Approach to Patients With High Anion Gap Metabolic Acidosis: Core Curriculum 2021

Andrew Z. Fenves and Michael Emmett

The anion gap (AG) is a mathematical construct that compares the blood sodium concentration with the sum of the chloride and bicarbonate concentrations. It is a helpful calculation that divides the metabolic acidoses into 2 categories: high AG metabolic acidosis (HAGMA) and hyperchloremic metabolic acidosis—and thereby delimits the potential etiologies of the disorder. When the [AG] is compared with changes in the bicarbonate concentration, other occult acid-base disorders can be identified. Furthermore, finding that the AG is very small or negative can suggest several occult clinical disorders or raise the possibility of electrolyte measurement artifacts. In this installment of AJKD's Core Curriculum in Nephrology, we discuss cases that represent several very common and several rare causes of HAGMA. These case scenarios highlight how the AG can provide vital clues that direct the clinician toward the correct diagnosis. We also show how to calculate and, if necessary, correct the AG for hypoalbuminemia and severe hyperglycemia. Plasma osmolality and osmolal gap calculations are described and when used together with the AG guide appropriate clinical decision making.

Complete author and article information provided at end of article.

Am J Kidney Dis. 78(4):590-600. Published online August 13, 2021.

doi: 10.1053/j.ajkd.2021.02.341

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

The recognition, differential diagnosis, and appropriate therapy of acid-base disorders are essential aspects of the clinical diagnosis and treatment of these conditions. Acid-base disorders are usually recognized and categorized by interpretation of the blood pH, pco_2, bicarbonate (or total CO_2), and electrolytes. The calculation and interpretation of the blood anion gap (AG) provides additional diagnostic and therapeutic information. The formulation we use has been called the "physiological approach." Other acid-base diagnostic models such as the construct introduced by Peter Stewart, which uses a combination of "strong ion difference," "total non-volatile weak acid concentration," and pco_2, have been adopted by some investigators and clinicians. However, most nephrologists continue to use the physiologic approach, which incorporates interpretation of the AG, and we believe this methodology is a logical and relatively easy way to interpret and diagnose acid-base disorders.

The concept of the AG was introduced in 1936 by James Gamble but did not become popular until the introduction of the flame photometer and autoanalyzers provided routine and rapid availability of serum electrolyte measurements in the 1950s and 1960s. Here, we will discuss a number of clinical scenarios and demonstrate how correct interpretation of the blood gas parameters, electrolytes, and the AG permit correct identification of even very complex acid-base disturbances, and help to rapidly develop the appropriate differential diagnosis.

Metabolic Acidosis and Compensatory Respiratory Response

Metabolic acidosis is a pathophysiologic disturbance that reduces the blood bicarbonate concentration, $[HCO_3^-]$, and generates an arterial acid blood pH (ie, <7.35). Metabolic acidosis also triggers a hyperventilatory compensatory response, which reduces the arterial pco_2 and thereby diminishes the degree of acidemia.

The normal $Paco_2$ is 35-45 mm Hg. The compensatory hyperventilatory response to metabolic acidosis is fully developed within 12 to 24 hours, and its intensity is proportional to the reduction in $[HCO_3^-]$. The response is similar across all forms of metabolic acidosis and is predictable. One commonly used relationship that identifies the appropriate respiratory response to metabolic acidosis is the Winters equation:

$$Paco_2 = \{1.5 \times [HCO_3^-] + 8\} \pm 2$$

This prediction relationship works well for mild to moderately severe metabolic acidosis ($[HCO_3^-]$ between 7 and 22 mEq/L). More severe metabolic acidosis ($[HCO_3^-]$ less than 5-7 mEq/L), should reduce the $Paco_2$ maximally, that is, to the 8 to 12 mm Hg range. Alternatively, adding 15 to the $[HCO_3^-]$ generates a number that should approximate the $Paco_2$ in mild to moderate metabolic acidosis. If metabolic acidosis exists and the

$Paco_2$ is not in the predicted range, a second, respiratory, acid-base disturbance probably exists.

The Anion Gap

The ionic profile of normal serum is shown in Figure 1. 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^+]) normally exceeds the sum of the anion concentrations: [Na^+] > ([Cl^-] + [HCO_3^-]). Consequently, if the sum of [Cl^-] and [HCO_3^-] is subtracted from [Na^+], an AG is noted (Fig 1). Although the normal [AG] is generally 8 to 12 mEq/L, normal electrolyte values can vary from laboratory to laboratory so each laboratory should determine their own normal [AG] range. To determine the increase (or decrease) from baseline of the [AG], it would be ideal to know each patient's own baseline. However, when that value is not known, we then suggest using a value of 10 mEq/L, with the adjustments for abnormal albumin concentrations, as we will be discussing.

