute daily (if minimum urine osm is 60 mosmol/kg, max urine output will be 10-15L/day: 900mosm/day / 60 mosmol/kg = 15)
- If daily intake poor, daily solute excretion may fall below 250 mosmol/kg, reducing the maximum urine output to below 4 L/day; Hyponatremia develops if greater than 4 L consumed in day
- Urine appears dilute (osm of 100)
- Treatment: normal saline, increased dietary solute

Pseudohyponatremia

- Plasma osmolality that is normal or elevated
- Usually not at risk for hypoosmolality induced cerebral edema
Cerebral Salt Wasting

- Looks like SIADH
- High urine Na concentration that is due to defective tubular reabsorption (natriuretic hormone, ?brain natriuretic peptide)
- Elevation of ADH
- Presence of volume depletion
- Hypouricemia differentiates from hyponatremia due to volume depletion alone (hormonally mediated impairment in renal tubular function)

SIADH Ddx

- Intracranial disease
- Pulmonary disease
- Chest wall disorder (surgery, VZV)
- Severe pain or emotional distress
- Severe N/V
- Ectopic ADH: Small cell lung cancer
- Drugs: opioids, carbamazepine, chlorpropamide, cyclophosphamide, cisplatin, vincristine, vinblastine, amitriptyline, SSRI, neuroleptics, bromocriptine, ecstasy (MDMA)

SIADH

**Diagnosis**
- Normal ECFv (or slightly increased)
- Hypothyroidism & AI ruled out
- ↓ serum Na/OSM
- U_Osm > 100 mM, U_Na > 40 mEq/L
- Low plasma uric acid (< 238 umol/L)

**Treatment**
- Fluid Restriction
- Oral Salt, Hi-protein diet or Urea(30 g/d): promote solute diuresis
- Lasix 20 mg po od-bid: Loop direct diminishes medullary gradient
- Demeclomycin 300-600 mg bid (can be nephrotoxic)
- Lithium (induces NDI)
- IV salt solution:
  - Rarely if ever needed (i.e. only if symptomatic with SZ/coma)
  - Solution given must be of greater OSM than U_Osm or in long run will just make hyponatremia worse (often IV NS not sufficient)

**Example**

U_Osm fixed 600 mM due to ADH action

1L NS given: 100 mM (154 mM each of Na and Cl)
All sodium will be excreted as renal sodium handling is intact in SIADH.
300 mmoles of osmols given excreted in 500cc urine (300mMoles/500mL = 600 mM)
Therefore net gain of 500 cc free water!

1L 3% saline given: 1026 mmoles
Excreted in 1.7L to keep U_Osm 600 mM
Therefore net loss of 700 cc free water!

NOT advocating use of any IV NS (0.9% or 3%) in SIADH unless absolutely necessary (i.e. SZ, coma). Most SIADH hyponatremia is chronic and should be corrected slowly with fluid restriction ONLY.

SIADH v.s. Cerebral Salt Wasting

<table>
<thead>
<tr>
<th></th>
<th>SIADH</th>
<th>CSW</th>
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<tbody>
<tr>
<td>Serum Na</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>ECFv</td>
<td>Normal</td>
<td>↓</td>
</tr>
<tr>
<td>U_Osm</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>U_Osm</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Urine volume</td>
<td>N or ↓</td>
<td>↑</td>
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<tr>
<td>Serum urate</td>
<td>↓</td>
<td>N or ↓</td>
</tr>
<tr>
<td>Urine urate</td>
<td>↑</td>
<td>N or ↑</td>
</tr>
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Reset Osmostat

- 25-30% of circumstances which cause SIADH
- Downward resetting of the threshold for both ADH release and thirst.
- Mild asymptomatic hyponatremia (Na 125-135 mEq/L)
- Distinguish from SIADH by observing response to water load (10-15 mL/kg po or IV)
- Normal subjects and those with reset osmostat will secrete the entire water load over 4h without any worsening of the hyponatremia
- Attempts to correct hyponatremia in reset osmostat are not needed and will cause severe thirst
1. What are the potential causes of hyponatremia in this patient?
   - Thiazide diuretic (complicating urine Na)
   - Underlying SIADH (suggested by inappropriately high urine osm)
   - Recent N/V and volume loss (although not orthostatic)
   - Poor solute intake/“tea and toast” diet (may be reason that urine osm is not as high as would be expected with SIADH alone)
   - CNS event (stroke, subdural)

2. Does her urine osm of under 300 rule out SIADH?
   - No; classically urine osmolality is 300 or greater, but the urine osm of 220 in the setting of a serum Na of 121 is inappropriately elevated (over 100 really is inappropriate)

3. What other laboratory data would be needed?
   - TSH
   - Cortisol level in am (although not orthostatic)
   - Consider uric acid to help differentiate hypovolemia from SIADH
     - Hypouricemia in SIADH,
     - Elevated/normal uric acid if dehydrated
   - Possibly neuroimaging given underlying dementia and risk for CVA, subdural

4. How might her diet be contributing to her hyponatremia?
   - Poor solute intake could result in dilute urine and hyponatremia as discussed previously

5. How is the urine Na helpful in differentiating SIADH from hypovolemia? What in this case would limit its usefulness?
   - Urine Na should be normal/elevated with SIADH and should be low with hypovolemia
   - Thiazide diuretic use may have elevated urine Na temporarily

6. How does water intake or Normal Saline intake worsen the hyponatremia with SIADH?
   - Example: patient with SIADH, urine osmolarity of 616 mosmol/kg; 1 liter of NS has 308 mosmol of NaCl, 1000 cc H2O;
     - Isotonic Saline NaCl H2O
     - In 308 1000 ml
     - Out 308 500 ml (conc 616)
     - Net 0 +500 of free H2O!
Case 2...

7. How would you manage this patient?

- Water restriction? Need to address amount of intake she has had
- Avoid rapid correction (osmotic demyelination)
- Discontinuation of Thiazide
- Would probably not give IVF initially as most may be due to thiazide, SIADH, poor diet, although may be complicating element of hypovolemia;
- If n/v persisted after holding thiazide, consider small amount of normal saline (relatively hypertonic with urine osm of 220)

Rx Hyponatremia

- Na deficit = 0.6 x wt(kg) x (desired [Na] - actual [Na]) (mmol)
- When do you need to Rx quickly?
  - Acute (<24h) severe (< 120 mEq/L) Hyponatremia
  - Prevent brain swelling or Rx brain swelling
  - Symptomatic Hyponatremia (Seizures, coma, etc.)
  - Alleviate symptoms
  - "Quickly": 3% NS, 1-2 mEq/L/h until:
    - Symptoms stop
    - 3-4h elapsed and/or Serum Na has reached 120 mEq/L
  - Then SLOW down correction to 0.5 mEq/L/h with 0.9% NS or simply fluid restriction. Aim for overall 24h correction to be < 10-12 mEq/L/d to prevent myelinolysis

Rx Hyponatremia (Example)

- 60 kg women, serum Na 107, seizure recalcitrant to benzodiazepines.
- Na deficit = 0.6 x (60) x (120 – 107) = 468 mEq
- Want to correct at rate 1.5 mEq/L/h: 13/1.5 = 8.7h
- 468 mEq / 8.7h = 54 mEq/h
- 3% NaCl has 513 mEq/L of Na
- 54 mEq/h = x
  - 513 mEq 1L
  - x = rate of 3% NaCl = 105 cc/h over 8.7h to correct serum Na to 120 mEq/h
- Note: Calculations are always at best estimates, and anyone getting hyponatremia corrected by IV saline (0.9% or 3%) needs frequent serum electrolyte monitoring (q1h if on 3% NS).

Treatment of hyposmolar (dilutional) hyponatremia

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Treatment Modality</th>
<th>Potential Adverse Outcomes</th>
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<tbody>
<tr>
<td>ACUTE</td>
<td>IV 3% saline, 300–500 mL over 4–6 h, followed by 100 mL/h until serum Na reaches ~125 mEq/L.</td>
<td>Central pontine myelinolysis, CHF</td>
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<tr>
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<td>IV furosemide 1 mg/kg body weight (with oral NaCl tablets)</td>
<td>Hypokalemia, hypomagnesemia</td>
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<td></td>
<td>K replacement if hypokalemic</td>
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<tr>
<td>CHRONIC</td>
<td>Correction of underlying cause</td>
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<td></td>
<td>Fluid restriction to 800–1000 mL per 24 h</td>
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<tr>
<td></td>
<td>Demeclocycline 600–1200 mg per 24 h</td>
<td></td>
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<tr>
<td></td>
<td>Thirst stimulation, dehydration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Photosensitivity, nephrotoxicity in hepatic disease or HF</td>
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Rx Hyponatremia: acute SAH/Head injury

- May have SIADH, CSW or Both!
  - Often difficult to tell which
  - Fluid restriction inappropriate for CSW as may exacerbate ECFv contraction and precipitate cerebral vasospasm and subsequent cerebral infarction
  - IV NS inappropriate for SIADH if U_Osm > 300 mOsm will make hyponatremia worse

Rx with IV NS:
- Start with 0.9% NS (as per hypervolemic therapy to prevent cerebral vasospasm)
- If hyponatremia worsens on 0.9% NS (due to an SIADH component to hyponatremia) consider switch to 3% NS
- Goal: 0.5-1.2 mEq/L/h (only if symptomatic 1-2 mEq/L/h)

Fludrocortisone
- 0.1-0.4 mg/d
- May also be beneficial in recalcitrant cases to alleviate CSW.

