High Anion Gap Metabolic Acidosis in the Hospitalized Patient

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Control of serum pH

- Serum $[\text{H}^+]$ or pH is maintained in a tight range via lung control of pCO2 and renal control of HCO3
- $\text{H}^+ = 24 \times \text{pCO2}/\text{HCO3}$ (modified Henderson Hasselbalch equation)
- If there is a decrease in HCO3 the body compensates by reducing the pC02 to maintain a normal pH
- If there is an increase in HCO3 the body compensates by increasing the pCO2
- Similarly if there is an increase or decrease in pCO2 the HC03 will change to maintain pH
Acidemia vs acidosis

- pH < 7.38 = acidemia
- pH > 7.44 = alkalemia
- Can have acidosis without acidemia or alkalosis without alkalemia eg. a combined metabolic acidosis (DKA) with metabolic alkalosis (vomiting)
Control of serum pH

• The kidneys control HCO3 by:
  1) reabsorbing all filtered HCO3 - about 4000 mEq/day (a defect in this is a proximal RTA)
  2) regenerating HCO3 utilized by acid produced from dietary protein - about 70 meq/day excreted primarily as NH4+ and HPO4 (a defect in this is distal RTA).
Metabolic acidosis

- Metabolic acidosis – a primary decrease in serum HCO3
- HCO3 also low in respiratory alkalosis – so a low HCO3 on chemistry panel is not always due to a metabolic acidosis
Respiratory compensation in metabolic acidosis

• The change in pCO2 is 1.2 times the change in HCO3 or alternatively put a thumb over the 7 in the pH for pCO2
• If is adequate respiratory compensation is a simple metabolic acidosis
• If inadequate respiratory compensation is a mixed disorder – combined metabolic acidosis and respiratory acidosis
Metabolic acidosis - high anion gap vs. normal anion gap
Anion gap

- Anion gap = Na+ - (Cl- + HC03-)
- Normal AG initially described as 12 +/-4, with new ion selective electrodes 12 is upper limit of normal
- Pronounced elevations (eg. >30) - the identity of the anion is usually obvious
- Less pronounced elevations – the unmeasured anions identity often not clear
AG in settings other than metabolic acidosis

- Another way of thinking of the anion gap is $AG = \text{unmeasured anions} - \text{unmeasured cations}$
- For each 1 gm decrease in serum albumin the expected AG would go down by 2.3
- Increased anion gap – increased unmeasured anions (elevated albumin, PO4, monoclonal anionic IgA), severe metabolic alkalosis, lab error
- Reduced anion gap - usually due to low albumin or increased K+, Ca++, Mg++, monoclonal cationic IgG
- Negative anion gap - hyperlipidemia, salicylate intoxication, bromide ingestion (one bromide anion is measured as 3 chloride anions)
delta HC03/delta AG ratio

- Theoretically is a 1:1 ratio between increase in anion gap and a decrease in HCO3. But baseline HCO3 & AG is not usually known.
- If the change in HCO3 is much more than the change in anion gap this suggests the presence of both a high and normal anion gap acidosis.
- If the change in anion gap is much more than the change in HCO3 suggests both a metabolic acidosis and metabolic alkalosis are present.
High AG metabolic acidosis

GOLDMARK

- Glycols - ethylene and propylene
- Oxoproline – pyroglutamic acid (from acetaminophen)
- L - lactic acid
- D - lactic acid
- Methanol – formic acid
- Aspirin – multiple organic acids
- Renal failure – multiple organic and inorganic acids
- Ketoacidosis – B-OH butyric and acetoacidic acids
Lactic Acid

- Lactic acid exists in 2 forms: L-lactate and D-lactate. In mammals, only L-lactate is a product of metabolism.
- The lab measures only L-lactate
- Normal daily production of lactate 15 to 30 mmol/kg per day
- All of this lactic acid is converted to CO2 and water with no net acid-base effect
Hyperlactatemia

