ENDOGENOUS NON-LACTIC ACIDOSIS IN POISONING

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DISCLAIMERS

• **NOTHING TO DECLARE**
DEDICATION

• This presentation is dedicated to the memory of Professor Chantal Favre-Bismuth.

• Her contributions to clinical toxicology were innumerable and lasting.

• Her boundless curiosity, razor-sharp mind, incisive wit, and gracious elegance will not be forgotten.

IUTOX – Paris, France, 1998
OBJECTIVES

- Describe the two major forms of metabolic acidosis and their etiologies
- Provide examples of various mechanisms for endogenous acid production
- Provide a framework for investigation of suspected acidosis
ABBREVIATIONS

- AG – Anion Gap
- APAP – Paracetamol or Acetaminophen
- HAGMA – High Anion Gap Metabolic Acidosis
- HCMA – Hyperchloremic Metabolic Acidosis
- NAGMA – Normal Anion Gap Metabolic Acidosis
- OG – Osmol Gap
- OP – Organophosphorus Compound
- SID – Strong Ion Difference
- SIG – Strong Ion Gap
FORMS OF METABOLIC ACIDOSIS
METABOLIC ACIDOSIS

HAGMA (HIGH ANION GAP)

• AG INCREASED: INCREASE IN UNMEASURED ANIONS IS ACCOMPANYED BY A DECREASE IN SERUM BICARBONATE
  • Metabolism to "unmeasured" anions
  • Generation of ketoacids
  • Generation of lactic acid
  • Disruption of metabolic pathways

METABOLIC ACIDOSIS

NAGMA (NORMAL ANION GAP)

- **AG UNCHANGED**: AN INCREASE IN SERUM CHLORIDE IS ACCOMPANIED BY A DECREASE IN SERUM BICARBONATE
  - Loss of bicarbonate from the G.I. tract or kidney
  - Substances metabolized to HCl
  - Impairment of net acid excretion
  - ↑↑ Excretion of organic acid ions with replacement by endogenous or administered chloride
  - Administration of chloride-rich solutions

EXAMPLE SUBSTANCES CAUSING ENDOGENOUS NON-LACTATE METABOLIC ACIDOSIS

HAGMA
- Acetaminophen
- Aminocaproic Acid
- 2-Butoxyethanol
- Diethylene Glycol
- Ethylene Glycol
- Methanol

NAGMA
- Iron
- Propylene Glycol
- Salicylates
- Toluene
- Triethylene Glycol
- Valproate

Judge 2006 Clin Lab Med 26, 31-48
Shiber 2010 J Emerg Med 38, 494-496
EXAMPLE SUBSTANCES & MECHANISMS
SUBSTANCES CAUSING HAGMA AC ETAMINO PHEN

- **THE GAMMA (Γ)-GLUTAMYL CYCLE CATALYSES, WITH GLUTATHIONE SYNTHASE, THE PRODUCTION OF GLUTATHIONE**
SUBSTANCES CAUSING HAGMA ACETAMINOPHEN

In normal conditions, glutathione acts as a feedback inhibitor of \(\gamma\)-glutamyl cysteine synthase, preventing excess glutathione production.
SUBSTANCES CAUSING HAG MA ACETAMINOPHEN

IN APAP POISONING, GLUTATHIONE IS CONSUMED, LEAVING DISINHIBITED \( \Gamma \)-GLUTAMYL CYSTEINE SYNTHASE TO PRODUCE EXCESS \( \Gamma \)-GLUTAMYL CYSTEINE, WHICH THEN ACTS WITH A CYCLO-TRANSFERASE TO PRODUCE PYROGLUTAMIC ACID, ALSO KNOWN AS 5-OXOPROLINE.

www.derangedphysiology.com
SUBSTANCES CAUSING HAGMA

ACETAMINOPHEN

- OVERPRODUCTION OF PYROGLUTAMIC ACID MAY PRODUCE HAGMA DURING PARACETAMOL POISONING
- MAY ALSO OCCUR WITH VIGABATRIN AND FLUCLOXACILLIN (FLOXACILLIN)

Modified from http://www.derangedphysiology.com
SUBSTANCES CAUSING HAGMA
ALCOHOLS AND GLYCOLS

Methanol
Formaldehyde
Formic acid

Alcohol dehydrogenase

Ethylene glycol
Glyceraldehyde
Glycolic acid

Aldehyde dehydrogenase
SUBSTANCES CAUSING HAGMA ALCOHOLS AND GLYCOLS

Diethylene glycol

Alcohol dehydrogenase

2-OH-ethoxy-acetaldehyde

2-OH-ethoxy-acetic acid → Diglycolic acid

Aldehyde dehydrogenase

2-butoxy-ethanol

2-butoxy-acetaldehyde

2-butoxy-acetic acid
SUBSTANCES CAUSING NAGMA TO PIRAMATE

- **Carbonic Anhydrase Inhibitor → Type 2 Renal Tubular Acidosis.** The distal tubule is unable to reclaim filtered bicarbonate, resulting in a hyperchloremic metabolic acidosis.