Indications for 3% NaCl

- Symptomatic hyponatremia (SZ, coma)
- Acute severe hyponatremia (<24h, < 120 mEq/L)
- SAH with hyponatremia worsening on 0.9% NaCl

Relatively Newer treatment of hyponatremia.

- Vasopressin receptor antagonists
  - V2 receptors primarily mediate the antidiuretic response
  - V1a and V1b receptors principally cause vasoconstriction and mediate ACTH release, respectively
  - Produce a selective water diuresis
  - Tolvaptan (oral) is selective for the V2 receptor
  - Conivaptan (IV) blocks both the V2 and V1a receptors

Role of Aquaretics in the Treatment of Hyponatremia

- AVP receptor antagonists, a class of drugs called “aquaretics,” which promote electrolyte-free excretion of water
- Highly effective in SIADH and in hypervolemic hyponatremia due to HF or cirrhosis, reliably increasing plasma Na+
- Tolvaptan is currently the only oral V1 antagonist to be approved by FDA
- Conivaptan, the only available IV vaptan, is a mixed V1a/V2 antagonist (risk of hypotension due to V1a receptor inhibition)
- Therapy with vaptans must be initiated in a hospital setting, with a liberalization of fluid restriction (>2 L/d) and close monitoring of plasma Na+

Indications for use of tolvaptan

- Outpatient management of SIADH if other modalities such as water restriction and increased solute intake are insufficient

  - The package insert suggests that patients should be in the hospital for the initiation or reinitiation of therapy due to the possibility of too rapid correction of hyponatremia (1.8% in studies)

Vaptans in the treatment of hyponatremia

- Cost about $490 per day
- Efficacy limited and variable
- Side Effects Thirst which negates efficacy
- Alternate options
  - Urea

O’Donoghue D, Trehan A. SIADH and Hyponatremia: Foreword. NDT Plus. 2009;2:iii1–4
Urea in the treatment of hyponatremia

- Oral urea was first used as a diuretic in 1892, and, in 1926, Crawford reported on its use in advanced heart failure, documenting a threefold increase in urine output at a daily dose of 45g.
- Urea's effects on brain swelling and water excretion make it an attractive agent to treat hyponatremia.
- Cost $30 for 8 doses available at most RiteAid/CVS

Hypernatremia Case

- 81-year-old male with acute gastroenteritis for 2 days. Underlying history of Alzheimer’s dementia, HTN, CHF and bipolar disorder
- Meds: Donepezil 10 mg daily, Furosemide 20 mg daily, Lithium 300 mg daily, Lisinopril 10 mg daily, Depakote 125 mg bid

Initial Lab Results

- Sodium = 164
- Potassium = 4.4
- Chloride = 115
- HCO₃⁻ = 26
- BUN = 57
- Creatinine = 1.4
- Calcium = 10.1
- Glucose = 100
- Urine Na⁺ = 41
- Urine Osmolality = 492
- Plasma Osmolality = 315
- Lithium level = 0.8

Hypernatremia (Na⁺ > 145 mEq)

- Hypernatremia is caused by a relative deficit of water in relation to sodium which can result from
  - Net water loss: accounts for majority of cases of hypernatremia
  - pure water loss
  - hypotonic fluid loss
  - Hypertonic gain results from iatrogenic sodium loading
Water homeostasis

- Water homeostasis is mediated by:
  - Thirst
  - Arginine Vasopressin (ADH)
  - Kidneys
- A disruption in the water balance leads to abnormality in serum sodium

ADH Mechanism of Action

Causes of Hypernatremia

- **Net water loss**
  - Pure water loss
    - Unreplaced insensible losses (dermal and respiratory)
    - Hypodipsia
  - Neurogenic diabetes insipidus
    - Post-traumatic
    - Tumors, cysts, histiocytosis, tuberculosis, sarcoidosis
    - Idiopathic
    - Aneurysms, meningitis, encephalitis, Guillain-Barre’ syndrome

Pure Water Loss (cont’d)

- Congenital nephrogenic diabetes insipidus
- Acquired nephrogenic diabetes insipidus
  - Renal disease (e.g. medullary cystic disease)
  - Hypercalcemia or hypokalemia
  - Drugs (lithium, demeclocycline, foscarnet, methoxyflurane, amphotericin B, vasopressin V₂-receptor antagonists)

Causes of Hypernatremia (cont’d)

- **Hypotonic fluid loss**
  - Renal causes
    - Loop diuretics
    - Osmotic diuresis (glucose, urea, mannitol)
    - Postobstructive diuresis
  - Polyuric phase of acute tubular necrosis
  - Intrinsic renal disease
**Hypotonic Fluid Loss (cont'd)**

- **Gastrointestinal causes**
  - Vomiting
  - Nasogastric drainage
  - Enterocutaneous fistula
  - Diarrhea
  - Use of osmotic cathartic agents (e.g., lactulose)

- **Cutaneous causes**
  - Burns
  - Excessive sweating

**Urine Specific Gravity USG**

- Estimates solute concentration of urine on basis of weight as compared with an equal volume of distilled water
  - Normal Pusm is 0.8-1.0% heavier than water so Pusm = 1.008-1.010
  - Each ↑ in Uosm 30-35 mM ↑ USG by 0.1% (0.001)
  - Therefore, USG of 1.006 ~ Uosm 300-350 mM
  - Larger MW urinary osm (glucose, radiocontrast, carbenicillin) if present will falsely elevate USG
  - Nothing falsely lowers USG

**Clinical Manifestations**

- CNS dysfunction s/s depend on large or rapid increases in serum Na+ concentration
  - Outpatients: Affects extremes of ages
  - Elderly: few sx until Na+ > 160; confusion, coma more related to coexisting condition
  - Inpatients: all ages, sx more elusive in presence of pre-existing neurologic dysfunction

**Diabetes Insipidus**

- Polyuria: > 3 L/d  
  - Polydipsia: > 3.5 L/d

**Ddx**

- Diabetes Mellitus
- Hypercalcemia
- Solute diuresis:
  - Volume expansion 2° saline loading
  - High-protein feeds (urea as osmotic agent)
  - Post-obstructive diuresis
- Diabetes Insipidus:
  - Central (CDI)
  - Nephrogenic (NDI)
- Primary (Psychogenic) Polydipsia

**Diabetes Insipidus Ddx**

- **Central (CDI)**
  - Idiopathic
  - Autoimmune
  - Neosurgery, head trauma
  - Cerebral hypoperfusion
  - Tumors
    - Cranopharyngioma, pituitary adenoma, suprasellar meningioma, pineal gland, metastasis
  - Infection
    - Fe, Sarcoid, Hemolytic anemia
- **Nephrogenic (NDI)**
  - X-linked recessive
  - Hypokalemia
  - Hypercalcemia (2° to HPT in particular)
  - Renal disease: post ATN, postobstructive, lupus, renal transplant, amyloid, Sickle cell anemia
  - Sjogren’s
  - Drugs:
    - Lithium, 20% of chronic users
    - Demeclocycline, amphotericin, colchicine

**Causes of Hypernatremia (cont’d)**

- Hypertonic sodium gain
  - Hypertonic sodium bicarbonate infusion
  - Ingestion of sodium chloride
  - Sodium chloride-rich emetics
  - Hypertonic saline enemas
  - Hypertonic sodium chloride infusion
  - Hypertonic dialysis
  - Primary hyperaldosteronism
  - Cushing’s syndrome
### Diabetes Insipidus

- **Intact thirst & access to water**
  - Hi-normal serum sodium (142-145 mEq/L)
  - Polydipsia (crave cold fluids)
  - Polyuria, Nocturia → sleep disturbance
  - 1st treatment is pharmacological

- **Impaired thirst or access to water:**
  - Hypernatremia
  - Insufficiently concentrated urine
  - 1st treatment is free water (enteral or IV DSW)

### Management

A two-pronged approach:

- Addressing the underlying cause: stopping GI loss, controlling pyrexia, hyperglycemia, correcting hypercalcemia or feeding preparation, moderating lithium induced polyuria
- Correcting the prevailing hypertonicity: rate of correction depends on duration of hypernatremia to avoid cerebral edema

### Correction of Hypernatremia

- Hypernatremia that developed over a period of hours (accidental loading)
  - Rapid correction improves prognosis without cerebral edema
  - Accumulated electrolytes in brain rapidly extruded
  - Reducing Na⁺ by 1 mmol/L/hr appropriate

- Hypernatremia of prolonged or unknown duration
  - A slow pace of correction prudent
  - Full dissipation of brain solutes occurs over several days
  - Maximum rate 0.5 mmol/L/hr to prevent cerebral edema
  - A targeted fall in Na⁺ of 10 mmol/L/24 hr

### Rate of Correction (Cont’d)

- Hypernatremia of prolonged or unknown duration
  - A slow pace of correction prudent
  - Full dissipation of brain solutes occurs over several days
  - Maximum rate 0.5 mmol/L/hr to prevent cerebral edema
  - A targeted fall in Na⁺ of 10 mmol/L/24 hr

### General Treatment

- Next, calculate the free water deficit
- Free water deficit = TBW x (serum Na - 140/140)
- Our patient’s FWD = 52 x (164-140/140)
  - = 52 x 0.1714
  - = 8.9 L free water deficit

### Avoiding Complications: Cerebral Edema

- **Acute hypernatremia**
  - occurring in a period of less than 48 hours
  - can be corrected rapidly (1-2 mmol/L/hr)

- **Chronic hypernatremia**
  - rate not to exceed 0.5 mmol/L/h or a total of 10 mmol/d
  - Change in conc of Na per 1L of infusate = conc of Na in serum - conc of Na in infusate / TBW + 1
Common Na Contents

<table>
<thead>
<tr>
<th>Fluid Type</th>
<th>Na Content (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% dextrose in water (D5W)</td>
<td>0 mEq Na</td>
</tr>
<tr>
<td>0.2% sodium chloride in 5% dextrose in water (D5 1/4 NS)</td>
<td>94 mmol/L</td>
</tr>
<tr>
<td>0.9 NS</td>
<td>154 mmol/L</td>
</tr>
<tr>
<td>0.45NS</td>
<td>77 mmol/L</td>
</tr>
<tr>
<td>Lactated Ringer’s</td>
<td>130 mmol/L</td>
</tr>
</tbody>
</table>

Goal of Treatment

- Reduce serum sodium concentration to 145 mmol/L
- Make allowance for ongoing obligatory or incidental losses of hypotonic fluids that will aggravate the hypernatremia
- In patients with seizures prompt anticonvulsant therapy and adequate ventilation

Administration of Fluids

- Preferred route: oral or feeding tube
- IV fluids if oral not feasible
- Except in cases of frank circulatory compromise, isotonic saline is unsuitable
- Only hypotonic fluids are appropriate—pure water, 5% dextrose, 0.2% saline, 0.45% saline—the more hypotonic the infusate, the lower the infusion rate required

Summary of Managing Hypernatremia

- Isotonic saline unsuitable except in ECF volume depletion causing hemodynamic instability
- Switch to hypotonic solutions as soon as circulatory status stabilized
- Avoid excessive rapid correction or over correction
- Select the most hypotonic infusate suitable with appropriate allowances for ongoing fluid losses
- Most important - reassess infusion prescriptions at regular intervals based on pt’s clinical status and electrolyte values

Questions?
Demystifying the Basic Metabolic Panel - Pandya

Speaker Disclosures

Dr. Pandya has no relevant financial relationship for this topic.

Learning Objectives

By the end of the session, participants will be able to:

- Interpret the BMP accurately, Diagnose and manage hyponatremia and hypernatremia.
- Identify causes work up and treatment of hyperkalemia and hypokalemia and acid base imbalance.
- Describe the differential diagnosis of hypercalcemia and hypocalcemia and appropriate management.

Hyperkalemia

Blood potassium > 5.5 mmol/L

Scope of the problem

- In the population-based Rotterdam study, (N=5179, age >55y), hyperkalemia noted in
  - 0.2% of 65-74 y-olds
  - 0.7% 75-y-olds
- Hypokalemia noted in
  - 2.3% 65-74 y-olds
  - 2.3% >74 y-olds
- Risk factors:
  - HTN (OR 2.73)
  - HF (OR 1.17)
  - thiazide diuretics (OR 7.86)
  - loop diuretics (OR 3.71)

G. Liamis et al. AJM 2013; 126:3

Case: Hyperkalemia

- A 63 year old woman residing in a high acuity facility was noted to have recurrent episodes of hyperkalemia which became more difficult to control with multiple doses of sodium polystyrene (Kayexelate) weekly
- PMH: COPD, chronic respiratory failure, type 2 DM, HTN, CHF, CKD stage 4, nephrolithiasis, hyperparathyroidism,
- Exam: BP 146/80, HR 84, tracheostomy, alert, regular S1 and S2, scattered ronchi, no flank pain, 2+ edema, strength 4/5
Demystifying the Basic Metabolic Panel - Pandya

Case: Hyperkalemia...

- Medications: Albuterol/ipratropium nebulizers, insulin glargine, and aspart, diltiazem, furosemide, citalopram, cinacalcet, levothyroxine, EPO
- Laboratory tests:
  - K 5.6 mol/L, Na 135 mmol/L, CO2 18 mmol/L, Cl 99 mmol/L
  - Bun 44 mg/dL, Creat 2.5 mg/dL
  - Ca 9.8 mg/dL, Alp 130 IU/L, phos 4.3 mg/dL

What is the most likely cause of hyperkalemia in this patient?

A. Renal tubular acidosis
B. Metabolic acidosis
C. Chronic kidney disease
D. Impaired urinary potassium excretion

Signs and symptoms

- Nonspecific (often incidental finding in blood test)
- Malaise
- Palpitations
- Muscle weakness and fatigue
- Hyperventilation (compensating for metabolic acidosis)
- Reduced reflexes, bradycardia

EKG – large T waves, small p waves, wide QRS

Differential dx of hyperkalemia by pathogenesis

**INCREASED INTAKE (URINE K > 20 mEq/L)**

- High K foods with underlying CKD
- Salt substitutes
- K supplements routinely with diuretics
- K-rich parenteral nutrition formulas

**DECREASED RENAL EXCRETION (URINE K < 20 mEq/L)**

- K-sparring diuretics (thiazides)
- ACEI, ARBs
- NSAIDs
- Hepatic
- Trimethoprim-sulfamethoxazole
- Cyclosporine and tacrolimus
- Chronic kidney disease
- Type 4 renal tubular acidosis (T2 DM, sickle cell disease, adrenal insufficiency, lower urinary tract obstruction [BPH or neurogenic bladder])

**SHIFT OUT OF THE CELLS (URINE K > 20 mEq/L)**

- Metabolic acidosis mostly due to inorganic acids
- Severe cell in PRBS
- β-blockers, methotrexate, digitalis
- Succinylcholine use in anesthesia
- Insulin deficiency and hyperglycemia
- Rhabdomyolysis, tumor lysis syndrome
- Neuropathic malignant syndrome following haloperidol

**PSEUDOHYPERKALEMIA**

- Prolonged tourniquet or repeated fist clenching
- Severe leukocytosis and thrombocytosis
- Traumatic amputations
- Delay in processing the blood sample in lab
Demystifying the Basic Metabolic Panel - Pandya

**Drugs known to induce hyperkalemia**

**Drug - inducing transmembrane K movement**
- Non-selective β
- Dipeptidyl peptidase
- Intravenous amino acids
- Mannitol
- Sucralfate

**Drugs that effect aldosterone secretion**
- ACE inhibitors
- ARBs
- Direct renin inhibitors
- NOACs and CTR-2 inhibitors
- Calcitonin inhibitors

**PREDICTORS OF THE DEVELOPMENT OF HYPERKALEMIA IN PATIENTS USING ACEI**
- Retrospective study of 119 patients in a renal clinic on ACEI
- The baseline serum Cr was 2.3 ± 1.2 (range 0.6–6.9) mg/dl, and the CrCl was 50 ± 27.1 ml/min
- 46 (38.6%) developed hyperkalemia (mean K 5.68 ± 0.3 mEq/l)
- Diabetes and serum creatinine were the main predictors of hyperkalemia (not GFR or serum HCO3)
- Also common in HF patients on guideline-recommended inhibitors of the renin-angiotensin-aldosterone system (RAAS)
- RAAS therapy is well known to reduce the risk of death and hospitalization in patients with HF and reduced ejection fraction (HFrEF)
- Difficult decision of down-titrating or discontinuing RAAS inhibitors

**Treatment of Acute Hyperkalemia - Do Not Decrease Total Body Potassium**
- Protect heart
  - Normal intracellular K
  - Early oral bicarbonate
  - Acetate 3 g slow IV
  - Delayed sodium bicarbonate
  - Use of insulin
  - Dextrose 10% and 50% in normal saline
  - Hypertonic saline
  - Insulin and glucose
  - Hyperkalemia in patients with severe failure or shock divided
  - Sodium bicarbonate
  - Serum bicarbonate when there is acidosis

- Shifting K into IC compartment
  - Intravenous hypotonic NaCl
  - Diuretics
  - Sodium bicarbonate
  - Use of insulin
  - Use of β-blockers
  - Sodium bicarbonate

**Evaluation of hyperkalemia - access Medicine**

**Treatment of ACUTE hyperkalemia**
- Protect heart
  - Calcium chloride (0.5 ml normal saline)
  - Calcium gluconate (1 ml normal saline)
  - High-dose sodium bicarbonate
  - Intravenous insulin
  - High-dose bicarbonate infusion

- Shifting K into IC compartment
  - Intravenous fluid bolus
  - Intravenous potassium
  - Sodium bicarbonate

- Remove Potassium from body
  - Loop diuretics
  - Oral sodium bicarbonate
  - Sodium bicarbonate

**Drugs known to induce hyperkalemia**
- Drugs cause tubular resistance to aldosterone
- Non-selective α antagonists
- Thiazide diuretics
- Bilateral nephrectomy
- Bilateral renal artery stenosis
- Alpha blockers
- Calcium channel blockers
- Beta blockers
- RAAS inhibitors
- Potassium-sparing diuretics
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Risk Stratification and Initial Management

- Weakness, paralysis?
- Cardiac conduction or arrhythmias?

HYPERKALEMIC EMERGENCY

Serum K>6.5 mEq/L

All present?
- K>5.5 mEq/L?
- Significant renal impairment?
- Tissue breakdown?
- Serum K>5.5 mEq/L (Renal impairment: ESRD or oliguria; Or surgery)

Lower K promptly
K can be lowered slowly.

TREATMENT OF CHRONIC HYPERKALEMIA

Remove K from the body
- Patiromer
- Zirconium Cyclosilicate ZS-9

Patiromer (Veltassa)- NEW THERAPY FOR THE TREATMENT OF HYPERKALEMIA

- Patiromer exchanges K+ for calcium and promotes fecal excretion of K+ in a dose-dependent manner in colon
- Administered as a powder mixed with 1/3 cup of water (max 25.2g)
- Multicenter, open-label, randomized, 52-wk study (AMETHYST-DN)
- OPAL-HK - multicenter, single-blind, randomized study with 2 phases: initial treatment phase and an 8-wk, placebo-controlled, randomized withdrawal phase.
- Reduction of mean serum K to normokalemic levels (<5.0 mEq/L) in 48 hours for with mild hyperkalemia and in 1 week for patients with moderate hyperkalemia
- Mean change in serum K was 0.99mEq/L in those >75y and well tolerated
- A significantly higher proportion of patients who received patiromer (94%) remained on RAASi therapy compared to 44% who received placebo

Case of Hypokalemia

- A 62 y-old LTC resident who came over to our service was noted to be on multiple antihypertensive medications and frequently elevated BP readings
- PMH: massive CVA with right hemiplegia and aphasia 5 y ago, HTN, hyperlipidemia, and anxiety
- MEDICATIONS: amlodipine, metoprolol, furosemide, losartan, and clonidine
- EXAMINATION: BP 162/94, normal CV exam, no carotid or abdominal bruits, right hemiplegia, dysarthria, gastrosomy tube, bilateral foot drop

YOUR THOUGHTS ON HIS POORLY CONTROLLED HYPERTENSION?
Major Causes of Hypokalemia

- Decreased potassium intake
- Increased entry into cells
- Increased gastrointestinal losses
- Increased urinary losses
- Increased sweat losses
- Dialysis

<table>
<thead>
<tr>
<th>Cause of Hypokalemia</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased potassium intake</td>
<td>Intake is normally 40 to 120 mEq per day. Most then excreted in the urine. Decreased intake alone rarely causes significant hypokalemia.</td>
</tr>
</tbody>
</table>

Increased gastrointestinal losses
- Vomiting
- Diarrhea
- Tube drainage, ileostomy
- Laxative abuse
- Celiac disease

Increased urinary losses
- Diuretics
- Primary mineralocorticoid excess
- Loss of gastric secretions
- Nonreabsorbable anions
- Renal tubular acidosis
- Hypomagnesemia
- Amphotericin B
- Salt-wasting nephropathies
- Polyuria

Increased sweat losses
- Exercising in a hot climate if not replaced
- Cystic fibrosis

Dialysis
- Dialysis potassium losses can reach 30 mEq/d in chronic peritoneal dialysis.
- Mild hypokalemia immediately following hemodialysis is expected and should not be treated with K supplementation.

Manifestations of Hypokalemia

- Severe muscle weakness or rhabdomyolysis (esp if K<2.5 mEq/L)
- Cardiac arrhythmias and ECG abnormalities
  - Palpitations, respiratory distress
  - EKG: flattened T waves, prominent U waves
  - Potentiation of dig toxicity
- GI symptoms
  - Nausea or vomiting
  - Abdominal cramping
  - Constipation, ileus
- Renal symptoms
  - Polyuria, nocturia, polydipsia
- Nervous system symptoms
  - Delirium, depression, psychosis
Approach to Treatment

- The treatment of hypokalemia has four facets:
  - Reduction of potassium losses
  - Replenishment of potassium stores
  - Evaluation for potential toxicities
  - Determination of the cause to prevent future episodes, if possible

Potassium Replacement

- For every 1 mEq/L decrease in serum potassium, the body potassium deficit is approximately 200-400 mEq (in the absence of abnormal K⁺ redistribution).
- If K<2.5 mEq/L, intravenous potassium should be given.
- Patients who have mild or moderate hypokalemia (K 2.5-3.5 mEq/L) are usually asymptomatic.
- If these patients have only minor symptoms, they may need only oral potassium replacement therapy.
- If cardiac arrhythmias, digoxin toxicity, or significant symptoms are present, then more aggressive therapy is warranted similar to the treatment of severe hypokalemia.

Potassium Replacement….

- Oral replacement with K⁺–Cl⁻ is the mainstay of therapy.
- Potassium phosphate, oral or IV, may be appropriate in patients with combined hypokalemia and hypophosphatemia.
- Potassium bicarbonate or potassium citrate should be considered in patients with concomitant metabolic acidosis.
- Hypomagnesemic patients are refractory to K⁺ replacement alone; concomitant Mg⁺⁺ deficiency should always be corrected with oral or IV repletion.
- Intravenous K⁺–Cl⁻ should always be administered in NSal rather than dextrose.
- Peripheral IV dose is usually 20-40 mmol of K⁺–Cl⁻ /L.

Questions?

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Hypercalcemia
CASE: Hypercalcemia

- A 78-yr old man in a ventilator unit was noted to have a Ca of 12.5 mg/dL on BMP for monitoring his CKD
- PMH – Chronic respiratory failure, tracheostomy, PEG tube, cardiomyopathy, pacemaker, gangrene both feet following CABG and pressor use, DM2, hypothyroidism, depression, chronic anemia
- Exam- Alert, functional quadriplegia, tracheostomy, ventilated 100%, no bony deformities, no adenopathy, regular heart sounds, clear lungs, benign abdomen, no CVAT, necrotic forefeet, absent posterior tibial pulses

Laboratory tests
- Ca 12.0 mg/dL, PO4 4.8 mg/dL, ALP 85 U/L
- Intact PTH 40 pg/mL (10-65)
- 25 OH Vit D 28 ng/mL
- Bun 45 mg/dL, Creat 2.5 mg/dL, gluc 120 mg/dL
- Hb 9.5 g/dL
- TSH 1.1 mIU/mL, Free T4 1.3 ng/dL
- AM cortisol 20 mcg/dL

What is the most likely cause of hypercalcemia in this patient?

A. Overtreatment with thyroxine
B. Primary hyperparathyroidism
C. Chronic kidney disease
D. Malignancy
E. Prolonged immobilization

Hypercalcemia

- Manifestation of a serious illness such as malignancy or detected coincidentally by lab testing with absent symptoms
- Whenever hypercalcemia is confirmed, a definitive diagnosis must be established
- Hyperparathyroidism is a chronic disorder in which manifestations, if any, may be expressed only after months or years
- Malignancy is the second most common cause of hypercalcemia in adults

Interpretation of serum calcium

- Hypercalcemia is due to an elevation in the physiologically important ionized (or free) calcium concentration
- 40 to 45 % of the calcium in serum is bound to protein, principally albumin
- Increased protein binding can cause an elevation in the serum total calcium concentration (dehydration, myeloma)
- In hypoalbuminemia (chronic illness or malnutrition) total serum calcium may be normal when serum ionized calcium is elevated; use a Calcium calculator
Causes of Hypercalcemia – The BIG Picture

- BONE RESORPTION
- CALCIUM ABSORPTION
- MISCHELANEOUS

Bone Resorption

- Primary hyperparathyroidism
- Secondary and tertiary hyperparathyroidism (CKD)
- Malignancy
- Thyrotoxicosis (20% of have high-normal or mild hypercalcemia)

Other
- Immobilization (spinal cord injury and paraplegia)
- Paget disease of bone (with bed rest)
- Hypervitaminosis A (>50,000 IU/d)

Bone Resorption

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Other
- Immobilization (spinal cord injury and paraplegia)
- Paget disease of bone (with bed rest)
- Hypervitaminosis A (>50,000 IU/d)

Calcium Resorption

- Hypervitaminosis D
- Vitamin D intoxication (2000 U/d recommended)
- 1,25(OH)2D in CKD, and 25(OH) D ingestion
- Increased calcium intake (rare- will lower PTH) unless there is also decreased urinary excretion combined with increased intake in;
  - CKD patients given calcium carbonate or calcium acetate to bind dietary phosphate in adynamic bone disease or calcitriol treatment
- Milk alkali syndrome (high intake of milk or calcium carbonate)
- Topical calcipodtriol for dermatological disorder
- Sarcoidosis and other granulomatous diseases (from 1,25(OH)2D)

Calcium Absorption…

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Miscellaneous

- Lithium (10% of pts)
- Thiazide diuretics (urinary Ca)
- Pheochromocytoma
- Adrenal insufficiency
- Rhabdomyolysis and acute renal failure
- Theophylline toxicity
- Familial hypocalciuric hypercalcemia (few sx, Ca sensing defect)

Clinical Features are Helpful in Differential Diagnosis

- Symptoms: fatigue, depression, confusion, anorexia, vomiting, constipation, urinary frequency, short QT
- Hypercalcemia in asymptomatic pts is usually due to primary hyperparathyroidism (PHPT)
- FH of HPTH (Multiple Endocrine Neoplasia)
- In malignancy - disease is usually evident
- Dietary history and use of vitamins or drugs
- Renal: nephrocalcinosis or recurrent nephrolithiasis (in <20% - ca oxalate or phosphate)
- Increase bone turnover (bone sp Alk Phos, osteocalcin)
- Cortical bone density (DEXA hips or distal radius), spine relatively preserved
- Do not cut corners on the physical exam! (breast, rectal, genital exam)

Severity of Hypercalcemia and Clinical Manifestations

<table>
<thead>
<tr>
<th>Calcium level</th>
<th>Clinical correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2.9 to 3 mmol/L (11.5 to 12.0 mg/dL)</td>
<td>Neuropsychiatric, GI, renal symptoms</td>
</tr>
<tr>
<td>&gt;3.2 mmol/L (13 mg/dL)</td>
<td>Calcification in kidneys, skin, vessels, lungs, heart, and stomach</td>
</tr>
<tr>
<td>3.7 to 4.5 mmol/L (15 to 18 mg/dL)</td>
<td>Medical emergency, coma and cardiac arrest</td>
</tr>
</tbody>
</table>
Primary hyperparathyroidism is the single most common cause of nephrocalcinosis in adults.

Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism

- Serum calcium (above normal): >1 mg/dL
- 24-h urinary calcium: No indication
- Creatinine clearance (calculated): If <60 mL/min
- Bone density: T score < -2.5 at any of 3 sites
  - Age < 50 years

Guidelines for Monitoring in Asymptomatic Primary Hyperparathyroidism

- Serum calcium: Annually
- 24-h urinary calcium: Recommended
- Creatinine clearance: Recommended
- Serum creatinine: Annually
- Bone density: Annually (3 sites)

How do the Elderly Fare After Parathyroidectomy?

- Minimally invasive parathyroidectomy is becoming the norm
- 72 patients (75-85 y) followed after surgery for PHPT
- Thirty-day perioperative mortality was 1.4%
- Morbidity was 8.7% (infection, vocal cord damage)
- 60 patients died of cardiovascular causes in the 4 yr follow-up period

Medical Management if Surgery is not an Option

- Bisphosphonates: 5% increase in bone density in the spine with alendronate in asymptomatic HPTH (no change in PTH or Ca)
- Raloxifene increased bone density (limited effectiveness)
- Estrogen-progesterin therapy
- Calcimimetics, (cinacalcet 30 mg BID) decrease calcium levels to normal in 73% and lower PTH levels by 8%, indicated for severe disease and parathyroid cancer
What is the most likely cause of hypercalcemia in this patient?

A. Overtreatment with thyroxine  
B. Primary hyperparathyroidism  
C. Chronic kidney disease  
D. Malignancy  
E. Prolonged immobilization

Treatment of Hypercalcemia Depends on Severity of Symptoms and Underlying Cause

- Volume expansion and saline diuresis
- Mobilization if possible
- Reduction of gastrointestinal calcium absorption
  - Reduction of dietary Ca and Vit D intake if hypercalcemia due to increased intestinal absorption
  - In vitamin D toxicity or extrarenal synthesis of 1,25(OH) D3 (eg, in sarcoidosis), prednisone reduces plasma Ca levels by reducing intestinal absorption.
- Oral phosphate also can be used to form insoluble calcium phosphate in the gut.
- Inhibition of bone resorption (next slide)
- Dialysis: Peritoneal or hemodialysis against calcium-free dialysate solution

Summary of the Approach to Hypercalcemia

- Correct calcium for albumin level
- Review all medications carefully
- A detailed history and physical examination is essential
- In addition, the intact PTH, 24h urinary calcium, vitamin D levels, TSH and free T4, am cortisol will assist in making most diagnoses

CASE: Hypocalcemia

- 84 yr old female admitted to your facility after a left hip replacement
- PMH: HTN, osteoporosis, cholecystectomy, hypothyroidism
- Medications: HCTZ 12.5 mg daily, levothyroxine, zolendronic acid IV for osteoporosis 6 months ago
- The patient has no complaints and the VS are normal; faint thyroidectomy scar, occasional myoclonus
- Ca 6.5 mg/dL (also low in older records), Phos 5.9 mg/dL, Albumin 3.8 mg/dL, eGFR 70 ml/min/1.73m2
What is a possible cause of hypocalcemia in this patient?

A. Vitamin D deficiency
B. Acquired post-surgical hypoparathyroidism
C. Chronic kidney disease
D. Use of zolendronic acid

What is a possible cause of hypocalcemia in this patient?

A. Vitamin D deficiency
B. Acquired post-surgical hypoparathyroidism (due to parathyroid damage during thyroidectomy)
C. Chronic kidney disease
D. Use of zolendronic acid

Pathophysiology

- Interpretation: serum total calcium concentration falls approximately 0.8 mg/dL for every 1 g/dL reduction in the serum albumin concentration (ionized calcium is normal)
- Ionized calcium is affected by:
  - Albumin
  - Blood pH
  - Serum phosphate
  - Serum magnesium
  - Serum bicarbonate

Role of the calcium-sensing receptor

- (CaSR) is a G protein–coupled receptor, which allows the parathyroid chief cells, the thyroidal C cells, and the ascending limb of the loop of Henle to respond to changes in the extracellular calcium concentration
- Essential for the appropriate regulation of PTH secretion by the parathyroid glands and for the regulation of passive paracellular calcium absorption in the loop of Henle
- Calcitonin secretion and renal tubular calcium reabsorption also are directly regulated by the action of Ca++ on the calcium receptor

Causes of Hypocalcemia

- With low PTH -hypoparathyroidism
- With high PTH -secondary hyperparathyroidism in response to hypocalcemia
- Drugs
- Disorders of magnesium metabolism (PTH or PTH resistance)
Hypocalcemia - With low PTH (primary hypoparathyroidism)

- Congenital
- Autoimmune
- APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome)
- Hypoparathyroidism
- Primary adrenal insufficiency
- Chronic mucocutaneous candidiasis

Acquired
- Thyroid surgery
- Parathyroidectomy
- Iron deposition with chronic transfusions
- Wilson’s disease
- Gram negative sepsis, toxic shock, HIV

Hypocalcemia - With High PTH (secondary hyperparathyroidism)

- Vitamin D deficiency or resistance
- Parathyroid hormone resistance – pseudohypoparathyroidism, hypomagnesemia
- Renal disease
- Loss of calcium from the circulation: Hyperphosphatemia, tumor lysis, acute pancreatitis, osteoblastic metastases, acute respiratory alkalosis, sepsis or acute severe illness, hungry bone syndrome post parathyroidectomy

Hypocalcemia - Due to Drugs

- Inhibitors of bone resorption (bisphosphonates, calcitonin), especially in vitamin D deficiency
- Cinacalcet
- Calcium chelators (EDTA, citrate, phosphate)
- Foscarnet (due to intravascular complexing with calcium)
- Phenytoin (due to conversion of vitamin D to inactive metabolites)
- Fluoride poisoning

Symptoms and Signs of Hypocalcemia

- Neuromuscular irritability
- Paresthesias
- Laryngospasm / bronchospasm
- Tetany (neuronal excitability overrides inhibition of muscle contraction)
- Seizures
- Chvostek sign
- Trousseau sign
- Prolonged QTc time on ECG

Positive Chvostek’s Sign

A blood pressure cuff is inflated to a pressure above the patient’s systolic level.
Pressure is continued for several minutes.
- Carpopedal spasm:
  - flexion at the wrist
  - flexion at the MP joints
  - adduction thumbs/fingers

Trousseau sign:
(very uncomfortable and painful)
EKG Changes in Hypocalcemia
- Long QT interval with normal T waves
- Prolongation of the ST segment with little shift from the baseline

Workup - blood
- Total and ionized calcium (se Ca <8.5 mg/dL or ionized Ca <1.0 mmol/L)
- Serum albumin (add 0.8 mg/dL for each 1.0 g/dL decrease in alb below 4.0 g/dL)
- BUN, Cr, eGFR (↑ phos and PTH in renal failure)
- Magnesium
- Phosphate (↑ in renal failure, ↓ in Vit D deficiency and hungry bone)
- ALP (normal or slightly decreased in low PTH states)
- PTH (low to NL in hereditary or acquired hypoparathyroidism, and hypomagnesemia)
- Vitamin D metabolites (25(OH)D and 1,25(OH)2 D)
- Urine-CMP (↑ in hypoparathyroidism and not pseudohypoparathyroidism)

Workup – Imaging and Other
- ECG
- CXR, rib films
- Pelvis and other X-rays (Looser’s zones, metastatic disease)
- CT brain (basal ganglia calcification in isolated hypoparathyroidism)
- Malabsorption workup if indicated

Management
1. Dependent on the underlying cause and severity
2. Administration of calcium alone is only transiently effective
3. Symptomatic: Treat immediately
4. Mild asymptomatic cases: Often adequate to increase dietary calcium by 1000 mg/day

Treatment of Acute Symptomatic hypocalcaemia

Symptomatic hypocalcaemia
- IV Calcium gluconate or chloride should only be given with close monitoring (90 vs. 272 mg elemental Ca)
- Should be on cardiac monitor
- Mix with NaCl or 5% D/W (not bicarbonate/lactate containing solutions)
- Administer CaCl by central line

Risks
- Tissue necrosis/calcification if extravasation
- Calcium can inhibit sinus node → bradycardia + arrest
- Avoid complete correction of hypocalcaemia (aim for 8-9 mg/dL)
- With acidosis and ↓ Ca – give Ca before correcting acidosis
- If ↓ Mg is cause of ↓ Ca – treat and correct hypomagnesemia

Treatment of Chronic Hypocalcemia

- Patients with hypoparathyroidism and pseudohypoparathyroidism can be managed initially with oral calcium supplements
- The hypercalcemic effects of thiazide diuretics may be beneficial
- Vitamin D in severe hypoparathyroidism (0.5-2 mcg of calcitriol or 1-alpha-hydroxyvitamin D3)
- Recombinant human parathyroid hormone (rHPTH, Natpara) is commercially available in the US and is indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism
Questions?

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A Review of Acid-Base Disorders
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Speaker Disclosures
Dr. Dharmarajan has no financial relationship(s) or disclosures, whatsoever, to report in relation to this presentation.

Learning Objectives
By the end of the session, participants will be able to:
• Understand terminology in relation to acid-base disorders
• Understand the compensatory mechanisms involved
• Understand the simple acid-base disorders
• Understand in brief the mixed acid-base disorders
• Illustrate with cases and discussion to enable understanding

Definitions and Terms
• Acid: a molecule that liberates H⁺ ions
• Base: a molecule that can combine with H⁺ ions
• pH: a measure of H⁺ ion concentration
  - Normal pH 7.35 – 7.45
  - Acidemia and alkalemia: refers to change in pH
  - Acidosis and alkalosis: refers to the process that shifts pH

The Primary acid-base disorders
• The 4 recognized primary acid-base disorders comprise:
  - Two metabolic disorders: acidosis and alkalosis
  - Two respiratory disorders: acidosis and alkalosis
• The pH is generally used in clinical medicine to denote acid-base status
• The terms “acidemia” and “alkalemia” refer to states in which blood pH is abnormally low (acidic) or high (alkaline)

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Demystifying the Basic Metabolic Panel - A Review of Acid-Base Disorders - Dharmarajan

Measurements that Hint!