• Elevated serum lactate without acidosis
• Normal lactate level in critical care patient <2 mm/L
• Minor elevations (as low as 0.75 mm/L) correlate with mortality in patients in ER, ICU, or with sepsis
Anaerobic lactate metabolism

- Glucose enters glycolytic cycle in cytoplasm to form pyruvate. Pyruvate then normally moves to mitochondria and enters Krebs cycle.
- If no O2 for oxidative phosphorylation, pyruvate cannot enter the mitochondria to enter Krebs cycle but is converted to lactate.
- Anaerobic glycolysis of 1 mole of glucose to pyruvate and then lactate generates ATP, but only 10% of that generated with aerobic glycolysis.
Type A lactic acidosis

- Mechanism – overproduction of lactic acid due to shock, hypoxemia, profound anemia, carbon monoxide, seizures (transient elevation with seizures)

- With marked anoxia body can generate 12 mm/min of lactic acid (12 meq/min of H+)
Type B lactic acidosis

- not due to overproduction of lactic acid
- usually due to decreased liver utilization
- commonly a mitochondrial problem not allowing pyruvate to be metabolized in the Krebs cycle but remains in the cytoplasm and converted to lactate
- mitochondrial problem can be genetic (eg. MELAS) or precipitated by toxins, or drugs: not dose dependent (highly active retroviral drugs, linezolid), or dose dependent (metformin, propylene glycol, ASA, propofol)
- can also rarely occur with cancer, diabetes, liver disease
Drugs associated with lactic acidosis

- highly active retroviral agents
- ethylene glycol, methanol, propylene glycol
- salicylate
- metformin, phenformin
- clenbuterol - beta-blocker contaminant in heroin
- linezolid
- propofol – propofol infusion syndrome (lactic acidosis, AKI, CHF, rhabdomyolysis)
- propylene glycol solvent – lorazepam, diazepam, NTG, phenytoin, esmolol, phenobarbital, TMP-SX (often is a D-lactic acidosis with PG)
- nitroprusside – cyanide formation
Metformin and lactic acidosis

- Package insert – do not give if creatinine >1.4 in female or >1.5 in male
- Canada and Europe base restrictions on eGFR not serum creatinine
- Debate on these restrictions since the vast majority of patients with renal failure taking metformin do not develop metabolic acidosis and those that do often have other reasons to develop it
- Precipitated by worsening of CKD via NSAIDs, ACE inhibitors, or contrast
- CRRT or HD can remove the metformin and also help correct the lactic acidosis  

Clinical Diabetes 2011;29:97
MELAS

- Mitochondrial encephalopathy, lactic acidosis, stroke-like episodes
- Usually presents with seizures
- Almost always diagnosed in childhood
- Diagnosis usually made by molecular genetic testing of mitochondrial DNA
- Adults – case reports, suspect if seizures worsened by valproic acid
Adverse consequences of severe acidemia

- Cardiovascular – impaired contractility, vasodilatation, vasoconstriction, sensitization to arrhythmias, reduced response to pressors.
- Respiratory - hyperventilation, respiratory muscle fatigue, dyspnea
- Metabolic -- insulin resistance, inhibition of anaerobic glycolysis, protein degradation, decreased ATP synthesis, hyperkalemia
NaHCO3 to Rx lactic acidosis

Up to Date recommends not to treat unless pH < 7.1
NaHCO3 dose estimation

- Volume of distribution of HCO3 is $\frac{1}{2}$ of the body weight, may be higher with severe acidosis
- To correct the serum HCO3 from 5 to 10 meq/L in a 100 kg man would be $5 \times 50$ or 250 meq which is about 5 amps of NaHCO3
- 1 amp IV NaHCO3 = 48 meq in 50 cc
- 1 gram po NaHCO3 = 12 meq
Complications of bicarbonate therapy

- Overshoot alkalosis – due to conversion of lactate or acetate to HC03
- Increase in lactate generation if use in lactic acidosis
- Volume expansion
- Increased CO2 production
- Hypocalcemia
- Hypernatremia – IV NaHCO3 (8.5%)
- Cardiac depression (due to alkalosis?)
THAM (tromethamine)