When metabolic acidosis is generated by extracellular fluid (ECF) accumulation of relatively strong acids (such as lactic acid, β-hydroxybutyric, or acetoacetic acids [but not hydrochloric acid]), [HCO_3^-] falls and the [AG] increases reciprocally. The degree of increase of the [AG] (or Δ[AG]) represents the plasma concentration of the accumulating acid anions (ie, lactate, ketoacid anions, etc). Furthermore, the Δ[AG] is generally similar to the Δ[HCO_3^-]. Consequently, the Δ[AG]/Δ[HCO_3^-] ratio is generally about 1. However, several factors may disrupt this 1:1 relationship. They include different distribution spaces for bicarbonate and the accumulating acid anions, intracellular proton buffering, and variable rates of kidney excretion of the protons and acid anions. Mixed acid-base disorders will also disrupt the classic 1:1 relationship.

The most common causes of high anion gap metabolic acidosis (HAGMA) are listed in Table 1. 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).

In contrast, when metabolic acidosis is due to either the accumulation of hydrochloric acid or the loss from the body of sodium bicarbonate (or sodium–organic acid

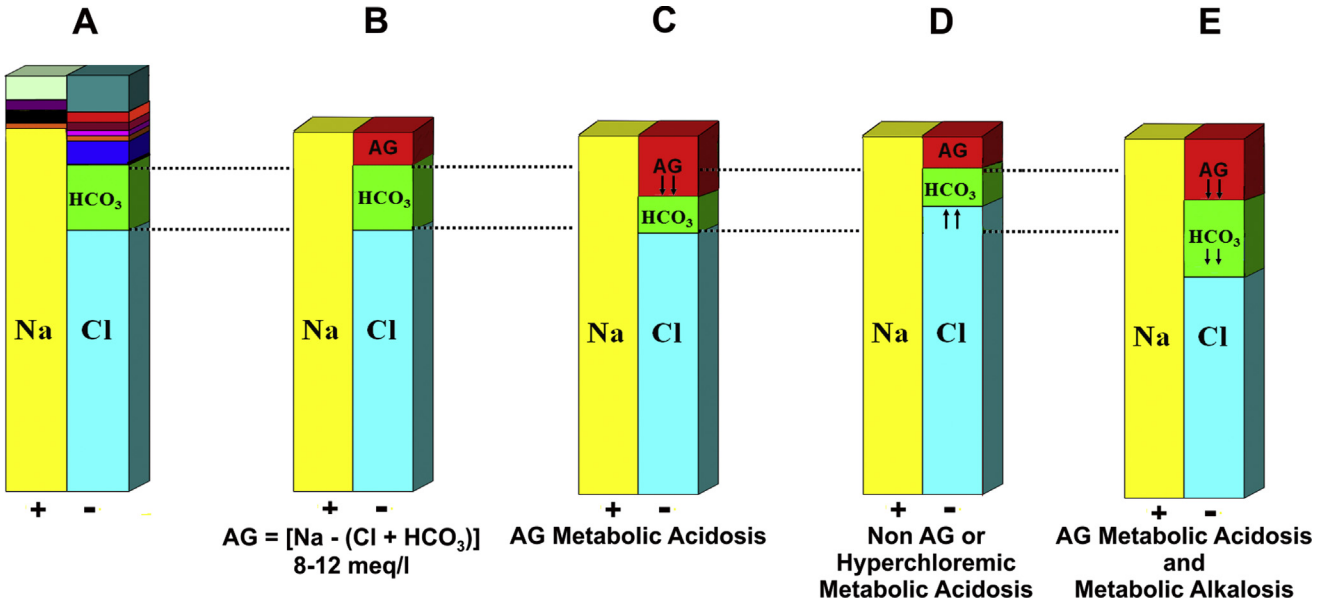

Figure 1. "GambleGram" depiction of blood serum electrolytes. (A) The total anion and total cation concentrations (measured in units of mEq/L) must be equal. (B) If only [Na^+], [Cl^-], and [HCO_3^-] are considered, an anion gap (AG) normally exists. (C) High AG metabolic acidosis reduces the [HCO_3^-] without changing [Cl^-] and thereby increases the [AG] in a reciprocal fashion. (D) Normal AG, or hyperchloremic acidosis, reduces the [HCO3$^-$] and increases the [Cl^-] in a reciprocal fashion. (E) Mixed AG metabolic acidosis and metabolic alkalosis. If the [AG] is increased but the [HCO_3^-] 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 [HCO_3^-] 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.