- Generally seen with chronic therapy and usually asymptomatic.

- Acute illness, including infections and dehydration or significant dosing increases may result in severe metabolic acidosis.

Shiber 2010 J Emerg Med 38, 494-496
TOluene causes both HAGMa and NAGMa.

- Toluene induces Type I (distal) renal tubular acidosis, resulting in sometimes severe hypokalemia, typically with a normal anion gap (~40%, Camara-Lemarroy 2015). Hyperchloremia may be present, resulting in HCMA.

- The majority of cases have HAGMa, with mean AG of 16±6.9, not due to lactate or ketoacids. Urinary excretion of hippuric acid results in increased excretion of sodium and potassium. Sodium loss results in extracellular fluid volume contraction, resulting in high anion gap metabolic acidosis, with accumulation of hippuric acid and other anions. (Carlisle 1991 J Am Soc Nephrol 1, 1019-1027)
SUBSTANCES CAUSING BOTH HAGMA AND NAGMA

TOLUENE

http://www.inchem.org/documents/ehc/ehc/ehc52.htm#SectionNumber:7.3
**HAGMA OR NAGMA?**  
**OP POISONING MIMICKING DIABETIC KETOACIDOSIS**

- Numerous authors have described hyperglycemia in OP poisoning. A few have further described metabolic acidosis, with ketonuria. Because of lack of data from the reported cases, it is not possible to say whether this is HAGMA or NAGMA.

- The hyperglycemia has been attributed to oxidative stress, inhibition of paraoxonase, stimulation of the adrenal glands and release of catecholamines. OPs alter the metabolism of liver tryptophan.

- The reasons for ketonuria and acidemia are less well defined, but may be due to severe loss of fluids and electrolytes through diarrhea and vomiting. OP's have also been shown to cause pancreatitis in some cases.

Zadik 1983 Clin Toxicol 20, 381-385  
Akyildiz 2009 Ann Trop Paediatr 29, 155-158  
Kumar 2011 Indian Pediatr 48, 74-76
NAGMA: PLANTS DO IT

- Cleistanthus collinus (Oduvan)
- Hypokalemia, Hyponatremia
- NAGMA (HCMA)
  - Inhibition of vacuolar H⁺ ATPase → Distal RTA

Nampoothiri 2010 Clin Toxicol 48, 193-197
Kettimuthu 2011 Clin Toxicol 49, 457-463
Das 2014 J Forensic Sci 59, 5
AN APPROACH TO THE PATIENT WITH SUSPECTED ACIDOSIS
PITFALLS IN ACID-BASE ASSESSMENT

• **PHYSICAL EXAM**
  • Accepting the respiratory rate, as counted by a triage nurse
  • Failure to appreciate extremes of minimum volume on physical exam
  • Failure to consider acid-base disorders in the settings of unexplained altered mental status, tachycardia, tachypnea, or hypotension.

• **ANION GAP**
  • Assumption that anion gap is standardized and sufficient
  • Failure to correct for markedly abnormal albumin, phosphorus or hydration status
  • Failure to consider a component of HCMA

• **BASE EXCESS**
  • Failure to correct for markedly abnormal albumin or hydration status

FencI 2000  Crit Care Med 162, 2246-2251
TENETS OF QUANTITATIVE ACID-BASE ANALYSIS

1. **Electro Neutrality Must Always Exist:** The sum of all positive charges must always be equal to the sum of all negative charges.

2. **Dissociation Equilibria of All Incompletely Dissociated Substances Must Always Be Satisfied.**

3. **Mass Is Conserved;** That is, the total concentration of an incompletely dissociated substance can always be accounted for as the sum of the concentrations of its dissociated and undissociated forms.

Fencl 1993 Respir Physiol 91(1):1-16.s
The central tenet of the strong ion approach is that neither \([H^+]\) nor \(\text{HCO}_3^-\) can change without a change in one or more of these three independent variables.
Figure 29-1 from Borron SW. in Brent J et al. Critical Care Toxicology 2nd Ed. 2016
Obtain:
- ABG, Na⁺, K⁺, Cl⁻, CO₂, Alb⁻
- Evaluate AG corrected for albumin (Eq 3), Delta gap (Eq 4)
  Consider osmol gap for suggestive history*, increased AG or AMS
  Consider ABG, lactate

Etiology of acid-based disorder clear?

Clinical suspicion for acid-base disorder and/or patient acuity

Obtain:
- ABG, Na⁺, K⁺, Cl⁻, CO₂, Ca²⁺, Mg²⁺, Pi, Alb⁻, lactate
  
  Consider quantitative analysis of specific toxicants based on history
  Perform quantitative acid-base analysis (SIG) or AG corrected and BE corrected (Figure 6)
  Consider osmol gap for suggestive history*, increased SIG or AG or AMS

Correct acid-base disorder, if present

Figure 29-3 from Borron SW. in Brent J et al. Critical Care Toxicology 2nd Ed, 2016
Anion Gap* Etiology

Decreased < 3 mmol/L

Consider:
- Increased serum lithium
- Increased serum bromide or iodide
- Multiple myeloma
- Severe hypomagnesemia or hypercalcemia
- Hypoalbuminemia: Correct AG**
- Renal transplantation

Increased > 11 mmol/L

Consider:
- Exogenous unmeasured anion sources (methanol, ethylene glycol, salicylates)
  Osmol gap
- Endogenous unmeasured anion sources (lactate, ketoacids)
- Hyperphosphatemia: Correct AG***

Correction for hypoalbuminemia:
AG observed + 0.25 × ([Albumin, nL] − [Albumin obs]) = AG corr Alb -

Correction for hyperphosphatemia:
AG obs − 0.32 × ([Pi obs] − [Pi, nL]) = AG corr Pi

Perform quantitative acid-base analysis (SIG***)
or corrected BE
ABG
Na+, K+, Cl−, CO2
Ca2+, Mg2+, Pi, Albumin

Figure 29-4 from Borron SW. in Brent J et al. Critical Care Toxicology 2nd Ed. 2016
Delta Gap*:

**Decreased** < -6 mmol/L
- Consider: Mixed increased AG acidosis and normal AG acidosis
- Mixed increased AG acidosis in chronic respiratory alkalosis with compensatory hyperchloremic acidosis
- Increased AG acidosis reduced by low AG state (bromism, lithium toxicity, hypoalbuminemia)

**Increased** > +6 mmol/L
- Mixed increased AG acidosis and primary metabolic alkalosis
- Mixed increased AG acidosis and respiratory acidosis

\[ \Delta \text{gap} = \Delta \text{AG} - \Delta \text{HCO}_3^- , \text{ where } \Delta \text{AG} = \text{observed AG} - \text{the upper normal limit of the AG} \text{ and } \Delta \text{HCO}_3^- = \text{lower normal HCO}_3^- - \text{observed HCO}_3^- . \]

**Albert formula**: Expected PaCO2 = 1.54 [HCO3–] + 8 ± 2.

*Perform quantitative acid-base analysis (SIG*** or corrected BE ABG Na+, K+, Cl–, CO2 Ca2+, Mg2+, Pi, Albumin)

**Treat as appropriate**
Critically ill or complex acid-base disorder

**Stewart Method**
- Obtain Na⁺, K⁺, Cl⁻, CO₂, BUN, Glucose
- Alb⁻, Pi⁻, Mg²⁺, Ca²⁺, ABG, Lactate
- Consider osmol gap and research for specific toxicants

**Modified AG-BE Method**
- Obtain Na⁺, K⁺, Cl⁻, CO₂, BUN, Glucose
- Alb⁻, Pi⁻, ABG, Lactate
- Consider osmol gap and research for specific toxicants

**Questions to consider:**
- Is the SID decreased, suggesting hyperchloremic acidosis?
- Is the serum sodium normal, or is there evidence of water excess or deficit?
- Is the serum albumin low, producing a metabolic alkalosis and masking acidosis?
- Is the SIG or AGc increased, suggesting unmeasured anions?
- Is the increase in the SIG or AGc accounted for by an increase in lactate?
- If not, what other organic acids could be responsible? Glycinate? Formate? Beta hydroxybutyrate?

**Figure 29-6 from Borron SW. in Brent J et al. Critical Care Toxicology 2nd Ed. 2016**
APPROACH TO NAGMA

Table 5. Systematic approach to diagnosis of nongap metabolic acidosis

Obtain a good history and physical examination to determine if acidosis is acute or chronic in nature and to look for evidence of disorders associated with nongap acidosis.

Examine the patient’s baseline anion gap corrected for serum albumin to determine if nongap acidosis or combined nongap and high anion gap acidosis is present.

Examine serum potassium concentration to determine if it is elevated/normal or low.

Examine eGFR to determine if renal insufficiency is present, which could be associated with nongap acidosis.

If this information is insufficient to make a diagnosis, obtain measures of renal acidification.

Measure urine osmolality Na⁺, K⁺, urea nitrogen, and glucose, if glycosuria present, to calculate urine osmolar gap.

If urine NH₄⁺ assay is readily available, determine urine NH₄⁺.

Once urine NH₄⁺ is determined to be low, measure urine pH.

If proximal RTA is suspected, evaluate renal bicarbonate reabsorption.

If proximal RTA is suspected, evaluate urine for glucosuria, aminoaciduria, and phosphaturia. Check serum for levels of these substances.
DIAGNOSTIC STUDIES FOR NAGMA

- Blood gases
  - Distinguish NAGMA from chronic respiratory alkalosis
- Albumin-corrected anion gap
- Delta gap
- Serum potassium

- Assessment of net acid excretion
  - Urine anion gap and osmolality
  - Direct measure of urinary NH4+
  - Modified urine osmolal gap
  - Urine pH

SERUM ELECTROLYTES IN NAGMA

Table 1. Typical electrolyte pattern in various acid-base disorders characterized by nongap acidosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Distal RTA</th>
<th>Proximal RTA</th>
<th>CKD&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Toluene Intoxication&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ketoacidosis&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Early</td>
<td>Late</td>
<td>Early</td>
</tr>
<tr>
<td>Na&lt;sup&gt;+&lt;/sup&gt; (mEq/L)</td>
<td>140</td>
<td>140</td>
<td>140</td>
<td>140</td>
<td>140</td>
<td>135</td>
</tr>
<tr>
<td>K&lt;sup&gt;+&lt;/sup&gt; (mEq/L)</td>
<td>4.0</td>
<td>3.5</td>
<td>3.5</td>
<td>4.4</td>
<td>4.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Cl&lt;sup&gt;−&lt;/sup&gt; (mEq/L)</td>
<td>105</td>
<td>110</td>
<td>110</td>
<td>110</td>
<td>110</td>
<td>100</td>
</tr>
<tr>
<td>HCO&lt;sub&gt;3&lt;/sub&gt;− (mEq/L)</td>
<td>25</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Anion gap (mEq/L)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>15</td>
<td>25</td>
</tr>
</tbody>
</table>

<sup>a</sup>An electrolyte pattern consistent with nongap acidosis, mixed nongap and high anion gap, or high anion gap alone can be present at any time during the course of this disorder.
## Table 2. Causes of nongap metabolic acidosis categorized based on serum K+\(^a\)

<table>
<thead>
<tr>
<th>High or Normal Serum K(^+)</th>
<th>Low Serum K(^+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration of HCl</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>TPN solutions</td>
<td>Intestinal fistulae</td>
</tr>
<tr>
<td>NH(_4)Cl(^b)</td>
<td>Proximal RTA ←</td>
</tr>
<tr>
<td>Hyperkalemic distal RTA</td>
<td>Distal RTA ←</td>
</tr>
<tr>
<td>hyporeninemic hypoaldosteronism</td>
<td>Ureteroileostomy</td>
</tr>
<tr>
<td>tubular resistance to aldrosterone</td>
<td>Ureterosigmoidostomy</td>
</tr>
<tr>
<td>aldosterone deficiency</td>
<td>Toluene intoxication ←</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Ketoacidosis(^b) ←</td>
</tr>
<tr>
<td>Gordon’s syndrome</td>
<td>D-Lactic acidosis ←</td>
</tr>
<tr>
<td>Decreased distal Na delivery</td>
<td>Administration of Cl-rich solutions(^b) ←</td>
</tr>
<tr>
<td>Administration of Cl(^-)rich solutions(^b) ←</td>
<td></td>
</tr>
<tr>
<td>Drugs such as triamterene, amiloride, pentamidine, NSAIDs, CEIs, ARBs, trimethoprim, spironolactone, or heparin ←</td>
<td></td>
</tr>
</tbody>
</table>

TPN, total parenteral nutrition; NSAIDs, nonsteroidal anti-inflammatory drugs; CEIs, converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

\(^a\)Includes the majority, but not all, causes of nongap metabolic acidosis.

\(^b\)Serum K\(^+\) can be high, normal, or low, depending on when it is determined during the course of the disorder.
Questions?

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