• An alternative to NaHCO3
• Benefit – does not increase CO2 production which can be a problem giving to a patient in respiratory failure. Does not increase Na+
• Problems – can build up in renal failure and can also cause hyperkalemia

• NEJM 1198; 339:1005
D-Lactic acidosis

- Usually with slow GI transit (blind loops, obstruction, drugs decreasing GI motility) or short gut syndromes (ingested carbohydrates go directly to the colon)
- GI tract bacteria convert ingested carbohydrate into organic acids – primarily D-lactic acid
- Often exacerbated by increased carbohydrate intake or antibiotics allowing for overgrowth of lactobacilli
- Can also occur with propylene glycol or DKA
- CNS findings – usually is associated with confusion, dysarthria, ataxia (due to other toxins made by the bacteria)
- So consider if have a gut abnormality + confusion + high AG acidosis + normal lactate level
Propylene Glycol Toxicity

• An alcohol used to enhance water solubility of many hydrophobic IV medications (lorazepam, diazepam, esmolol, nitroglycerin)

• Propylene glycol toxicity from solvent accumulation has been reported in 19%-66% of ICU patients receiving high-dose lorazepam or diazepam for >2 days.

• D-lactic acidosis

• Signs of toxicity - agitation, coma, seizures, tachycardia, hypotension
Diabetic ketoacidosis

• Measurement of keto acids – can be missed if patient has primarily a beta-hydroxybutyric acidosis as can occur with increased NADH from ETOH or lactic acidosis
• May initially be high AG but often evolves into a normal anion gap acidosis if the anion is excreted in the urine
• NaHCO3 Rx – not usually necessary since the acetate is eventually converted to HCO3
• Reports of brain edema/death in children with DKA Rx with NaHCO3 (not proven cause and effect)
Alcoholic ketosis

- Usually a history of long-term alcohol use
- Reduced food intake (eg. vomiting) which results in hypoglycemia which stimulates lipoprotein lipase to break down fat to FFA which are transported to liver and forms acetyl CoA which is converted to ketones
- Main function of ketones in the body is to in the setting of hypoglycemia provide an alternative nutrition source those organs that normally require glucose eg. brain
- Rx - give glucose which increases insulin secretion reducing breakdown of FFA to ketones
- Thiamine - for body to metabolize glucose in glycolysis requires thiamine (vitamin B1) and if alcoholic is deficient in this and give glucose without B1 can precipitate Wernicke’s encephalopathy
\[
\beta\text{-hydroxybutyric acid} \rightleftharpoons \text{NAD}^+ \rightarrow \text{Acetoacetic acid} \rightarrow \text{Acetone}
\]
Isopropyl alcohol

- Disinfectant, antifreeze, wood alcohol
- Ingest to become intoxicated or harm themselves
- When ingested a CNS depressant like alcohol
- Metabolic acidosis - not usually cause present
- Osmolality gap - increased
- Classic case - marked ketosis, no metabolic acidosis, normal blood sugar, obtundation, and high osmolal gap
Salicylate intoxication

- Acid-base disorder: respiratory alkalosis or metabolic acidosis
- Anion gap: usually high, but not always
- Salicylate toxicity mostly due to penetration of salicylate into brain
- Protonated ASA is much more permeable into brain than dissociated ASA-.
Salicylate intoxication Rx

- NaHCO₃ – reduces brain ASA penetration
- Urinary alkalization - excretion of ASA much higher at pH of 8 vs 5
- Acetazolamide: alkalinizes urine, but avoid since can cause a metabolic acidosis increasing the movement of protonated ASA into the brain cells
- Hemodialysis consider if: ASA >60 mg/dl, institute: ASA>90 mg/dL
Pyroglutamatic acidosis

- First described 1989
- Chronic acetaminophen ingestion usually with levels that are not toxic
- Malnourished
- Chronically ill
- Mechanism – glutathione deficiency?
- Rx – stop the acetaminophen, recovery appears to be sped up with N-acetylcysteine
Metabolic acidosis due to renal failure

• Usually is high anion gap due to retention of those proteins normally ingested each day that are not excreted

• As opposed to the acidosis due to renal failure can have acidosis due to renal disease without renal failure – various types of RTA
High AG metabolic acidosis

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Ethylene glycol or methanol ingestion

- Consider in the proper setting – obtunded alcoholic: EG suggested by flank pain or oliguria, M suggested by visual difficulties or history of moonshine distillation
- Dozens of deaths yearly, EG survivors may end up on dialysis and M survivors may end up blind
- Can not measure levels in ER, a send out
- If are considering seriously call the Poison Control Center
- Try to obtain the container to confirm agent ingested since may treat proven case differently than suspected case
Methanol poisoning

- Methyl alcohol or wood alcohol
- Can be from bootleg alcohol unknowingly contaminated
- Can be in shellac, varnish, windscreen, antifreeze, or a fuel for alcohol burning devices
- Toxic ingestion 1 gm/kg
- No symptoms for the first 12 hours
- Toxicity primarily CNS and optic nerve damage
- MW=32 so a level of 20 mg/dl increases OG by 6 mm/L & 100 mg/dL increases OG by 31 mm/L
Ethylene glycol poisoning

• Suicide attempt, substitute for alcohol, homicidal
• Antifreeze - but not all antifreeze has EG
• 3-phase clinical picture
  1) 4-12 hrs - CNS/GI phase: inebriation, mimics ETOH intoxication
  2) 12-24 hrs - worse acidosis, cardiopulmonary dysfunction, increased HR, increased BP, myocarditis, pneumonia, pulmonary edema, myositis
  3) 36-72 hrs - oliguric renal failure
• Lactic acid also commonly elevated
• Toxic ingestion 1 gm/kg
• MW=62 so a level of 20 mg/dl increases OG by 3 mm/L and a level of 100 mg/dL by 16 mm/L
Metabolism of ethylene glycol and methanol

- The major toxicities of these agents are not from the agents themselves but from metabolites
- Methanol produces formic acid & formaldehyde; EG produces glycolic acid, glycolate, etc
- Absorption – usually complete within 2 hours
- Both are metabolized by alcohol dehydrogenase so if the patient has consumed ETOH this would slow formation of the lethal metabolites
- If one inhibits alcohol dehydrogenase the half life for removal of EG is about 12 hours and for M is about 48 hours so will often do hemodialysis with large M overdose due to this very long half life
Osmolal gap

- Measured osmolality - measured by freezing point depression
- Calculated osmolality - 2 Na+ + glucose/18 + urea/2.8
- Osmolal gap: measured – normal is 1.9+- 3.7 mosm/kg (10 is upper of normal)
- To determine a chemical’s contribution to the calculated osmolality convert the concentration in mg/dl to mm/L by dividing the serum concentration in mg/dL by the MW divided by 10  eg. MW of urea is 28 and if urea level is 84 mg/dl that would be 28/10 = 2.8  84/2.8=30 contribution to the calculated osmolality
- If alcohol is present must add to this formula but it is not a perfect osmole.  MW=46 but divide by 3.7 not 4.6
- Elevated also in alcoholic ketoacidosis, diabetic ketosis, isopropyl alcohol, alcohol intake, other serious illnesses
Osmolal gap in ethylene glycol or methanol ingestion

• Cannot measure either M or EG in our ER - a send out
• Osmolarity - can measure the quickly and accurately
• The metabolites of EG and M do not affect OG so the OG as a screening test is insensitive in a late presentation
• Toxic level of EG or methanol is 20 mg/dl. This would increase the OG by 6 mm/L with M and 3 mm/L with EG.
• So OG not very sensitive for small ingestion and can not definitively exclude a significant ingestion if the OG is <10.
• But since the typical M or EG overdose has OG > 25-30 it is a helpful tool when screening for toxin-associated high AG acidosis
Criteria for Rx in methanol or ethylene glycol poisoning

- plasma concentration >20 mg/dl OR
- documented recent history of ingestion of toxic amounts and osmolal gap >10 OR
- at least 3 of the following – arterial pH<7.3, serum HCO3<20, osmolal gap >10, oxalate crystalluria (with ethylene glycol)

Unexplained anion gap: NEJM 2009:2216
Methanol and ethylene glycol treatment

- Sodium bicarbonate - correction of acidosis reduces concentration of the more permeable dissociated anion
- Competitive inhibitors of alcohol dehydrogenase: fomepizole a much stronger inhibitor than alcohol; agent of choice but expensive
- Adjunctive therapy – folic acid, thiamine, and pyridoxine can have small effects to optimize nontoxic metabolic pathways for the elimination of the parent alcohol or its metabolites
Hemodialysis in EG or M from UptoDate

• Known methanol or ethylene glycol OD
  – do HD if high anion gap gap regardless of drug level or if clear evidence of end organ damage

• Suspected OD - do HD if unexplained severe AG gap acidosis and significant osmolal gap (difficult to be provide precise thresholds, depends on how likely it is M or EG has been ingested)
Difficulties in Rx of M or EG

• Can not measure levels locally, but can do OG
• Osmolal gap (OG) not sensitive test for small but significant ingestions
• It is not EG or M that is toxic but the metabolites
• We can not measure metabolites
• Metabolites not detected by osmolal gap
• Formation of metabolites is blocked by ETOH so can have a potentially lethal blood level with minimal metabolite formation if had been drinking ETOH
• Hemodialysis – we can not measure the toxic metabolites that we are trying to remove with HD but are relying on non specifics: pH, anion gap, osmolal gap
High AG metabolic acidosis
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Normal anion gap metabolic acidosis - mechanisms

• **Gastrointestinal HCO₃ loss** – diarrhea, loss of pancreatic or biliary secretions, ureteroileostomy or ureterosigmoidostomy, sevelamer

• **Renal acidification defects**
  RTA, hypoaldosteronism
  drugs (topiramate, acetazolamide, amiloride, trimethoprim, cyclosporine, pentamidine, toluene (from glue sniffing), spironolactone

• **Acid administration** – cationic aminoacids (TPN)
urine AG to distinguish renal vs GI cause non AG metabolic acidosis

- The acid excreted by the kidney each day is excreted primarily in the form of NH4+
- Estimation of urine NH4+ can be done by measuring urine osmolar gap
- Measured urine osm = 2( Na + K) + glucose/18 + BUN/2.8
- Value < 40 suggests renal origin (distal RTA) and > 75 suggests non renal origin
Reasons for differences in HCO3 on ABG vs chemistry panel

- Not simultaneous
- Venous vs. arterial
- Arterial is a calculated value based on the pH and the PCO2
- Venous is not just the HCO3 but is the total CO2 total CO2 = HCO3 (eg. 23) and dissolved CO2 (eg. 1.2)
Determination of correctness of ABGs

- pH 7.4 – 40 nanomoles H+ per liter
- pH 7.1 – 80 nanomoles H+ per liter
- pH 7.7 – 20 nanomoles H+ per liter
- $H^+ = 24 \times \frac{pCO2}{HCO3}$
- Example of normal values $40=24$ $40/24$
Ketoacidosis - ketamine

- 19 year old diabetic who presented with pH 6.7 and only moderately elevated beta hydroxybutyrate levels
- Drug screen – ketamine
- Intentional or via spiked drinks and gives rise to dose-dependent effects ranging from relaxation referred to by users as “K-land” or near death experiences “K hole”
- Metabolic acidosis, seizures, rhabdo
Hemodialysis for methanol or ethylene glycol

• Goal – to prevent end-organ toxicity

• Mechanism – corrects metabolic abnormalities & removes methanol or EG

• Indications – level>50 mg/dL, HCO3<15 or pH<7.3, optic injury from methanol