- An abnormal serum total carbon dioxide content is **definite evidence** of an acid-base disorder.
- An abnormal serum anion gap is very **suggestive**.
- An abnormal serum potassium is **suspicious**.

Serum Carbon Dioxide or Bicarbonate?

- The bicarbonate in plasma can be estimated by measuring the total carbon dioxide in venous serum.
- The serum total carbon dioxide is 1-3 mmols/L greater than the bicarbonate derived from an ABG measure, because it includes bicarbonate + other compounds in venous serum.

The Primary Acid-base Disorders

- **CO2 generation** occurs through oxidative phosphorylation in Kreb’s cycle from metabolism of glucose and free fatty acids.
- **Generation of HCO3** is through:
  - Kidney: H+ ion secretion via Na+/K+ exchanger, H+ proton pump
  - Stomach: H+ ion secreted via proton pump
  - In cells: \( CO_2 + H_2O = H_2CO_3 = H^+ + HCO_3^- \)

- The process by which the H ion concentration is increased is termed **acidosis**.
- The process by which the H ion concentration is decreased is called **alkalosis**.
- An acid base disorder is respiratory when it is caused by a primary respiratory function disorder and metabolic when the primary change is due a variation in the bicarbonate concentration.

The Renal Role in Acid-Base Balance

- Most bicarbonate (85 – 90%) filtered by the glomerulus returns to the circulation, through Na-H exchange in the PCT.
- Remaining 10% is reclaimed at the distal nephron via H⁺ ion secretion by proton pumps (H-ATPase and H-K ATPase).
- The excretion of daily hydrogen ion load is a function of the collecting tubule. The average load in a Western diet is 1mEq/kg, or 50 – 70 mEq of acid; hard to excrete without buffers.
- The principal buffers in urine involves the combination H⁺ and urinary titrable acid: HPO₄ to form H₂PO₄ and ammonia to form ammonium (NH₃ + H⁺ to form NH₄) which is trapped in urine.

Assessment of an Acid-Base Disorder

- Step 1: careful clinical exam
  - Vital signs: suggest infection, volume status, resp failure, etc
  - e.g. fever, hypotension, Kussmaul respiration, visual loss, etc
- Step 2: medications: diuretics, metformin, laxatives; include OTC drugs and others (ethanol, ethylene glycol, isopropyl alcohol).
- Step 3: determine the primary acid-base response and the secondary response; is the response appropriate?
- Step 4: evaluate the metabolic component of an acid-base disorder
- Step 5: is there a Mixed acid-base disturbance?

Determining the Primary and Secondary Response

- Range of pH compatible with life is 6.8 to 7.8
- Reference values
  - for pH: 7.40 ± 0.02,
  - for PaCO₂ it is 38 ± 2 mm Hg and
  - for HCO₃ it is 24 ± 2 mmol/L
- Homeostatic response for acid-base disorders is predictable & can be calculated
- For metabolic disorders changes in respiration develop quickly and a new steady state PaCO₂ results in hours
- For respiratory disorders, metabolic compensation develops slowly, with 2-5 days required for bicarbonate to reach steady state levels

Compensation: Basics

- Remember: compensatory responses are always towards normal pH but not to normal or beyond normal.
- Directions of deviations of buffer pair: the HCO₃ and PCO₂ change from normal in the same direction in all simple acid-base disorders.
- If they change in opposite directions (up-down, down-up), the disorder is mixed.
- When the secondary response differs from what is expected, mixed acid-base disorders are diagnosed.

Defense of Acid Base Disorders

<table>
<thead>
<tr>
<th>Phase</th>
<th>Metabolic</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Chemical Buffering</td>
<td>Chemical Buffering</td>
</tr>
<tr>
<td>II</td>
<td>Respiratory Compensation</td>
<td>Renal Compensation</td>
</tr>
<tr>
<td>III</td>
<td>Renal Correction</td>
<td>Respiratory Correction</td>
</tr>
</tbody>
</table>
Primary Acid Base Disorder and Compensatory Response: Metabolic Acidosis

- pH < 7.38 and HCO₃ < 22 mmol/L
- Secondary (compensatory) respiratory response
  - PaCO₂ = 1.5 x [HCO₃] + 8 ± 2 mm Hg or [HCO₃] + 15 mm Hg
  - The adaptive response occurs within 12 – 24 hours
- If the respiratory response (PaCO₂) is greater or lesser than predicted, superimposed respiratory alkalosis or acidosis may be diagnosed


Primary Acid Base Disorder and Compensatory Response: Metabolic Alkalosis

- pH > 7.42 and HCO₃ > 26 mmol/L
- Secondary (compensatory) respiratory response
  - PaCO₂ = 0.7 x ([HCO₃] – 24) + 40 ± 2 mm Hg, or [HCO₃] + 15 mm Hg, or 0.7 x [HCO₃] + 20 mm Hg
  - The adaptive response occurs within 24 – 36 hours
- If the respiratory response (PaCO₂) is greater or lesser than predicted, superimposed respiratory alkalosis or acidosis may be diagnosed


Primary Acid Base Disorder and Compensatory Response: Respiratory Acidosis

- pH < 7.38 and PaCO₂ > 42 mm Hg
- Secondary (compensatory) metabolic response
  - Acute: [HCO₃] increases by 1 mmol/L for each PaCO₂ increase of 10 mm Hg above 40 mm Hg
  - Chronic: [HCO₃] increases by 4 mmol/L for each PaCO₂ increase of 10 mm Hg above 40 mm Hg
  - The adaptive response occurs within 2 – 5 days
- If the calculated [HCO₃] is greater or lesser than predicted, superimposed metabolic alkalosis or acidosis is diagnosed


Primary Acid Base Disorder and Compensatory Response: Respiratory Alkalosis

- pH > 7.42 and PaCO₂ < 38 mm Hg
- Secondary (compensatory) metabolic response
  - Acute: [HCO₃] decreases by 2 mmol/L for each PaCO₂ decrease of 10 mm Hg below 40 mm Hg
  - Chronic: [HCO₃] decreases by 4 mmol/L for each PaCO₂ decrease of 10 mm Hg below 40 mm Hg
  - The adaptive response occurs within 2 – 5 days
- If the calculated [HCO₃] is greater or lesser than predicted, superimposed metabolic acidosis or alkalosis is diagnosed

Geeks!

• Osmolal gap
• Anion Gap

Serum (or Plasma) Osmolal Gap

• One must note the serum osmolal gap in any patient with an unexplained high anion-gap acidosis, or suspicion of ingestion of a toxin (alcohol) e.g. ethylene glycol.
• Lab confirmation often delayed; so may infer diagnosis!
• Osmolal gap is the difference between measured and calculated serum osmolality, and is calculated as follows:
  \[ 2 \times \text{Na (mEq/l)} + \text{glucose (mg%)} /18 + \text{BUN (mg%)} /2.8 \]
• A normal osmolal gap is <10 mOsm
• A high gap may suggest ethylene glycol or methanol intoxication

The Anion Gap

• There is No Real Gap!!!
• A true gap does not exist because the sum of the +ve and –ve ion charges in plasma must be equal.
• AG helps narrow the differential diagnosis in metabolic acidosis
• When acid is generated, there is an increased AG
• All non-sodium cations comprise the unmeasured cations
• All anions other than chloride and bicarb are unmeasured anions
• Serum AG = Measured Cations – Measured Anions
• Serum anion gap = Na – (Cl + HCO₃⁻) (some sources include serum K)

Causes of Increased Anion Gap

• Increased unmeasured anions
  • Organic anions: lactate, ketones
  • Inorganic anions: phosphate, sulfate
  • Proteins: hyperalbuminemia (rare)
  • Exogenous anions: salicylate, formate, nitrate, penicillin, carbenicillin
  • Incompletely identified: ethylene glycol, methanol, uremia
• Decrease in unmeasured cations
  • Hypokalemia
  • Hypocalcemia
  • Hypermagnesemia

For every 1 g reduction in albumin, the AG falls by 2.3 – 2.5

The sum of all anions = the sum of all cations
Thus Measured Anions + UA = Measured Cations and UC
The AG is also = Unmeasured Anions – Unmeasured Cations
The Anion Gap (AG): Limitations

- Lactic acidosis (LA) accounts for half the cases of a high anion gap, due to shock or tissue hypoxia
- But, the AG is an insensitive reflection of LA; 50% of patients with serum lactate 3 - 5 mmol/l have a normal AG (sens. / spec. <80%)
- Hence AG cannot replace a measure of serum lactate, which is often not measured or readily available
- AG should be always adjusted for albumin conc; serum albumin may account for 75% of the AG; for a decline in serum albumin by 1 g/dl, the AG is increased by approximately 2.3 – 2.5 mmol/l
- Conversely an increase in unmeasured cations (e.g. IgG in myeloma will decrease the anion gap)

Metabolic Acidosis: Mechanisms

- Increased acid generation
  - Lactic acidosis, ketoacidosis, ingestion of methanol, ethylene glycol, aspirin, etc
- Loss of bicarbonate
  - Diarrhea, ureteral implantation into the sigmoid, proximal (type 2) RTA
- Diminished renal acid excretion
  - Reduction in GFR as in AKI or CKD, distal (type 1) RTA and type 4 RTA
- Evaluation involves a history and P/E, measure of electrolytes, calculation of the AG, measure of arterial pH and PCO₂ and determining if respiratory compensation is appropriate

The Anion Gap (AG) in Ketoacidosis

- The AG is helpful in the diagnosis of diabetic ketoacidosis and alcoholic ketoacidosis
- When the lactate level is normal, the diagnosis may be missed because the test used to assess ketonuria (nitroprusside test) reacts only with acetoacetate and not β-hydroxybutyrate, the primary keto acid in alcoholic ketoacidosis and at times the keto acid in DKA

Normal Anion - Gap Acidosis

- Normal AG acidosis occurs when the decrease in HCO₃ ions corresponds with an increase in Chloride to retain electro-neutrality.
- Hence the term hyperchloremic metabolic acidosis; causes
  - GI loss of bicarbonate: diarrhea or ureteral division
  - Renal loss of bicarbonate from RTA or early renal failure
  - Hospital acquired: infusion of large volumes of normal saline (0.9%)
  - Urinary AG (Na + K – Cl) is usually negative in normal AG acidosis

Metabolic Acidosis Based on the Anion Gap

<table>
<thead>
<tr>
<th>High Anion Gap</th>
<th>Normal Anion Gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic acidosis: Type A: hypoxia, ischemia, shock, sepsis</td>
<td>Loss of Bicarbonate: Renal: proximal or distal RTA</td>
</tr>
<tr>
<td>Lactic acidosis: Type B: non-hypoxic</td>
<td>Loss of Bicarbonate: Renal: acetazolamide</td>
</tr>
<tr>
<td>Under-excretion of acid: AML, CKD</td>
<td>Decreased renal acid excretion: Uremia</td>
</tr>
<tr>
<td>Liver failure: impaired lactate clearance (LA, type R)</td>
<td>Type 4 renal tubular acidosis</td>
</tr>
<tr>
<td>Medications: salicylate, metformin (LA, type B)</td>
<td>Infusion of normal saline, and hyperalimentation in hospitalized patients</td>
</tr>
<tr>
<td>Toxins: methanol, ethylene / propylene glycol</td>
<td>Ureteral implants into colon (or malfunctioning (end loop bladder))</td>
</tr>
</tbody>
</table>

Manifestations of Acidosis

Acidosis and Acidemia
- CNS: Coma and seizures
- Shock (metabolic acidosis)
- Depressed sensorium
- Depressed myocardial function
- Headache, asterixis, papilledema (respiratory acidosis)
- Oliguria, polyuria (metabolic acidosis)
- Diarrhea (metabolic acidosis)

Normal Vs RTA: Urine Bicarbonate Loss

Renal Tubular Acidosis: Types

<table>
<thead>
<tr>
<th>Renal Tubular Acidosis: Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal (Type 2)</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
<tr>
<td>Fanconi’s syndrome</td>
</tr>
<tr>
<td>Drugs: aminoglycosides</td>
</tr>
<tr>
<td>Amyloidosis, multiple myeloma</td>
</tr>
<tr>
<td>Heavy metal toxicity</td>
</tr>
<tr>
<td>Renal transplantation</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
</tr>
</tbody>
</table>

Type IV Renal Tubular Acidosis

- Aldosterone stimulates distal nephron H+ and K secretion, along with Na absorption; urinary acidification is intact
- In CKD, hyperkalemia is uncommon until eGFR < 15 ml/min
- Absent or reduced aldosterone secretion, primarily or with low renin leads to hyperchloremic metabolic acidosis, hyperkalemia and volume depletion, termed hyporeninemic hypoaldosteronism
- Strictly type IV RTA is used for cases with normal renin and aldosterone production, but impaired tubular responsiveness, due to a distal tubular voltage defect
- Acidosis is mild, HCO3 is in the 18 - 22 mEq range.

Type IV Renal Tubular Acidosis

- Renal tubular damage involves atrophy of the juxtaglomerular apparatus of the nephron, site where renin is released
- Typically occurs in older adults, with mild DM, mild CKD; causes include HIV, SLE, sickle cell disease and obstructive nephropathy
- Provoked or unmasked by: spironolactone, triamterene, ACEI, sulfa-TMP, β blockers (non-selective > selective), NSAIDs etc
- Management strategies:
  - Withdraw offending agents (medication, dietary K)
  - Diuretics are first line therapy
  - Liberalize salt intake; sodium bicarbonate may have an adjunct role
  - Consider fludrocortisone as third line therapy

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### Metabolic Acidosis: Therapy
- Key attempt to reverse the underlying pathophysiologic process
- Acute metabolic acidosis
  - Treatment is controversial (poor data from research)
  - Na bicarbonate or other buffers when pH falls <7.1; a drop to 6.8 in DKA is tolerated
  - Raising pH may have adverse effects, including myocardial depression
  - IV sodium bicarb preferred over tromethamine (THAM), a non sodium salt and an amino alcohol that buffers H ions through its amine
- Chronic metabolic acidosis
  - Exogenous alkali (Na or K salt of bicarb, citrate or lactate (metabolizable), the latter in RTA)
  - DOSE 50 – 100 mEq
  - Na bicarb: 50 ml vials, 8.4% with 50 mEq/50 ml; 7.2% with 44.6 mEq/50 ml
  - A vial raises the bicarb by 1.3 – 1.5 mEq/L in a 70 kg pt; approx. 250 mEq of IV Na bicarb can be given over 4 to 8 hours, to raise bicarb from 6 to 12

### Metabolic Alkalosis: Basics
- The normal kidney is highly efficient in excreting large amounts of HCO₃⁻; hence generation of metabolic alkalosis requires both an increase in alkali and impairment in renal excretion of HCO₃⁻
- Loss of gastric fluid and diuretic use account for most cases
- A measure of urine Cl distinguishes between Cl-responsive and Cl-resistant metabolic alkalosis
- When effective volume declines, the kidneys will avidly reabsorb sodium, bicarbonate and chloride, through activation of the renin-angiotensin-aldosterone system, reducing urinary chloride
  - A spot urine chloride <25 mmol/L suggests Cl-responsive metabolic alkalosis
  - Administration of saline (with potassium) restores effective volume, replenishes K and corrects metabolic alkalosis

### Metabolic Alkalosis: Mechanisms
- Gastric secretions have a high conc of HCl and low conc of K and NaCl. When vomiting or NG suction removes HCl from the body, the bicarbonate that is added to the ECF is not neutralized by secrections
- Antacid absorption (calcium carbonate, magnesium hydroxide) typically does not cause metabolic alkalosis; the cation is excreted with matched distal excretion and bicarb remains
- By contrast, secondary aldosteronism, due to reduced effective arterial blood volume (HF, cirrhosis, nephrotic syndrome), does not develop metabolic alkalosis or hypokalemia, in absence of diuretic therapy (prox. Na absorption)
- Diarrhea: typically stool has high alkali conc and causes metabolic acidosis
  - Exceptions: villous adenoma can be associated with metabolic alkalosis
  - Congenital chloride losing diarrhea, due to a genetic mutation disorder (involving intestinal chloride-bicarbonate exchanger)

### Chloride Resistant Metabolic Alkalosis
- Metabolic alkalosis with urinary chloride conc >40 mmol/L results from inappropriate renal excretion of sodium chloride
- Mineralocorticoid excess (primary aldosteronism), with generous distal sodium and water delivery; results in hypokalemia with hypertension
- Severe hypokalemia (K < 2 mmol/L)
- Genetic disorders: Bartter syndrome (loop defect), Gitelman syndrome (diluting segment defect), Pendred syndrome (distal type B cell defect)
- Administration of sodium chloride does not correct such metabolic alkalosis; hence, in the above instances, the term “chloride-resistant”
- Diuretic induced metabolic alkalosis is an exception; it responds to Cl administration; it is a secondary aldosteronism with distal sodium and water delivery that enhances urinary H and K secretion, with hypokalemia and metabolic alkalosis.

### Metabolic Alkalosis: Other Causes
- Post-hypercapnic acidosis: chronic resp. acidosis increased renal H⁺ excretion and bicarbonate reabsorption. The rise in plasma HCO₃⁻ conc with hypochloremia returns the pH to normal. If the elevated pCO₂ is rapidly lowered (e.g. by mechanical ventilation), the elevated plasma bicarb remains for a while resulting in a metabolic alkalosis. Tt: IV saline to restore volume
- Hypercalciemia and milk (or calcium) alkali syndrome: due to aggressive mild and antacid therapy for peptic ulcer disease; often calcium supplements rather than milk; associated with vomiting, reduced volume and reduced eGFR
- Alkali admn: of sodium bicarbonate results in rapid renal excretion of alkali load and minimal increase in bicarb conc. Large amounts administered over time for the treatment of lactic acidosis or DKA can cause a post correction metabolic alkalosis
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Metabolic Alkalosis

<table>
<thead>
<tr>
<th>Chloride Responsive</th>
<th>Chloride Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting or Nasogastric suction</td>
<td>Primary Aldosteronism</td>
</tr>
<tr>
<td>Diuretic related</td>
<td>Bartter Syndrome</td>
</tr>
<tr>
<td>Post-hypercapnic alkalosis</td>
<td>Gitelman Syndrome</td>
</tr>
<tr>
<td></td>
<td>Severe magnesium deficiency</td>
</tr>
<tr>
<td></td>
<td>Milk alkali syndrome: hypercalcemia</td>
</tr>
</tbody>
</table>

Manifestations of Alkalosis

<table>
<thead>
<tr>
<th>Alkalosis and Alkalemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS: coma, seizures</td>
</tr>
<tr>
<td>Heart failure (resp alkalosis)</td>
</tr>
<tr>
<td>Tachypnea (resp alkalosis)</td>
</tr>
<tr>
<td>Vomiting (metabolic alkalosis)</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
</tr>
<tr>
<td>Tetany</td>
</tr>
<tr>
<td>Muscle weakness</td>
</tr>
</tbody>
</table>

Metabolic Alkalosis: Management

- As always begin with addressing the cause
- In chloride responsive alkalosis, administer saline, usually with KCl
- In some settings, acetazolamide 500 mg may be given intra-venously
- Hydrochloric acid, ammonium chloride or arginine hydrochloride infusions are used for serious metabolic alkalosis, when NaCl is not tolerated, as in heart failure or advanced renal failure
  - Dilute HCl (0.150 mmol/L) is administered at 250 ml/hour into a central vein. The complications include hemolysis and vascular necrosis, and is best avoided
  - Ammonium chloride can be toxic, in presence of abnormal liver function
- H2 blockers have been used to reduce gastric HCl secretion

Respiratory Acidosis

- Daily production of CO2 equals up to 15,000 mmol/L
- Presentation of acute hypercapnia is invariably with hypoxemia, which dominates the picture, along with altered consciousness, tachycardia, restlessness, dyspnea
- Causes of acute respiratory acidosis:
  - Neuromuscular: brain stem or high cord injury, Guillain-Barre syndrome
  - Narcotics, sedatives, drug overdose
  - Airway related: bronchospasm, aspiration
  - Vascular disease: pulmonary embolism
  - Lung disease: asthma, pneumonia, pulmonary edema
- Treatment: restore effective ventilation

Respiratory Acidosis: Chronic

- Chronic respiratory acidosis exhibits few manifestations due to CO2 retention and acidosis, with signs of chronic lung disease dominant
- Plasma Na and K are normal; with HCO3 elevated, Cl decreased
- Causes of chronic respiratory acidosis:
  - Neuromuscular abnormalities: hypoventilation, narcotics, obesity
  - Thoraco-pulmonary disorders: COPD, interstitial lung disease
- Treatment involves restoring the ability to excrete CO2
- Fluid expansion may be needed to treat post hypercapnic metabolic alkalosis: caution, as it may cause pulmonary edema
- Fluid expansion may be needed to treat post hypercapnic metabolic alkalosis: caution, as it may cause pulmonary edema

Respiratory Alkalosis

- The CO2 can fall only if the excretion by the lungs exceeds the production of HCO3 by metabolic processes
- As CO2 production is constant, a low CO2 can only occur as a result of alveolar hyperventilation
- Causes of respiratory alkalosis:
  - Central: anxiety, head trauma, fever, salicylates
  - Peripheral: pulmonary emboli, heart failure, pneumonia
  - Uncertain: gram negative sepsis, hepatic
  - Mechanical or voluntary hyperventilation
- The only treatment is to ameliorate or correct the basic disorder
Mixed Acid Base Disorders

• Refers to the simultaneous presence of more than one acid-base disorder.
• There is a lesser or greater than expected compensatory respiratory or renal response; the pH may be normal or grossly abnormal.
• There may be 2, 3 or more independent acid base disorders. Examples:
  - Vomiting is expected to lead to metabolic alkalosis due to loss of acid; if the patient developed hypotension and shock, the ensuing lactic acidosis would lower the serum bicarb and even lead to acidemia
  - Salicylate intoxication may be associated with primary respiratory alkalosis and primary metabolic acidosis
  - COPD with respiratory acidosis and diarrhea with metabolic acidosis
  - Respiratory acidosis and diuretic therapy developing metabolic alkalosis

Case 1: Metabolic acidosis in CKD

• 65 year old male nursing home resident with type 2 diabetes mellitus, CKD and hypertension presents with recent onset of muscle weakness. Laboratory values:
  - Na 138, Cl 112, K 5.7, HCO3 18, Gl 142, Cr 1.9 (eGFR 27 ml/mt).
• What is the cause of acidosis?
  1. Type 1 RTA
  2. Type 2 RTA
  3. CKD (renal failure)
  4. Type 4 RTA

Basics of Type 4 RTA

Case 2: Chronic Fatigue

• 55 year old female presents to the ED with fatigue for months. She is marginally overweight and has been conscious of her appearance. Patient has caregiver burden in taking care of her husband with advance heart failure. P/E is non-contributory. She is hospitalized; upon discharge enters post-acute rehab.
  - In the ED: pH 7.52; pCO2 46; Na 136; Cl 88; K 2.6; HCO3 36
• What is the differential diagnosis?
  - What is the next test one would order to determine approach?
  - Is CT abdomen indicated for primary aldosteronism
  - Could the patient have secondary aldosteronism?

Case 2: Chronic Fatigue, Metabolic Alkalosis

• The differential diagnosis is that for metabolic alkalosis.
• The first test would (ideally) be a Urine Chloride to distinguish between Chloride Responsive and Resistant alkalosis.
• Urine may also be sent for drug (diuretic) analysis
• Absence of hypertension: less likely to be primary aldosteronism
• The absence of edema rules out secondary aldosteronism (HF; nephrotic syndrome, cirrhosis with ascites); these disorders do not cause an alkalosis, unless diuretic based
• It is likely that she was abusing diuretics (note husband has HF!); she probably has a chloride responsive alkalosis
Case 3: Dementia and Seizure Disorder

- 80 year old female with Alzheimers dementia develops a witnessed seizure. She is hypertensive and well controlled on an ACEI. The patient is on donepezil.
- Lab: pH 7.14; Na 140; Cl 98; HCO₃ 17; K 4; PCO₂ 45
- Does the patient need bicarbonate?
- What is the basis for the disorder?
- Is the compensation appropriate?
- What is the acid base disorder?

Case 3: Dementia and Seizure Disorder

- Lab: pH 7.14; Na 140; Cl 98; HCO₃ 17; K 4; PCO₂ 45
- The extreme pH (acidemia) suggests a severe metabolic or respiratory acidosis or a mixed acid base disorder.
- The patient has lactic acidosis: seizure induced hypoxia causes lactic acidosis; the respiratory compensation is poor (central, impaired); ideally, should be around 34 (not 45); patient has a respiratory acidosis + lactic acidosis, a mixed acid base disorder
- Normally K would be required upon correction, but in lactic acidosis the K change is minimal (no shift)
- Attempt seizure control; do not give bicarbonate or potassium

Case 4: Patient with Diarrhea

- A 90 year old nursing resident with dementia develops diarrhea. The patient is now more lethargic and remains confused. BP is 110/60 mm Hg. Electrolytes are pending.
- ABG confirms a pH of 7.25, PCO₂ of 26 and HCO₃ of 12 mEq/l.
- All of the following statements are correct except which one?
  - The patient has metabolic acidosis, likely low anion gap
  - The respiratory component demonstrates appropriate compensation
  - The patient has a mixed acid base disorder
  - The patient does not have primary respiratory alkalosis

Case 4: Patient with Diarrhea

- A 90 year old nursing resident with dementia develops diarrhea. The patient is now more lethargic and remains confused. BP is 110/60 mm Hg. Electrolytes are pending.
- ABG confirms a pH of 7.25, PCO₂ of 26 and HCO₃ of 12 mEq/l.
- All of the following statements are correct except which one?
  - The patient has metabolic acidosis, likely low anion gap
  - The respiratory component demonstrates appropriate compensation
  - The patient has a mixed acid base disorder
  - The patient does not have primary respiratory alkalosis

Case 5: Alkalemia

- 65 year old female, H/O hypertension, has been weak and depressed for a while. Psychiatry evaluation and management has not been helpful. No history of diabetes or CKD. Exam is non-revealing for abnormalities, except for BP of 160/90 mm
- Na 146 mEq/L; K 2.7 mEq/L; bicarb 30; ABG: pH 7.5; PCO₂ 42
- The acid base disorder is alkalemia due to what disorder?
- What will the urine exam likely demonstrate?
- What blood tests would be helpful?
- What would you like to exclude in this case?

Case 5: Alkalemia from Metabolic Alkalosis

- The patient has alkalemia from metabolic alkalosis, with efforts at respiratory compensation
- The urine exam likely will demonstrate a high chloride, typical of aldosterone secreting tumors, indicating chloride resistance alkalosis, and unlikely to respond to chloride (saline)
- Plasma renin and aldosterone levels along with abdominal imaging are likely to be helpful in diagnosis
- One should exclude the use of diuretics and surreptitious vomiting, both off which cause chloride responsive alkalosis
Summary: Approach to Acid Base Disorders

- Clinical suspicion is derived from focused history and P/E.
- Evaluate acid base variables to determine type of disorder: the arterial pH, PaCO₂, plasma HCO₃⁻.
- Remember the PaCO₂ and plasma HCO₃⁻ are never altered from normal in opposite directions in a simple acid-base disorder.
- Alterations in opposite directions means a mixed acid base disorder.
- Estimate the appropriateness of compensation to judge whether the acid-base disorder is simple or mixed, using basic rules.

Summary: Approach to Acid Base Disorders

- Construct a differential diagnosis for the disorder: in most cases, the underlying cause is apparent from just the clinical evaluation.
- The anion gap in metabolic acidosis may offer further clues.
- The urine chloride in metabolic alkalosis may offer clues.
- Treatment is almost invariably directed at the underlying cause.
- Replacement of Na, water, K (and P, Mg) must be addressed.

Thank You!