Table 1. GOLDMARK Mnemonic for the High Anion Gap Metabolic 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 acids including sulfuric and phosphoric acid.
K	Ketoacidosis	B-OH butyric and acetoacetic acid.

Based on mnemonic proposed in Mehta et al, *Lancet.* 2008;372(9642):892.

anion salts such as sodium butyrate, citrate, acetate, lactate—representing potential bicarbonate), then a normal AG, or hyperchloremic acidosis, develops (Fig 1).

Serum albumin has a net negative charge of about 2.5 mEq/g, and this anion is the largest component of the normal AG. Therefore, hypoalbuminemia will reduce the [AG] (and hyperalbuminemia will increase the [AG]). The [AG] must be "corrected" when the albumin concentration is reduced or elevated. For each 1 gram per 100 milliliters that the albumin concentration is reduced below a normal level of 4.5 g/100 mL, the [AG] falls by about 2.5 mEq/L. The [AG] can be corrected for hypoalbuminemia with the following formula:

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

Also note that, by convention, the AG calculation uses the "$[HCO_3^-]$" reported by the laboratory as a component of the venous blood "electrolyte" profile. This number 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 $[HCO_3^-]$.

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Assessing and Using the Anion Gap

Case 1: *A 68-year-old man with a history of well-controlled hypertension and benign prostatic hypertrophy presents to the emergency department (ED) with 3 days of fever, dysuria, and weakness and 1 day of rigors. His vital signs are temperature 38.6 °C; blood pressure, 90/70 mm Hg; and pulse, 110/min and regular. The physical examination is notable for dry mucous membranes and lethargy. His laboratory values are [Na^+], 138 mEq/L; potassium ([K^+]), 3.1 mEq/L; [Cl^-], 111 mEq/L; [HCO_3^-], 17 mEq/L; serum urea nitrogen (SUN), 26 mg/dL; creatinine, 1.1 mg/dL; glucose, 126 mg/100 mL; albumin, 2.0 g/dL. His arterial blood gas (ABG) values are pH 7.30; pCO_2, 32 mm Hg; [HCO_3^-], 15 mEq/L; and pO_2, 72 mm Hg.*

Question 1: Which of the following acid-base abnormalities exist in this patient?

a) HAGMA with appropriate respiratory compensation
b) Hyperchloremic (normal AG) metabolic acidosis
c) Mixed metabolic acidosis and respiratory alkalosis
d) Metabolic alkalosis and metabolic acidosis

For the answer to the question, see the following text.

This patient has signs and symptoms of a urinary infection and probable sepsis. His ABG reveals acidemia (pH 7.30), a reduced $[HCO_3^-]$ of 15 mEq/L, and a reduced pCO_2 of 32 mm Hg. The Winters equation predicts that his pCO_2 should be about 31 mm Hg $\{(1.5 \times [HCO_3^-]) + 8\} = 31$. The patient's laboratory results are therefore all consistent with appropriately compensated metabolic acidosis.

Is this acidosis a HAGMA, hyperchloremic, or a mixed disorder? The initial AG calculation is $(138 - [111+17]) = 10$ mEq/L and this suggests a normal AG (or hyperchloremic) metabolic acidosis. However, this calculation did not consider the patient's marked hypoalbuminemia (2.0 g/100 mL). This degree of hypoalbuminemia will reduce the [AG] by $2.5 \times (4.5 - 2) = 6.2$. Therefore, the [AG], after correction for hypoalbuminemia, is actually increased to about 16 mEq/L. Subsequently the patient's lactate level was reported to be 6 mEq/L. These results are all consistent with an HAGMA due to L-lactic acidosis. Therefore, the correct answer to question 1 is (a), HAGMA with appropriate respiratory compensation.

Lactic Acidosis

In hospitalized patients, lactic acidosis is a very common cause of metabolic acidosis. It occurs when lactic acid production exceeds lactic acid clearance (both

normally about 1 mmol/min). Usually lactate production increases because of impaired tissue oxygenation, due to either decreased oxygen delivery or a defect in mitochondrial oxygen utilization.

Lactate is primarily derived from glucose metabolism via the glycolytic pathway and a smaller amount is from the deamination of alanine. The liver, kidneys, and heart are the major lactate-utilizing organs. The generation of lactic acid from anerobic glycolysis primarily by muscle and the conversion of this lactic acid back to glucose by the liver defines the Cori cycle.

One commonly used classification system divides the clinical causes of lactic acidosis into those associated with clear impairment in tissue oxygenation (type A), and those in which a systemic impairment in oxygenation is absent or is not easily apparent (type B). In some cases, overlap exists between type A and type B lactic acidosis.

The classic causes of type A lactic acidosis include hypovolemia, sepsis, major gastrointestinal hemorrhage, cardiac failure, or cardiopulmonary arrest. Unless tissue perfusion can be rapidly restored, the prognosis is poor.

The causes of type B lactic acidosis include a variety of toxins, drugs, and vitamin deficiencies (ie thiamine) that impair cellular and/or mitochondrial metabolism or generate regional areas of ischemia. One classic cause of type B lactic acidosis is metformin toxicity, which usually occurs in patients with acute or chronic kidney injury because of the systemic accumulation of metformin. Other causes of type B lactic acidosis include various malignancies, particularly leukemia and lymphoma, chronic severe alcohol use disorder, and some antiretroviral medications used to treat patients infected with human immunodeficiency virus (HIV).

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Diabetic Ketoacidosis

Case 2: *A 25-year-old man with a 10-year history of type 1 diabetes mellitus becomes anorexic after developing gastroenteritis and reducing his insulin dose. He then develops nausea, vomiting, polyuria, and dyspnea and presents to the ED. The patient also has a long history of depression and is taking fluoxetine. He has orthostatic hypotension. His breath has a fruity odor. The initial laboratory studies reveal SUN, 40 mg/dL; creatinine, 1.5 mg/dL; glucose, 800 mg/100 mL; [Na^+], 120 mEq/L; [Cl^-], 75 mEq/L; [HCO_3^-], 12 mEq/L; K^+, 3.0 mEq/L; ([AG], 32 mEq/L); and albumin, 4.0 g/100 mL. The measured osmolality is 330 mOsm/L; serum β-hydroxybutyrate, >8 mEq/L; and urine ketones, 3+ by dipstick. Blood ethanol level is nondetectable. ABG values are pH 7.16; P_{O_2}, 90 mm Hg; p_{CO_2}, 35 mm Hg; and [HCO_3^-], 12 mEq/L.*

Question 2: What is his acid-base disorder?

a) HAGMA due to diabetic ketoacidosis (DKA)
b) HAGMA due to DKA and metabolic alkalosis
c) HAGMA due to DKA, metabolic alkalosis, and respiratory acidosis
d) HAGMA due to DKA and hyperchloremic acidosis

For the answer to the question, see the following text.

This patient's history, examination, and initial laboratory studies were entirely consistent with DKA. This form of HAGMA is due to the ECF accumulation of the 2 "ketoacids" (β-hydroxybutyric acid and acetoacetic acid). When the concentration of these 2 acids increases, the [HCO_3^-] falls reciprocally, and the [AG] increases. At the time of admission, patients with DKA have an average "delta/delta" or $\Delta[AG]/\Delta[HCO_3^-]$ ratio of about 1. However, to the extent that ketoacid anions are excreted into the urine, together with sodium and potassium ions, this will reduce the [AG] and partially convert the metabolic acidosis from a HAGMA to a hyperchloremic acidosis. This phenomenon usually develops after hospitalization, as the patient's volume status is re-expanded with NaCl-containing intravenous fluids, and kidney function improves.

If we assume his baseline [AG] was 10 and his baseline [HCO_3^-] was 24; then his [AG] increased by 23, from 10 to 33 and his [HCO_3^-] fell by 12, from 24 to 12 (all mEq/L). Thus, his Δ[AG], or [AG] increase, far exceeded the fall in his [HCO_3^-]; that is, his $\Delta[AG]/\Delta[HCO_3^-]$ was >>1. Consequently, we must assume that either additional bicarbonate was generated during the illness or that his initial [HCO_3^-] was not normal, but instead was already increased to about 34 mEq/L when the DKA developed. This patient reported that he had been vomiting so gastric metabolic alkalosis was the likely etiology of a high [HCO_3^-]. Whenever the Δ[AG] increase markedly exceeds the $\Delta[HCO_3^-]$ decrease, this suggests coexisting HAGMA and metabolic alkalosis (or less commonly HAGMA and chronic respiratory acidosis, which increases the [HCO_3^-] due to a compensatory response).

Now consider this patient's degree of respiratory compensation. His [HCO_3^-] was 12 mEq/L and the Winters equation predicts that his P_{CO_2} should be about 26 mm Hg. However, this patient's P_{CO_2} was 35 mm Hg, which is too high. This indicates respiratory acidosis exists in addition to his HAGMA and metabolic alkalosis. Hypokalemia may have produced respiratory muscle weakness. Therefore, this patient has a triple A-B disorder (HAGMA due to DKA, metabolic alkalosis due to vomiting, and respiratory acidosis probably due to hypokalemia) and the answer to question 2 is (c).

Note the [AG] was calculated using the reported [Na^+] of 120 mEq/L. Hyperglycemia reduces the blood [Na^+] because ECF hypertonicity moves water from the intracellular fluid (ICF) into the ECF and expansion of the ECF dilutes the ECF [Na^+]. A glucose value of 800 mg/100 mL

will reduce the [Na^+] by about 14 mEq/L (expect about a 2 mEq/L [Na^+] decrease per 100 mg/100 mL glucose increase above normal). With treatment, as the glucose concentration falls toward normal and water shifts back into the ICF, the [Na^+] will increase from 120 to about 134 mEq/L. Hence, the [Na^+] "corrected" for hyperglycemia is 134 mEq/L. However, the water shift generated by hyperglycemia will also have similar dilution effects on the ECF chloride and bicarbonate concentrations. Therefore, by convention, the "uncorrected" (for glucose) electrolyte concentrations are used for the AG calculations when hyperglycemia exists.

Another issue that must be addressed is this patient's measured osmolality (323 mOsm/L), which is 25 mOsm/L greater than his calculated osmolality ($2 \times [Na^+] + (glucose/18) + (SUN/2.8)) = 298$ mOsm/L. (The "uncorrected" [Na^+] of 120 mEq/L is also used in the osmolality equation because this is his "true" admission plasma [Na^+]; the denominators 18 and 2.8 convert the glucose and SUN concentrations from mg/100 mL to mmol/L, or roughly mOsm/L.),

Question 3: What is the most likely cause of this patient's 25 mOsm/L osmolal gap?

a) Accumulated ketoacids
b) Ingestion of an alcohol or glycol (other than ethanol, which was not detectable on admission)
c) Acetone
d) The sodium reduction generated by hyperglycemia

For the answer to the question, see the following text.

When a HAGMA develops, the increase in acid anions is generally matched by the reduction in [HCO_3^-]. Therefore, multiplying the [Na+] by 2 accounts for the chloride, bicarbonate, and any additional strong acid anions. Consequently, a HAGMA should not directly generate an osmolal gap. However, the addition to the blood of alcohols, acetone, glycerol, and so on will raise the measured osmolality and create an "osmolal gap." This osmolal gap disappears if the alcohol/glycol/etc. is metabolized to an acid. Patients with ketoacidosis often develop an osmolal gap because of increased levels of acetone (and to a smaller extent glycerol). This phenomenon also occurs commonly in patients with alcoholic ketoacidosis, so be cautious about diagnosing a toxic alcohol or glycol poisoning in that situation on the basis of a high osmolal gap. Also, note that acetone is not an acid and does not reduce the [HCO_3^-] or raise the [AG]. Thus the correct answer to question 3 is (c), this patient's osmolal gap is most likely due to acetone.

Case 2, continued: *The patient is appropriately treated with intravenous fluids (mainly normal saline), intravenous potassium chloride, and intravenous regular insulin. The next morning, he feels much better and is hungry. His blood chemistries now show the following: SUN, 18 mg/dL; creatinine, 0.9 mg/dL; glucose, 150 mg/100 mL; [Na^+], 139 mEq/L; [Cl^-], 110 mEq/L; [HCO_3^-], 17 mEq/L; [K^+], 4.0 mEq/L; and [AG], 12 mEq/L.*

Question 4: Which of the following statements is most correct about the development of a hyperchloremic metabolic acidosis in this patient?

a) The normal saline infusion diluted his [HCO_3^-] and thereby generated hyperchloremic metabolic acidosis.
b) This is a common measurement artifact that develops after acute treatment of DKA.
c) Different volumes of distribution of ketoacids anions and chloride generate hyperchloremic metabolic acidosis.
d) The loss of ketoacids anion salts into the urine converts a HAGMA to a hyperchloremic metabolic acidosis.

For the answer to the question, see the following text.

When patients with DKA are appropriately treated with saline to expand ECF volume, their glomerular filtration rate (GFR) generally improves, and avid renal tubular sodium reabsorption, stimulated by volume contraction, abates. Insulin therapy stops peripheral lipolysis, reduces long chain fatty acid delivery to the liver, and slows the mitochondrial uptake and oxidation of these fatty acids. These metabolic/hormonal effects rapidly reduce hepatic ketoacid generation. The ketoacid anions, which have accumulated in the ECF, have replaced decomposed bicarbonate. These anions represent "potential" bicarbonate and constitute most of the patient's Δ[AG]. If they remain in the body and are oxidized, their ECF concentration falls, and an equimolar quantity of bicarbonate will be generated.

However, oxidation of the accumulated ketoacid anions takes many hours. During this time frame, the appropriate restoration of ECF volume increases the kidney excretion of the sodium and potassium salts of the 2 ketoacid anions (β-hydroxybutyrate and acetoacetate). The loss of these ketoacid salts in the urine reduces the high [AG] or may even return it to the normal range. The [Cl^-] increases because the loss of sodium ketoacid salts in a relatively large volume of urine contracts the ECF "around" a relatively fixed quantity of chloride (ECF volume contraction eliminates chloride from the urine). The infusion of normal saline, with a relatively high [Cl^-] and its retention, generated by reduced ECF volume, also contributes to the generation of hyperchloremia but is usually a less important factor than the loss of urinary Na^+ and K^+ ketoacids salts. This phenomenon, conversion of a HAGMA to a hyperchloremic metabolic acidosis, occurs routinely during the recovery phase from DKA. Over the ensuing days a normal electrolyte pattern is usually restored because the kidney excretes ammonium chloride, raising the [HCO_3^-] and reducing the [Cl^-]. Thus, the correct answer to question 4 is (d): the loss of ketoacid anion salts in the urine converts the HAGMA to a hyperchloremic metabolic acidosis.

A similar mechanism also explains why patients who inhale toluene (via "glue sniffing" or spray paint inhalation) often present with severe hyperchloremic hypokalemic metabolic acidosis. Toluene itself is not an acid but is

rapidly metabolized to benzoic (benzyl) acid, which is then quickly converted to hippuric acid. The accumulation of hippuric acid (and/or benzoic acid) in the ECF will generate a HAGMA. The [HCO_3^-] falls, and the hippurate concentration increases reciprocally. Yet most patients with this disorder do not present with a HAGMA but instead typically manifest a hyperchloremic metabolic acidosis and severe hypokalemia. The explanation is the rapid and efficient kidney excretion of hippurate (indeed, the para-amino hippurate clearance is a measure of total kidney plasma flow because it is both freely filtered and very efficiently secreted by the kidney tubules).

If the hippurate was efficiently excreted with ammonium ion, the metabolic acidosis and AG increase would be ameliorated or eliminated. However, it takes several days for the kidneys to generate a large increase in ammonium excretion. Therefore, during the early phase of this disorder, a large fraction of the efficiently excreted hippurate is lost with sodium instead of ammonium. ECF volume contraction and secondary hyperaldosteronism develop. Generous distal kidney delivery of sodium hippurate combines with secondary hyperaldosteronism to generate avid distal tubule sodium ion reabsorption and very generous potassium ion secretion. Consequently, marked potassium depletion and hypokalemia develop.

Over several days, the combination of hypokalemia and metabolic acidosis combine to markedly increase ammonium ion excretion. Therefore, after several days many patients with this disorder manifest a hypokalemic hyperchloremic metabolic acidosis and a relatively high urine pH (due to the high urine ammonium concentration). This pattern strongly suggests distal renal tubular acidosis (RTA), and indeed in past years toluene poisoning was reported as a cause of distal RTA. However, high urine ammonium ion levels represent bound protons and raise the urine pH. Very high urine ammonium ion concentration rules out distal RTA.

If toluene is inhaled by a patient with underlying advanced kidney disease, or if acute kidney injury (AKI) develops, then efficient hippurate excretion is blunted. Under those conditions, the systemic accumulation of hippuric acid then generates a HAGMA.

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Toxic Alcohols/Glycols

Case 3: *A 60-year-old man is brought to the ED by his wife who says he has become increasingly depressed over the past 3 months and that he may have tried to hurt himself. He is confused and uncooperative and smells of alcohol. