Review of Clinical Disorders Causing Metabolic Acidosis

Michael Emmett

The various mechanisms responsible for the development of metabolic acidosis are briefly reviewed, and the metabolic acidoses are categorized both by mechanism and by the presence or absence of an increased anion gap. When a diagnosis of metabolic acidosis is established, it becomes imperative to identify the primary causative etiology as quickly as possible. This is often readily apparent from the history and physical exam (ie, diabetic ketoacidosis when the glucose is very high in a patient with diabetes mellitus; lactic acidosis in a patient with sepsis and hypotension, etc.). However, when the etiology is not obvious, it is very helpful to determine if the metabolic acidosis is of the hyperchloremic or high-anion-gap type (or a combination of both). Once this categorization has been established, a stepwise consideration of each of the potential causative etiologies will usually direct the clinician to order the appropriate diagnostic studies.

Key Words: Metabolic acidosis, Hyperchloremia, Anion gap, Renal tubular acidosis, Toxic alcohols

Adults generate about 15,000 mmol of CO_2 each day. CO_2 is a volatile acid because, in aqueous solution, it rapidly combines with water to form 15,000 mEq/l of H_2CO_3. This volatile acid is excreted by the lungs. In addition, individuals ingesting a typical Western diet generate 50 to 100 mEq of nonvolatile acids each day—mainly sulfuric acid derived from the metabolism of sulfur-containing amino acids and smaller amounts of phosphoric, hydrochloric, and other strong acids. In contrast, a vegetarian diet generates much less net acid due to the ingestion of Na and K salts of organic anions which are oxidized in the body to generate Na and K bicarbonate. The daily net nonvolatile ("fixed") acid load generated by most individuals ingesting a Western diet is normally excreted by the kidneys.

Most nonvolatile strong acids that are generated by metabolism (in subjects ingesting a "Western" meat-based diet) cannot be excreted in the urine as such. This is because their very low pK_a would require the urine pH to be reduced to levels that cannot be generated by the human kidney. (For example, the major strong acid generated from meat diets is H_2SO_4.[1]) Instead, renal excretion of the protons and the acid anions is accomplished by separate parallel processes. The protons of these strong acids are excreted in the urine either by combining them with buffering anions such as urinary phosphate to form "titratable acid" (TA) or by combining them with ammonia to form ammonium:

$$HPO_4^{2-} + H^+ \rightarrow H_2PO_4^-$$

OR

$$NH_3 + H^+ \rightarrow NH_4^+$$

The major TA anion in urine is phosphate (the pK_a for the reaction shown above is 7.2) with much smaller contributions from creatinine (pK_a 4.8), urate (pK_a 5.5), and others (eg, beta-hydroxybutyrate—pK_a 4.8—becomes a very important component of TA in patients with ketoacidosis). Most TA anions are filtered and enter the proximal tubule lumen as sodium salts (some are secreted). Then, in the renal tubules, the Na^+ is reabsorbed in exchange for H^+. The secreted H^+ binds to the TA anions as the urine pH falls, from the 7.4 pH range in the normal glomerular filtrate to acidic levels as low as the 4.5-4.8 range in the distal tubules and collecting ducts. Other secreted protons bind to NH_3 forming NH_4^+. These protons, bound to TA or ammonia, are then excreted into the urine together with the original acid anions (ie, SO_4^{-2}, Cl^-, etc.). Therefore, 2 parallel processes ensue: glomerular filtration of the anions of both ingested and metabolically generated strong acids and tubule secretion of the protons which were originally generated with those anions, bound to either NH_3 or TA anions, and combine to remove the strong acids from the body.

Renal ammonia production, largely derived from metabolism of glutamine, can sharply increase over a period of several days, in response to increased acid loads. In comparison, the quantity of TA is relatively fixed by dietary intake. Therefore, the major adaptive response to increased acid loads is a rise in renal NH_4^+ excretion. As described above, the NH_4^+ is excreted with the anions of the acids responsible for the acidic load. The relevance of these renal mechanisms for acid excretion in any discussion of the spectrum of clinically relevant metabolic acidosis will become apparent below.

FOUR MAJOR PATHOPHYSIOLOGIC MECHANISMS ARE RESPONSIBLE FOR THE DEVELOPMENT OF METABOLIC ACIDOSIS

1. Abnormally increased rate of systemic acid generation (or acid ingestion/infusion).
2. Abnormally increased rate of $NaHCO_3$ (or "potential bicarbonate salt") loss.

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3. Reduced/inadequate rate of renal acid excretion.
4. Combinations of the above 3 mechanisms.

Table 1 lists the major causes of metabolic acidosis.

ABNORMALLY INCREASED RATE OF SYSTEMIC ACID GENERATION (OR ACID INGESTION/INFUSION)

Anion Gap Metabolic Acidoses Type 1

When nonvolatile acid generation rates increase to levels that exceed the rate at which they can be excreted (mainly by the kidneys), protons are retained in body fluids. The retained protons are immediately buffered within body fluids, largely by HCO_3^-.

$$HA + HCO_3^- \rightarrow H_2CO_3 + A^- \rightarrow \text{dissolved } CO_2 + A^-$$

This reaction sequence converts a nonvolatile acid (HA) to H_2CO_3 and A^- and then to the volatile acidCO_2, which is removed by the lungs. It can be seen that the anions of the accumulating acid (A^-) increase in concentration while the HCO_3^- concentration falls reciprocally to a similar degree. (Note this is an oversimplification of the body's buffering mechanisms. Some of the H^+ will be taken up in cells by non-bicarbonate molecules.) The strong acids which can accumulate in the body can be divided into 2 groups: HCl and all other nonchloride acids. This division is one of the basic underlying principles of the anion gap [AG] approach to acid-base analysis (discussed below). In addition, the loss of $NaHCO_3$-rich fluids and/or Na-organic acid anion salts from the body will also generate a non-AG, or hyperchloremic, metabolic acidosis (see below Increased Rates of Loss of Bicarbonate Salts or "Potential Bicarbonate" Salts From the Body).

CLINICAL SUMMARY

- Most "Western" diets will result in the generation of about 70 – 100 mEq of strong acids (mainly sulfuric and phosphoric acid) each day.
- The kidney must excrete both the protons and the anions of these acids to maintain acid-base and electrolyte balance, and kidney dysfunction will usually generate metabolic acidosis; the severity of the reduction in glomerular filtration relative to the severity of the reduction in tubular acid secretion determines if the disorder is characterized as a "uremic" or "tubular" acidosis.
- Other forms of metabolic acidosis are generated by overproduction and/or reduced oxidation of endogenous acids (lactic acidosis, ketoacidosis), and/or the generation of strong acids from various toxic chemicals (formic, oxalic, benzoic acids), or the excessive loss of bicarbonate salts from the body.
- The metabolic acidoses can be readily subdivided into those generating an increasesd anion gap and those associated with hyperchloremia.

The 2 most common endogenous causes of high-AG metabolic acidosis (HAGMA) are
1. L-lactic acidosis
2. Ketoacidosis

L-lactic acidosis is usually divided into 2 subcategories:
1. Type A L-lactic acidosis
2. Type B L-lactic acidosis

Type A L-lactic acidosis is the result of marked tissue hypoperfusion which may occur with hypovolemia, cardiac failure, sepsis, acute severe anemia, seizures, or cardiopulmonary arrest. The initial serum lactate level and the rate at which lactate levels improve are predictors of survival in patients with shock due to sepsis. The prognosis is generally very poor if tissue perfusion cannot be rapidly restored.

Systemic hypoperfusion is not apparent with Type B L-lactic acidosis. The causes of this condition include disorders which generate regional areas of ischemia and a variety of disorders which impair or block mitochondrial oxidation. The mitochondrial defects may be due to inherited disorders, such as a spectrum of defects called the Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes disorders (MELAS disorders) or acquired defects related to thiamine deficiency, or generated by medications or toxins/poisons (such as early generations of nucleoside reverse transcriptase inhibitors, linezolid, carbon monoxide poisoning, high-dose propofol, toxic salicylate levels). Biguanides, used to treat type 2 diabetes (phenformin in the past, and metformin currently) can generate Type B L-lactic acidosis when their levels reach toxic concentrations. Metformin is most likely to generate lactic acidosis when very high levels result from accidental or intentional acute overdose. However, metformin can also accumulate when the drug is administered in the face of markedly reduced kidney function. Severe, usually acute, liver disease can reduce lactate metabolism and generate lactic acidosis. High levels of beta-adrenergic agonists—either generated by therapeutic interventions (ie, during treatment of severe asthma) or in association with a pheochromocytoma—can generate Type B L-lactic acidosis. Type B L-lactic acidosis can also develop in patients with some malignancies. This may be partially related to local areas of hypoxia in the tumor and also because some tumors and hematologic malignancies develop preferential anaerobic glycolysis (the "Warburg" effect). For unclear reasons, patients with diabetes mellitus have an increased risk of lactic acidosis.[2]

Ketoacidosis

Ketoacidosis results from uncontrolled diabetes mellitus or in association with chronic alcohol abuse. Three "ketone bodies" accumulate in the extracellular fluid (ECF)—beta-hydroxy butyrate, acetoacetate, and acetone (Fig 1). The metabolic acidosis is generated by increased levels of beta-hydroxyl butyrate and acetoacetate, which are both strong acids (high acetone levels generate the "ketosis" smell, but acetone is not an acid and does not contribute to the metabolic acidosis). These 2 acids are responsible

Table 1. Disorders Causing Metabolic Acidosis

AG Metabolic Acidosis Type 1
- Abnormally increased rate of systemic acid generation and/or The ingestion/infusion/absorption of acids or acid precursors
  1. L-lactic acidosis
     a. Type A
     b. Type B
  2. Ketoacidosis
     a. Diabetic
     b. Alcoholic
     c. Congenital enzymatic defects
  3. Toxins/poisons which increase endogenous strong acids
     a. Salicylate poisoning
     b. Chronic acetaminophen ingestion (5-oxoproline)
  4. Compounds metabolized to strong acids
     a. Methanol metabolized to formic acid
     b. Ethylene glycol
     c. Diethylene glycol
     d. Propylene glycol
     e. Toluene ingestion/inhalation
  5. D-lactic acidosis

AG metabolic acidosis type 2

Reduced rate of renal proton and acid anion excretion
1. Kidney failure—uremic acidosis

Hyperchloremic acidosis
1. Infusion or ingestion of HCl or molecules metabolized to HCl
   NH_4Cl, arginine-HCl, lysine-HCl
2. Loss of Na(K)HCO_3 and/or Na(K)organic metabolizable anion salts
   a. Proximal renal tubular acidosis (RTA)
   b. Watery diarrhea
   c. Pancreatic fluid loss
   d. Urine exposed to GI epithelium, especially colon or ileum
3. Excretion of Na(K) with the anions of strong acids which have been added to the ECF (instead of the excretion of these strong acid anions with either NH_4^+ or titratable acid)
   a. Distal renal tubular acidosis (type I RTA)
   b. Reduced renal NH_4^+ excretion
      i. Type IV (hyperkalemic) renal tubular acidosis
      ii. Reduced renal NH_4^+ excretion due to chronic kidney disease
   c. Conversion of high [AG] metabolic acidosis to hyperchloremic metabolic acidosis
      1. During recovery from ketoacidosis—loss of Na(K) with beta-hydroxybutyrate and acetoacetate
      2. Toluene ingestion/inhalation—loss of Na(K) with hippurate and benzoate and retention of the protons
      3. Conversion of other AG acidoses to hyperchloremic metabolic acidoses
         a. D-lactate renal excretion as Na(K) D-lactate

Abbreviations: ECF, extracellular fluid; GI, gastrointestinal.

for the reciprocal decrease in bicarbonate and increase of the AG. It is important to understand that ketoacidosis often evolves from a HAGMA to become a hyperchloremic metabolic acidosis.[3,4] This process responsible for this development is discussed below.

Other relatively less common causes of AG metabolic acidosis are also discussed below:

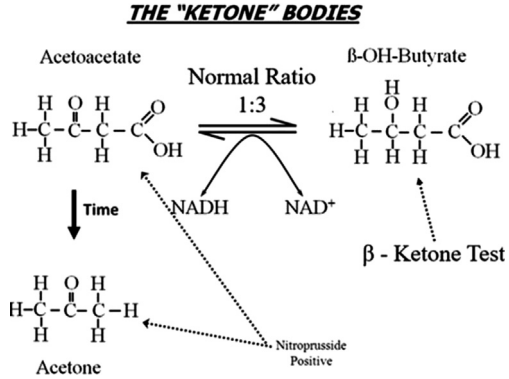

Figure 1. When the "ketone bodies"—acetoacetic acid and beta-hydroxybutyric acid, both strong acids—increase in concentration, the [AG] increases and the [HCO3-] falls in a relatively reciprocal fashion. As shown, they are normally present in plasma in a ratio of about 1:3. If the NADH/NAD^+ redox ratio increases, then this acetoacetate/beta-hydroxybutyrate ratio may shift to 1:10 or more. But it is the sum of acetoacetic acid and beta-hydroxybutyric acid that determines the magnitude of rise of the [AG] and fall of [HCO3-]. Acetoacetic acid is nonenzymatically decarboxylated to acetone, which is not an acid.

Ingestions/Infusions/Poisonings (Note HCl and HCl precursors do not generate AG metabolic acidosis—see below.)

a. Methanol
b. Ethylene glycol
c. Diethylene glycol
d. Propylene glycol
e. Toluene ingestion/inhalation (but this can also generate hyperchloremic acidosis due to the renal loss of Na and K salts of benzoic and hippuric acid—see below)
f. Aspirin overdose/poisoning
g. Chronic acetaminophen use—especially by malnourished/chronically ill women.

None of these toxins, except aspirin (acetylsalicylic acid), is a strong acid itself when ingested. Therefore, they do not directly reduce the [HCO_3^-] or raise the [AG]. Instead, they generate an AG metabolic acidosis because they are either converted to strong acids or they cause increased generation rates of endogenous strong acids.[5] The metabolic pathways for a number of alcohols and glycols are shown in Figure 3. Methanol is converted to formic acid; ethylene glycol to oxalic and glycolic acid; diethylene glycol to 2-hydroxyethoxyacetic acid; propylene glycol is converted to D and L lactic acid; toluene is metabolized to benzoic and hippuric acid (note the benzoate and hippurate anions are very rapidly excreted by relatively normal kidneys, and this can convert an AG metabolic acidosis to a hyperchloremic metabolic acidosis [see below]).[6]

Aspirin itself is a strong acid, and toxic levels do directly contribute to the AGmetabolic acidosis, but a major component of the AG metabolic acidosis that develops with aspirin poisoning is due to the accumulation of multiple endogenous organic acids including lactic acid and ketoacids.[7] Chronic acetaminophen ingestion, especially by malnourished women, can cause accumulation of an

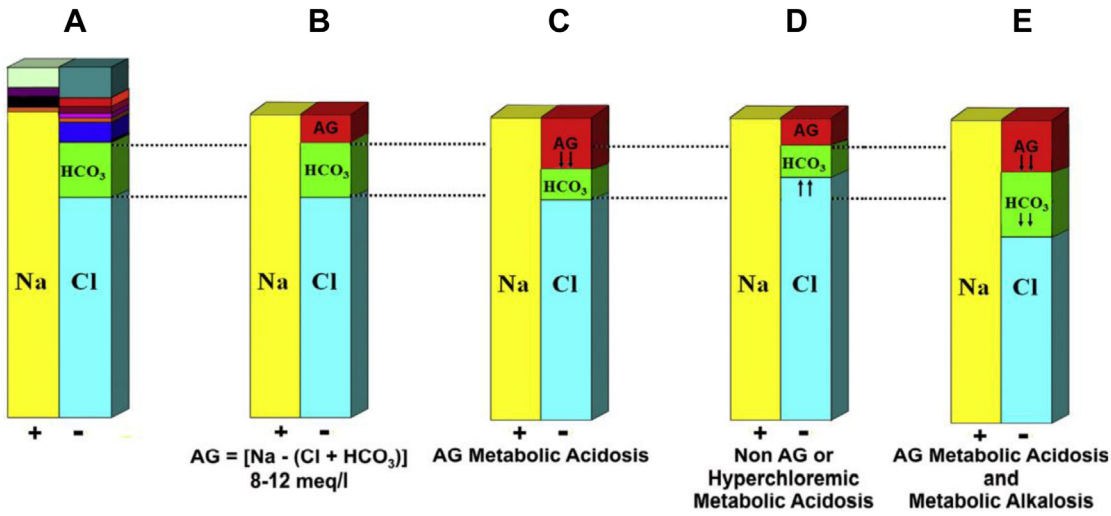

Figure 2. "GambleGram" depiction of blood serum electrolytes. (A) The total anion and total cation concentrations (measured in units of mEq/L) must be equal. (B) If only $[Na^+]$, $[Cl^-]$, and $[HCO_3^-]$ are considered, an anion gap [AG] normally exists. (C) High AG metabolic acidosis reduces the $[HCO_3^-]$ without changing $[Cl^-]$ and thereby increases the [AG] in a reciprocal fashion. (D) Normal AG, or hyperchloremic acidosis, reduces the $[HCO_3^-]$ and increases the $[Cl^-]$ in a reciprocal fashion. (E) Mixed AG metabolic acidosis and metabolic alkalosis. If the [AG] is increased but the [HCO3-] is not reciprocally reduced, consider mixed AG metabolic acidosis and metabolic alkalosis (or AG metabolic acidosis and chronic respiratory acidosis—the arterial blood pH will differentiate). These relationships assume that the other "unmeasured" anions and cations in serum are initially in their normal ranges and stable. Marked increases or decreases in "unmeasured" anion and/or cation concentrations will impact the [AG] calculated value. The issue related to hypoalbuminemia is discussed in the text. Marked hyperphosphatemia, hypercalcemia, hypermagnesemia, or other conditions will also increase or reduce the [AG]. Also, electrolyte measurement artifacts can occur; this is discussed in the text. Although these [AG] and [HCO3-] relationships are very useful concepts, they are not quantitatively exact. The astute clinician will incorporate these relationships into their analysis of the patient's entire clinical and historical picture. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.) Reproduced with permission from Reference #30 figure #1.

unusual endogenous organic acid—pyroglutamic acid (also called 5-oxoproline).[8,9]

D-lactic acid can be generated by gastrointestinal (GI) bacteria when abnormally large quantities of carbohydrate are delivered to the colon. Excessive generation and GI absorption of D-lactate usually develop in patients with a variety of "short-gut" abnormalities such as jejunoileal bypass or s/p extensive small-bowel resection.[10] Rapid infusion, or ingestion, of propylene glycol can generate high D-lactate acid levels.[11] Propylene glycol is a solvent for intravenous preparations of several medications; this is especially important when lorazepam infusions are administered. Propylene glycol is also used as an alternative to ethylene glycol in some automotive antifreeze products. It has been reported that significant D-lactic acid levels may develop in patients with diabetic ketoacidosis.[12]

HCl OR HCl PRECURSOR INGESTION OR INFUSION—A CAUSE OF HYPERCHLOREMIC METABOLIC ACIDOSIS

A major exception to the general rule that HAGMA develops whenever strong acids are ingested or infused is the ingestion, or infusion, of HCl or substances that are metabolically converted to HCl, such as NH_4Cl, arginine-HCl, or lysine-HCl. These substances will generate a hyperchloremic metabolic acidosis. Obviously, direct or indirect addition of HCl to the ECF will reciprocally decrease the $[HCO_3^-]$ and increase $[Cl^-]$ without much effect on the AG. (However, it should be noted that arginine-HCl has been used to treat patients with inherited forms of lactic acidosis due to the spectrum of MELAS disorders.[13])

ABNORMALLY INCREASED RATES OF $NaHCO_3$ (OR "Potential BICARBONATE SALTS) LOSS (HYPERCHLOREMIC METABOLIC ACIDOSES)

When $NaHCO_3$-rich fluids are lost from the body, the blood $[HCO_3^-]$ level falls, and the blood $[Cl^-]$ level increases. The magnitude of these concentration changes is generally reciprocal. There are 2 main reasons that $[Cl^-]$ increases when $NaHCO_3$-rich fluids are lost. First, the loss of $NaHCO_3$-rich fluids contracts the ECF volume (ie, chloride space) "around" a relatively stable chloride content. Second, the $[Cl^-]$ increases because the ECF volume contraction stimulates renal retention of ingested and/or infused chloride salts. The major clinical causes of *direct* $NaHCO_3$ loss include external drainage of pancreatic secretions,[14] the presence or development of proximal renal tubular acidosis (type 2 RTA),[15] or the development of large-volume watery diarrhea—as with cholera or a VIPoma.[16,17] In addition, the loss of Na (or K) salts of metabolizable anions such as lactate, acetate, citrate, butyrate, propionate, etc. has a similar systemic acid-base impact as the loss of Na (or K)HCO_3. This is generally what occurs with most forms of watery diarrhea which are less fulminant than severe cholera or VIPoma-related diarrhea.

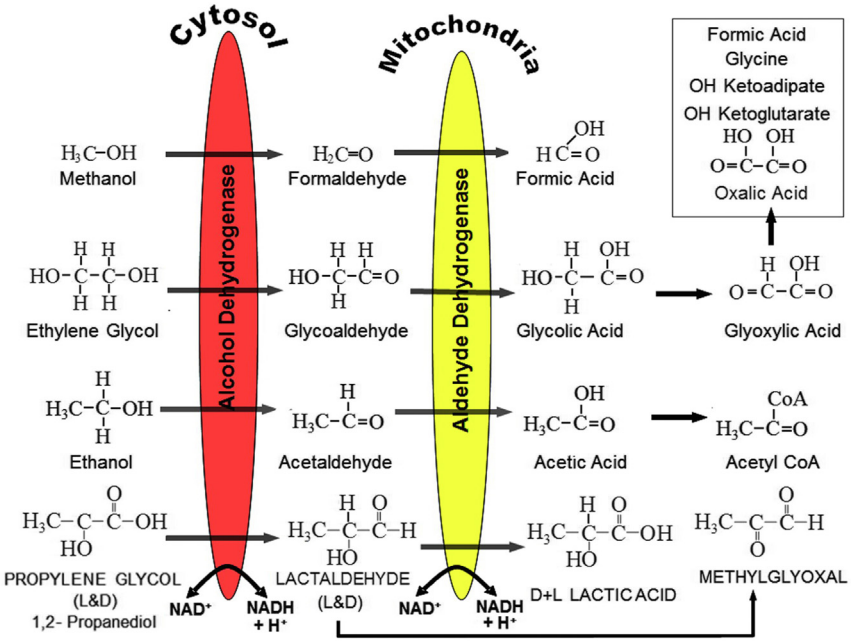

Figure 3. Hepatic oxidation of methanol, ethanol, ethylene glycol, and propylene glycol. A number of aldehydes, strong acids, and other metabolites, many of which are toxic, are generated. The metabolites in the box are downstream products of glyoxylic acid. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.) Reproduced with permission from Reference #30 figure #2.

Patients with these less-fulminant forms of diarrhea often continue to eat and therefore deliver metabolizable carbohydrates to the colon where they are oxidized to multiple organic acids. These organic acids then react with Na (or K)HCO_3 forming Na (or K) salts of the organic acids. External loss of these organic acid salts has a very similar acid-base impact as the direct loss of Na (or K)HCO_3.[18] (However, there are other clinical implications—eg, the loss of these anions does represent a loss of calories from the body which is not the case with $NaHCO_3$ loss.) There are 3 major subcategories in this group.

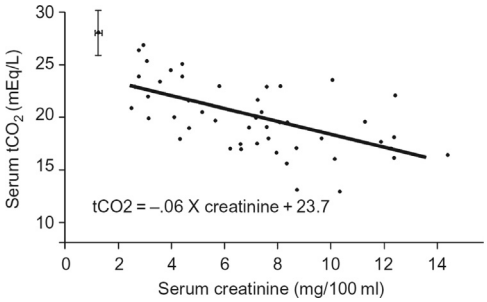

Figure 4. The relationship of serum total CO_2 to serum [Cr] in control patients (point with the ±standard deviation error bars) and in patients with graded degrees of renal failure. Line drawn through data for the renal failure group obtained by least squares. The slope of this line of 0.6 is significantly different from zero ($P < .01$). Redrawn from data in Figure 1 from reference.[23]

Watery Diarrhea

Watery diarrhea leads to the loss of $NaHCO_3$/$KHCO_3$ and Na/K acetate, lactate, citrate, butyrate, propionate, etc. As noted above, HCO3- is often not the major anion lost in watery diarrheal fluid. Instead, an organic acid anion is often lost. A number of intestinal Cl^-/HCO_3^- exchangers (the most important anion exchanger in the colon is the "downregulated in adenoma - or the DRA" exchanger) reduce the [Cl^-] and increase the [HCO_3^-] in colonic fluid. However, much of the $NaHCO_3$ delivered into the colon reacts with multiple organic acids such as lactic, butyric, acetic, and others, in the GI lumen. This generates Na-lactate, Na-butyrate, Na-acetate, etc. To the extent these organic acids are systemically absorbed, they are oxidized and regenerate $NaHCO_3$. However, the external loss of Na-lactate, Na-butyrate, Na-acetate, etc. into the stool generates hyperchloremic acidosis, similar to the direct loss of $NaHCO_3$.

Exposure of Urine to GI Epithelium

If urine comes in contact with GI epithelium for a period of time (eg, after creation of a ureteral enterostomy or an artificial bladder created from a GI segment such as an ileal loop bladder, or other pathologic connections between the urinary system and the GI tract), the Cl^-/HCO_3^- exchangers in the GI epithelium will rapidly remove Cl^- from the urine in exchange for HCO_3^-. NaCl, KCl, and NH_4Cl are thereby converted to $NaHCO_3$, $KHCO_3$, and NH_4HCO_3, respectively, which are then lost from the body.[19]

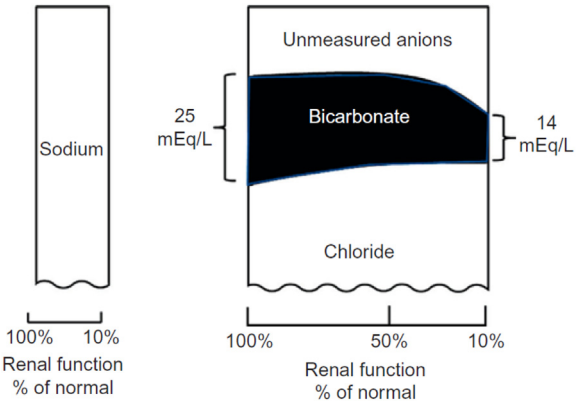

Figure 5. The changing pattern of serum electrolyte composition that occurs during progression of chronic, uncomplicated renal failure. Vertical axis reflects serum electrolyte concentrations in mEq/L. Note that [Na] does not change appreciably as renal function declines. In contrast, serum anion composition changes considerably. Early in the development of progressive renal failure, a sizable reduction in [HCO3-] occurs that is entirely offset by an increase in [Cl-] while the [AG] remains normal. Only when renal function falls to levels below 30% to 50% of normal does this pattern of hyperchloremic acidosis evolve into the more familiar [AG] metabolic acidosis of azotemia. Even under these circumstances, [Cl^-] remains elevated at levels achieved during more moderate renal insufficiency. Redrawn from reference.[23]

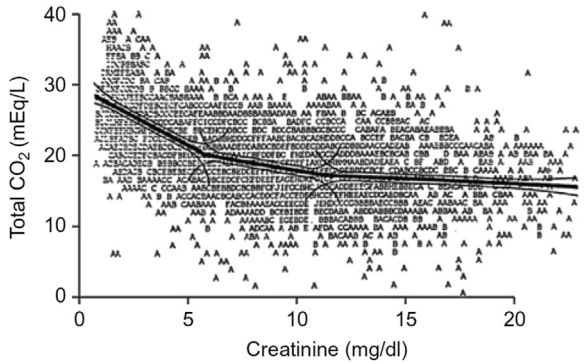

Figure 6. The change of total CO_2 (mEq/L) correlated with [Cr] (mg/dL). This figure contains approximately 4000 data points. Each letter may represent more than 1 point. (A = 1 point, B = 2 points, C = 3 points, etc.) The line is drawn for the slope of total CO_2 vs [Cr], for 3 ranges of [Cr]: [Cr] <5 mg/dL, [Cr] between 5 and 10 mg/dL, and [Cr] >10 mg/dL. The 95% confidence limit of each line slope is shown. Redrawn from data in Figure 2 from reference.[24]

Proximal RTA (Also Called Type 2 RTA)

Proximal RTA is a disorder of proximal tubule $NaHCO_3$ reclamation (reabsorption). As a result, $NaHCO_3$ diuresis ensues. The serum [HCO_3^-] falls until it reaches an abnormally reduced threshold level. At this reduced level, [HCO_3^-] can be completely reclaimed (reabsorbed), and the urine can be acidified. However, any attempt to raise the serum [HCO_3^-] above this abnormally reduced threshold level results in a brisk $NaHCO_3$ and $KHCO_3$ diuresis.[15]

Each of these disorders results in hyperchloremic metabolic acidosis.

Abnormally Reduced Rate of Renal Acid Excretion

As discussed in the introductory paragraph, nonvolatile strong acids generated by metabolism cannot be directly excreted in the urine because this would require the urine pH to be reduced to levels that cannot be generated by the human kidneys. Instead, renal excretion of the protons of the strong acids is accomplished by combining the protons with either NH_3 to form NH_4^+ or with $NaHPO_4^{-2}$, creatinine, or other molecules to create TA. The anions of the strong acids are excreted in parallel fashion. Thus, the renal excretion of strong acids generated by metabolism or ingested as such is accomplished by parallel interconnected processes.

Pathologic processes can impair each of these 2 parallel proton/anion excretory pathways to a relatively equal degree or can affect one of these excretory pathways more severely than the other. Moderate to severe generalized renal dysfunction will often result in relatively equal reduction of (1) glomerular filtration and secretion of strong acid anions and (2) tubule proton secretion. This generates the HAGMA typical of advanced renal failure. The serum [HCO_3^-] falls, and the AG increases. But note that these chemical excursions derive from 2 relatively independent pathologies: the AG increases because reduced glomerular filtration and reduced tubule anion secretion cause the concentration of a number of inorganic anions ($SO4^{-2}$, $HPO4^{-2}$, Cr^-, etc.) to increase while reduced tubule proton secretion causes the [HCO_3^-] to fall.

In contrast, if renal tubule acid secretory function is impaired while glomerular filtration remains relatively normal, then the metabolic acidosis which develops is of the hyperchloremic variety. This is because the acid anions—sulfate, phosphate, urate, etc.—are excreted as Na and K salts (instead of being excreted with NH_4^+ and TA). The tubule acidification defect may be an inability to generate or maintain a normal level of urinary acidity, and this prevents normal titration of the urine buffers which constitute TA and also reduces urine NH_4^+ excretion. Such defects represent "classic" or type 1 RTA.[20] Alternatively, if the defect primarily affects renal ammonium excretion, this will also generate a metabolic acidosis without retention of anions. This type of acidification defect is called type 4 RTA when it is associated with, and partially generated by, hyperkalemia. Impaired renal ammoniagenesis is also common with early progressive kidney dysfunction. These forms of acidosis are all of the hyperchloremic (normal AG) variety.[21]

Thus, the metabolic acidoses generated by an impairment of renal acid excretion can be divided into 2 types:

A. The defect in renal tubule acid excretion is disproportionally worse than the degree of generalized kidney dysfunction, ie, the estimated GFR is normal or relatively better preserved than reduced renal tubule acid secretory function.

a. Classic distal RTA (type 1 RTA)—abnormally reduced proton secretion due to an inability to generate, or maintain, an appropriately acid urine.
b. Type 4 RTA due to an inability to excrete normal quantities of NH_4^+ associated with hyperkalemia.
c. Reduced renal NH_4^+ excretion related to interstitial renal disease and dysfunction (ie, earlier stages of progressive kidney disease). Note Proximal, or Type 2 RTA, is categorized above with he acidoses due to excessive bicarbonate loss.

B. Reduced renal acid excretion that develops in patients as a result of generalized kidney dysfunction—when glomerular filtration and renal tubule acid excretion are impaired to a relatively similar degree—"uremic acidosis." It should be noted that as renal function gradually declines, the acid-base pathology often evolves from a hyperchloremic metabolic acidosis in the earlier stages (because the tubular acidification defect predominates, generally due to impaired renal NH_4^+ excretion or development of a type 4 RTA) to a more overt HAGMA when kidney dysfunction becomes more generalized and reduced acid anion excretion combines with reduced proton excretion.[22-24] This evolution was nicely documented by Widmer and colleagues[23] and was also demonstrated in a much larger data base by Hakim and Lazarus.[24] Figure 4, 5, 6 and 7 show the evolution of hyperchloremic to AG metabolic acidosis as kidney function deteriorates.

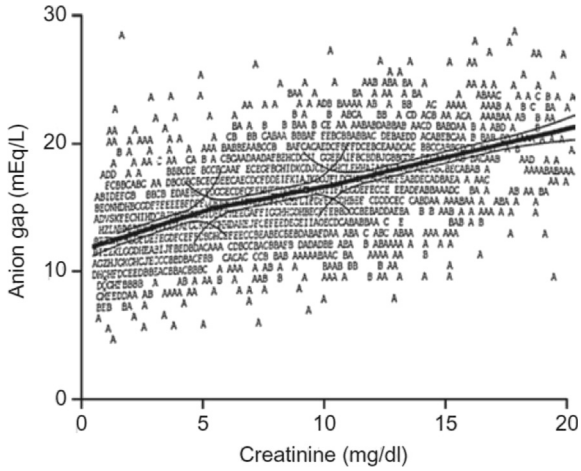

Figure 7. The change in the [AG] as a function of [Cr]. The other notations are similar to those in Figure 6. Note that the slope of the line is positive throughout the range of [Cr]. Redrawn from data in Figure 4 from reference.[24]

Dilution Acidosis

Dilution acidosis is a disorder generated by rapid expansion of the ECF volume with large volumes of saline, usually "normal saline" (with a NaCl concentration of 154 mEq/l). These fluids do not contain sodium bicarbonate nor sodium salts of organic anions that can be metabolized to bicarbonate, ie, potential bicarbonate (such as lactate or acetate). The [HCO_3^-] falls and [Cl^-] increases for 2 reasons. First, the ECF is expanded with [Cl^-]-rich fluids devoid of bicarbonate, and this increases the [Cl^-] and reduces [HCO_3^-]. Second, ECF expansion will often generate renal $NaHCO_3$ excretion. This form of metabolic acidosis most often occurs when large volumes of isotonic saline fluid are given rapidly. Although it is generally of very moderate severity, concern has been raised that this form of hyperchloremic metabolic acidosis may have an adverse effect on patient outcomes (in part related to potentially adverse renal effects of hyperchloremia). Multiple studies of this issue have reached different conclusions. If this modest degree of hyperchloremic metabolic acidosis has any adverse clinical effects, they are likely of the very modest severity.[25-28]

THE ANION GAP

The ionic profile of normal serum is shown in Figure 2. In any solution, the total charge concentration (measured in units of mEq/l) of dissolved cations must equal the total charge concentration of dissolved anions. However, if only the concentrations of the 3 major serum electrolytes (sodium [Na+], chloride [Cl^-], and bicarbonate [HCO_3^-]) are considered, then the cation concentration [Na^+] exceeds the sum of these 2 anion concentrations [Cl^-] and [HCO_3^-]:

$$[Na^+] > ([Cl^-] + [HCO_3^-])$$

Therefore, if the sum of [Cl^-] and bicarbonate [HCO_3^-] is subtracted from [Na^+], an "AG" exists.

$$AG = [Na^+] - ([Cl^-] + [HCO_3^-])$$

Although the normal [AG] is generally about 8 to 12 mEq/l, normal electrolyte values vary from laboratory to laboratory, in part because of different analytic instruments. Therefore, each laboratory should ideally determine its own normal [AG] range.

When metabolic acidosis is generated by ECF accumulation of relatively strong acids (such as lactic, β-hydroxybutyric, or acetoacetic acids, but not HCl), the [HCO_3^-] falls and the [AG] increases reciprocally. The magnitude of [AG] increase above its baseline (or Δ[AG]) then represents the plasma concentration of accumulating acid anions (ie, lactate, ketoacid anions, etc.). Furthermore, the Δ[AG] is generally similar to the Δ[HCO_3^-]. Consequently, the increased excursion of the [AG] should be of similar magnitude to the decrease in [HCO_3^-]—thus, the Δ[AG]/Δ[HCO_3^-] ratio is generally about 1.[29,30]

However, several factors can disrupt this 1:1 relationship. They include different distribution spaces for HCO_3^- and the accumulating acid anions, intracellular proton buffering, and variable rates of kidney excretion of the protons and acid anions. Mixed acid-base disorders also disrupt the 1:1 relationship.

In order to determine the magnitude of [AG] increase, or decrease, from the baseline it would be ideal to know each individual patient's "baseline" [AG]. In the absence of such information, I suggest using a baseline [AG] value of 10 mEq/l, with the appropriate adjustments if the albumin

Table 2. GOLDMARK Mnemonic for the High Anion Gap Metaboic Acidoses

Letter	Parameter	Potential Causes
G	Glycols	Ingestion/infusion of ethylene, propylene, or diethylene glycol; metabolism generates glyoxylic, oxalic, $_D$ and $_L$ lactic acid.
O	5-Oxoproline	Chronic acetaminophen use can generate 5-oxoproline (a strong acid that is also called pyroglutamic acid).
L	$_L$-Lactic acidosis	Multiple etiologies of types A and type B lactic acidosis.
D	$_D$-Lactic acidosis	Carbohydrate loading in patients with short gut syndromes.
M	Methanol	Metabolism generates formic acid.
A	Aspirin	Toxic levels generate multiple organic acids including keto acids.
R	Renal failure	Accumulation of multiple inorganic and organic acid including sulfuric and phosphoric acid.
K	Ketoacidosis	B–OH butyric and acetoacetic acid.

From: Mehta AN, Emmett JB, Emmett M. GOLD MARK: an anion gap mnemonic for the 21st century. Lancet. 2008 Sep 13; 372(9642):892.

concentration is abnormal or if extreme hyperkalemia or hypokalemia exists (see below).

The most common causes of HAGMA are listed in Table 2. They are arranged as the mnemonic "GOLDMARK" (Glycols [ethylene, propylene, and diethylene], 5-Oxoproline [acetaminophen], L-Lactic Acid, D-Lactic acid, Methanol, Aspirin, Renal failure, Ketoacidosis).[31]

In contrast, when metabolic acidosis is due to either the accumulation of HCl or the loss of $NaHCO_3$ from the body (or sodium-organic acid salts), a hyperchloremic metabolic acidosis develops as described above.

EFFECT OF SERUM ALBUMIN CONCENTRATION ON THE AG

Serum albumin has a net negative charge of about 2.5 mEq/g, and thus albumin comprises the largest component of the normal AG. Hypoalbuminemia will reduce the [AG] (and hyperalbuminemia will increase the [AG]). Consequently, the [AG] must be adjusted or "corrected" whenever the albumin concentration is reduced or elevated. For each 1 gm/100 mL reduction in the albumin concentration below a normal level of 4.5 g/100 mL, the [AG] falls by about 2.5 mEq/l.[30,32] Therefore, the [AG] can be corrected for hypoalbuminemia with the following formula:

$$[AG]_{CORRECTED} = [AG]_{UNCORRECTED} + 2.5 \times (4.5 - [albumin])$$

In addition, because the AG calculation in the United States does not include potassium, marked hyperkalemia may affect the interpretation of the AG (potassium is an "unmeasured" cation). Thus, a serum potassium of 6 mEq/l will reduce the AG by 2 mEq/l. Marked hypercalcemia and/or hypermagnesemia can similarly reduce the AG (but only their ionized concentrations will contribute). Another cause of a reduced, or rarely a negative, [AG] is a high concentration of immunoglobulin G due to multiple myeloma. These abnormal proteins often have a net positive charge and therefore circulate as unmeasured cations. Other monoclonal proteins such as immunoglobulin A are often negatively charged unmeasured anions which can increase the [AG].[33]

The AG reported by the laboratory is typically based on the venous blood "electrolyte" profile. This [HCO_3^-] value usually represents the total venous CO_2, which includes [HCO_3^-], [carbonic acid], and dissolved CO_2. The venous [total CO_2] is typically 2-4 mEq/l greater than the arterial [HCO_3^-] reported with arterial blood gas results.

Uncomplicated metabolic acidosis should be suspected whenever the serum [HCO_3^-] is reduced. However, the compensatory response to chronic respiratory alkalosis will also reduce the serum [HCO_3^-]. If the differentiation cannot be made on the basis of the history and physical exam, measurement of the arterial pH with a blood gas analysis may be required. Furthermore, the mixed acid-base disorder of metabolic acidosis and metabolic alkalosis can generate a [HCO_3^-] which is low, normal, or high. When the metabolic acidosis component of this mixed disorder is of the AG type, comparing the degree of increase of the [AG] with the reduction of [HCO_3^-] (the delta/delta) can be a very helpful clue to this disorder.

When metabolic acidosis has been identified, it becomes imperative to diagnose the primary causative etiology as quickly as possible. This is often readily apparent from the history and physical exam (ie, diabetic ketoacidosis when the glucose is very high in a patient with diabetes mellitus; lactic acidosis in a patient with sepsis and hypotension, etc.). When the etiology is not obvious, it is very helpful to determine if the metabolic acidosis is of the hyperchloremic or high-AG type (or a combination of both). Once this categorization has been established, a stepwise consideration of each of the potential causative etiologies will usually direct the clinician to order the appropriate diagnostic studies.[29-31,34,35]

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