Non Gap Metabolic Acidosis

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Definition of Non-Gap Acidosis
- Low Bicarbonate, low pH (vs. Resp Alk)
- Normal Anion Gap (~10 mEq/L)
  - Note Albumin
  - Use of AG assumes normal plasma Albumin
  - Always correct to Alb of 4
- Compensatory decrease in PCO₂
  - Winter Equation: PCO₂ = 1.5 (HCO₃⁻) + 8 ± 2
  - Add 15 to Patient’s [HCO₃⁻]

Clinical Examples: NAG Acidosis

<table>
<thead>
<tr>
<th>Electrolyte Values (mEq/L)</th>
<th>Normal</th>
<th>NAG-MA</th>
<th>AG-MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>140</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>Chloride</td>
<td>105</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>25</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Anion gap</td>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Δ[HCO₃⁻]</td>
<td>0</td>
<td>+10</td>
<td></td>
</tr>
<tr>
<td>Δ[HCO₃⁻]</td>
<td>-10</td>
<td>-20</td>
<td></td>
</tr>
</tbody>
</table>

Need pH₄ to R/O Chronic Respiratory Alkalosis

Causes of Non-Gap Acidoses
- Diarrhea or other GI losses of alkali (e.g., tube drainage)
- Ureteral diversion (e.g., ileal loop, ureterosigmoidostomy)
- Posttreatment of ketoacidosis (dilutional)
- Progressive chronic kidney disease
- Toluene ingestion (excretion of hippurate)
- Drugs
  - Carbonic anhydrase inhibitors: acetazolamide, topiramate, sulfamylon
  - Amphotericin B
  - CaSO₄, MgSO₄, Cholestyramine
  - Acid loads (NH₄Cl, acidic amino acids –TPN)
  - For Hyperkalemia: amiloride, triamterene, spironolactone, TMP
- Post - hypocapnic state
- RTA’s – proximal, classical distal, mixed, type 4

Mnemonic for Non-Gap Acidosis
- HAARDUPS
  - Hyperalimentation
  - Acetazolamide or any CA Inhibitor
  - Amphotericin B
  - RTA
  - Diarrhea
  - Ureterosigmoidostomy
  - Post hypocapnic state, pancreatic fistula
  - Sulfamylon

UNDERSTANDING NON-GAP METABOLIC ACIDOSIS

1. Overview of Renal Pathophysiology
2. Distinguishing Renal from Non-Renal Forms
  - Role of the Kidney in the Defense Against Metabolic Acidosis
Kidney Defends Against Acidosis by Reabsorption of Bicarbonate (Proximal Tubule) and Excretion of Acid (Ammonium)

Role of Kidney in Acid-Base Balance
1. Reabsorption of filtered bicarbonate ~ 4,000 mEq/day
2. Production of “new” bicarbonate via net acid excretion ~ 70 mEq/day
Both are the result of H+ secretion
Body Balance Equation: Net acid production = Net acid excretion
NAE is highly responsive to acidosis. Upregulation of ammonium production and excretion by normal kidney is expected in non-renal acidosis.

The daily dietary response: defense against metabolic acidosis by the kidney
- Metabolism of protein from a Western diet
  - Releases acid into extracellular space
  - Consumes bicarbonate that must be replaced
- Kidney responds by increasing net acid excretion as NH4+ to make new bicarbonate

Acidification of Urine: Defense Against Metabolic Acidosis
1. R HCO3-
2. NAE = NAP

Urine Anion Gap to Approximate Urine Ammonium Excretion
- Spot Urine Electrolytes: Na+, K+, Cl- in a patient with hyperchloremic metabolic acidosis
- Calculate Urine Anion Gap:
  \[ \text{UAG} = (\text{Na} + K) - \text{Cl}_u \]
- Interpretation:
  - (Na + K)_u > Cl_u: NH4+ low (Ammonium excretion impaired)
  - Cl_u > (Na + K)_u: NH4+ adequate (non-renal hyperchloremic acidosis)
- Pitfalls: Unusual Anions (Drugs)
  - Ketonuria
  - Toluene

Urine osmolal gap to approximate urine ammonium concentration
Urine Osmolal Gap = Measured Urine Osmolality – Calculated Urine Osmolality
\[ \text{U_{osm}} = U_{\text{osm}} \div 2 \]
Urine ammonium of 75 mEq/L with NAG acidosis if renal tubule function is normal
Renal Tubular Acidosis

Inability of the kidney to excrete sufficient acid or retain sufficient bicarbonate, resulting in a clinical syndrome characterized by non-gap metabolic acidosis, hyperchloremia, and impaired urinary acidification.

Types of Renal Acidoses

- Hypokalemic Forms
  - Proximal RTA (Type 2)
  - Classical Distal RTA (Type 1)
- Hyperkalemic Forms
  - Aldosterone Deficiency or Resistance (Type 4)
  - Non-mineralocorticoid Voltage Defect
- Normokalemic
  - Progressive CKD
  - Uremic Acidosis

NAG Acidosis of Progressive CKD

- Technically a renal tubule defect
  - Elevated urine NH4+ excretion per functional nephron
  - Declining number of functional nephrons
    - Shift from Non-Gap to Gap Acidosis with advanced CKD
- Acidosis contributes to progression of CKD
- Mild acidosis is under recognized and treated
- What is target bicarbonate level?

Features of Proximal RTA
(Type 2)

- Non-gap acidosis in untreated steady state
- Urine pH < 5.5; hypokalemia
- Proximal tubule fails to reabsorb large amounts of filtered HCO3−; HCO3− spills into urine increasingly with treatment; so that urine pH > 5.5
- Hypokalemia becomes worse with bicarbonate therapy
- Acquired forms often associated with Fanconi Syndrome

Would you recognize and/or treat acidosis in this patient?

- Na 140, Cl 110, HCO3 21, K 4
- What groups of patients might fall into this category?
  - Elderly patients with "presynephric RTA" (Morris)
  - Some stone formers
  - Some with osteoporosis
  - Stage 3b and >CKD
- Acidosis contributes to progression of CKD
- Therefore, treat to target of >22 mEq/L

Etiology of PRTA
Proximal RTA - Causes

1. Inherited - isolated pure bicarbonate wasting - mis-sense mutations in NBCe1/SLC4A4, several examples associated with ocular abnormalities
2. Inherited proximal-distal RTA (Type 3 RTA) with osteopetrosis and ocular abnormalities, CA II deficiency (Guibaud-Vainsel)
3. Acquired: Myeloma, ifosfamide, CA inhibitors, topiramate, heavy metals

TREATMENT: PROXIMAL RTA

Requires large amounts of alkali:
10-20 mEq/Kg/day; typically increases urinary K loss
Requires large amounts of potassium
Potassium (K-Shohl’s: Polycitra®-LC: Citric acid 334 mg, sodium citrate 500 mg, and potassium citrate 550 mg per 5 mL (480 mL) [alcohol free, sugar free])
Thiazides may be helpful

Distal Renal Tubular Acidosis

1. Classical Distal RTA - Type 1
2. Generalized Distal RTA - Type 4

1. Classical Distal RTA

- Inherited
  - Autosomal Recessive
  - Autosomal Dominant
- Acquired
- Features:
  - Complete or Incomplete
  - The renal phenotype, in the complete form, consists of hyperchloremia, metabolic acidosis and impaired urinary acidification. Bone disease, nephrocalcinosis, and nephrolithiasis are common.

Cell Types - Collecting Duct

Type A Intercalated Cell: 4 Causes of dRTA
Transport Abnormalities Causing Metabolic Acidosis in “Distal” RTA

1. Defect in Net H⁺ Secretion
2. Decrease in NAE because of decrease in $U_{Am}$V

Disorders Associated With Acquired Classical Distal RTA

- Autoimmune Disorders
  - Hyperglobulinemia- autoimmune diseases
    - Sjogrens, thyroiditis, primary biliary cirrhosis
- Hypercalciuria and Nephrocalcinosis
  - Hypervitaminosis D, HPT, Graves’ disease
- Drug or Toxin-induced Disease
  - Amphotericin B, ifosfamide, topiramate, lead, lithium, tetracycline, toluene
- Tubulointerstitial Diseases
  - MCD, classical analgesic nephropathy

Acquired tubule injury and cDRTA

- Drug Toxicity
  - Increase in apical membrane hydrogen ion permeability (gradient defect: amphotericin B)
  - Topiramate (CA inhibitor)
  - Ifosfamide (Prox and Distal Tubule cell injury)
- Interstitial Disease
  - Nephrocalcinosis (Cause/Result)
  - Autoimmune – Sjogren’s Syndrome
  - Chronic Tubulointerstitial Disease

Clinical Example

Case Presentation
Case 1

- Na 140, K 2.5, Cl 125, HCO₃ 5
  - AG 10
- BUN 28, Cr 1.7
- ABG: pH 7.11, P₃CO₂ 16, HCO₃ 5, P₉O₂ 90
- Urine studies:
  - pH 6.0, Cl 18, Na 35, K 40
  - UAG = + 57
  - UAm = 10 mEq/L
- Sicca complex: xerostomia, keratoconjunctivitis sicca, Schirmer’s positive
- SS-B positive, RF positive, SS-A negative


Question

Which disease from list below is most frequently associated with dRTA?

a) Mixed connective disease
b) Rheumatoid arthritis
c) Lupus
d) Sjogren’s syndrome

Kidney Biopsy: Sjogren’s Syndrome

Diagnostic Features of Classical Distal RTA

- Hypokalemia
- Urine anion gap positive during acidosis
  - Abnormally low NH₄⁺ excretion in face of acidosis
- Urine pH > 5.5
- Modest bicarbonaturia, < 10% FEHCO₃ > 5%
- Absence of Fanconi syndrome
- Abnormal calcium metabolism (hypercalciuria, nephrocalcinosis, nephrolithiasis, bone disease)
  - Low urine citrate
- Hyperglobulinemia

Consequences of cDRTA

- Bone Disease (Acidosis - Hypercalciuria)
- Nephrocalcinosis
- Nephrolithiasis
  - Hypercalciuria and hypocitraturia
    - Acidosis leads to hypocitraturia
- Progression of Renal Failure
- Hypokalemia - may be severe at times
- Pyelonephritis - difficult to eradicate
- Stunted Growth

Sources of Alkali for treatment of RTA

- Shohl’s Solution (Na⁺ citrate and citric acid) or Cytra 2
  - Sodium citrate 500 mg and citric acid 334 mg per 5 mL (480 mL). HCO₃⁻ equivalent 1 mEq/mL and Na⁺ 1 mEq/mL
- NaHCO₃ Tablets
  - 325 mg [3.8 mEq]; 650 mg [7.6 mEq]
- Baking soda (60 mEq/tsp.)
- K-Lyte (25 or 50 mEq/tablet)
- Polycitra (K⁺ Shohl’s), Urocit K, Oracit K, Cytra K (flavored) for stone formers
- Granules, effervescent (Brioschi®)
Classification of dRTA

1. Associated with Hypokalemia
   Classical Distal RTA (Type 1)
   Defects of acid transporters in MCT

2. Associated with Hyperkalemia
   a. Mineralocorticoid Deficiency
   b. Non-mineralocorticoid voltage defect
      (Defect of K secretion and H secretion in CCT and MCT)

Distinguishing Features of Hyperkalemic (Generalized) DRTA - Type 4 RTA

- Only variant associated with hyperkalemia
- Collecting duct fails to excrete protons and potassium
  - Situation arises when aldosterone is insufficient in quantity or activity
  - Or, intrinsic (genetic) or acquired molecular defect in transport of Na⁺, K⁺, and H⁺
- Hyperkalemia contributes to acidosis by blunting NH₄⁺ production and excretion

Localization of Defect in Generalized DRTA

Regulation of K⁺ Secretion by Principal Cell

Determinants of K⁺ Secretion

- Activity of parallel transporters and channels
- Mineralocorticoid activity
- Distal delivery of Na⁺
  - Na⁺ and absorbable anions
  - Nonabsorbable anions
- Tubular Flow Rate
- Acid-Base Status
- Total Body K⁺ Homeostasis

Transtubular Potassium Gradient (TTKG)

\[
TTKG = \frac{[K^+]_{\text{urine}}}{U_{\text{osm}}} + \frac{[K^+]_{\text{plasma}}}{P_{\text{osm}}}
\]

Non-renal etiology

- Hypokalemic patient: <3
- Hyperkalemic patient: >7
- "Renal" hyperkalemia
  - <7 in presence of hyperkalemia

Note: Unlike FE, the TTKG is not a %
Drugs that Mimic or Cause Type 4 RTA

- NSAIDs
- ACE inhibitors, ARBs
- K-sparing diuretics: amiloride, triamterene, spironolactone
- Heparin
- Cyclosporin A, tacrolimus (CNIs)
- TMP, pentamidine

Clinical Features of Generalized Defect in Distal Nephron Function

- Hyperkalemia
  - Urine pH < 5.5 or > 5.5
    - Hyperkalemic DRTA urine pH > 5.5
    - Typical SAD urine pH < 5.5
- Aldosterone deficiency or resistance
- Low urinary ammonium excretion and production
- Tendency toward renal salt wasting in some
- Volume expansion and hypertension

Relationship Between K⁺ and NH₄⁺ in the Renal Tubule

- Hyperkalemia decreases and hypokalemia increases renal ammonium production
- NH₄⁺ Transport
  - K⁺ and NH₄⁺ compete for common site on tALH Na-2Cl-K co-transporter (lowers interstitial Am)
  - NH₄⁺ and K⁺ compete for K-secretory site on basolateral membrane sodium pump

Pathophysiological Classification of Clinical Syndromes of Hyperkalemia and Metabolic Acidosis

Pathophysiologica\n
Pathophysiological Basis of Hyperkalemic Acidosis and gDRTA (Type 4)

- Abnormal CCD - MCD (intrinsic)
- Primary decrease in mineralocorticoid (extrinsic)
- Voltage defect - compromises H⁺ and K⁺ secretion
  - Abnormal ENaC
  - Chloride Shunt

Aldosterone Has Direct Na⁺-Independent Affect on H⁺ Secretion in CCT and OMCD
Renal Tubular Dysfunction

• “Voltage defects” impairing K⁺ and H⁺ secretion
  o Inherited
  o Acquired

Case 2

A 38 year old woman presents with chronic weakness. FH is positive for HTN. PE is only remarkable for blood pressure of 148/100

Lab: Na 141, K 6.0, Cl 109, HCO₃⁻ 19, creatinine 0.9, PRA and Aldosterone both low, Urine: Na 75, K 41, Cl 50

During follow up the following is noted:
  o HCTZ controls BP and improves hyperkalemia
  o Na restriction improves BP
  o K excretion in response to NaCl administration is subnormal but normal in response to NaHCO₃

Question

What is the diagnosis?

a) PHA I
b) Hyporeninemic hypoaldosteronism
c) Hyperkalemic periodic paralysis
d) PHA II (Familial Hyperkalemic Hypertension)

Pseudohypoaldosteronism-Type II (Familial Hyperkalemic Hypertension)

• Phenotype: Adults with autosomal dominant hypertension, volume expansion, low renin and aldosterone, mild hyperkalemic HCMA, normal GFR
• Pathophysiology: Prototypical Voltage defect
  o Hyperkalemia (Responds to Na₂SO₄ i.v. = chloride shunt)
  o Unresponsive to mineralocorticoid
  o Genetic Basis
    • Inherited abnormalities of WNK 1 and WNK 4 interacting proteins
    • Affects NCC expression at cell surface causing increase in NaCl absorption and decrease in K secretion.
  o Acidosis due to reduction in JH⁺ and JNH⁺
• Treatment: thiazides and dietary salt restriction
Drug Mechanisms of Type 4 RTA

- Acquired Voltage defects impairing K⁺ and H⁺ secretion
  - Drugs that interfere with Na⁺ channel:
    - Amiloride, triamterene, pentamidine, trimethoprim
  - Drugs that reduce Na,K-ATPase and ROMK in CCD PC; and increase NCC in DCT:
    - Calcineurin inhibitors: CsA, Tacrolimus

Other Manifestations of CNI Tubule Effects

- CNI associated with Salt Sensitive Hypertension, Hyperkalemia and Acidosis
- Resembles phenotype of Familial Hyperkalemic Hypertension (PHA II)
  - Gain of function of NCC in DCT
- CNIs decrease WNK and SPAK expression, activating NCC in DCT

Voltage Defect Due to Trimethoprim-Sulfamethoxazole

- More prevalent with higher doses (>20mg/kg/d)
- Hyperkalemia most frequent complication
- Seen in children and older HIV-negative patients on “conventional” doses
- Reversible most often
- Etiology of Metabolic Acidosis
  - Voltage Defect
  - Hyperkalemia and decreased UₐₙV

Pathophysiological Basis of Hyperkalemic Acidosis and gDRTA (Type 4)

- Abnormal CCD - MCD (intrinsic)
- Primary decrease in mineralocorticoid (extrinsic)
- Voltage defect - compromises H⁺ and K⁺ secretion
  - Abnormal ENaC
  - Chloride Shunt

Pathophysiological Basis of Hyperkalemic Acidosis and gDRTA: Decrease in Aldosterone

- Hyporeninemic hypoaldosteronism
- Inhibition of Aldosterone Synthase
  - Unfractionated and LMW Heparin
- Addison’s disease
Hyporeninemic Hypoaldosteronism

Clinical Features

• Mean age, 65 years
• Asymptomatic hyperkalemia (50-75%)
  o Weakness-25%
• Cardiac Disorders
  o Arrhythmia (25%), Hypertension and CHF
• Hyperchloremic metabolic acidosis (>50%)
• Renal insufficiency (70%)
• Diabetes mellitus (50%), Tubulointerstitial nephritis, or obstructive nephropathy are leading causes

Drugs and RAAS

• Impaired RAAS
  o Cyclo-oxygenase inhibitors
  o Renin inhibitors (aliskiren)
  o Angiotensin converting enzyme inhibitors – ACE-Is
  o AT₁ receptor antagonists – ARBs
  o Inhibitor of aldosterone synthesis: Heparin (un-fractionated and LMW)

Pathophysiology of Hyperkalemic Acidosis and gDRTA: Intrinsic Kidney Tubule Impairment

• Tubulointerstitial abnormalities that affect collecting tubule cell function
  • Obstructive nephropathy
  • Lupus nephritis
  • Sickle cell nephropathy
  • Analgesic nephropathy
  • Myeloma kidney

Treatment of Generalized Dysfunction of the Nephron with Hyperkalemia

• Low potassium diet
• Avoid drugs associated with hyperkalemia
  o OTC NSAID’s
  o Herbal Meds or High K foods Chan su, Noni juice
• Alkali therapy
• Loop Diuretic
• Thiazide for Familial Hyperkalemic Hypertension
• Sodium polystereen sulfonate (Kayexalate)
• Fludrocortisone (0.1-0.3 mg/d)
  o Avoid in hypertension, heart failure, edema
  o Combine with loop diuretic

Clinical Features of RTA

<table>
<thead>
<tr>
<th>RTA Type</th>
<th>Hyperchloremic Acidosis</th>
<th>Bone Disease</th>
<th>Response</th>
<th>Causes</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>cDRTA 1 Type 1</td>
<td>Yes, hypocitraturia</td>
<td>Yes, osteomalacia, rickets</td>
<td>All manifestations respond to alkali</td>
<td>Familial, Acquired</td>
<td>Not with alkali</td>
</tr>
<tr>
<td>gDRTA 4 Type 4</td>
<td>rare</td>
<td>rare</td>
<td>Alkali, Low K diet, loop diuretics, Kayexalate</td>
<td>Acquired, Low, Obstruction, Drugs</td>
<td>Usual</td>
</tr>
<tr>
<td>PRTA 2 Type 2</td>
<td>No, hypocitraturia</td>
<td>some</td>
<td>KHCO₃, NaHCO₃, thiazides, U, Increases with alkali Rx</td>
<td>Acquired or inherited</td>
<td>Not with alkali</td>
</tr>
</tbody>
</table>

Questions - Discussion

Thanks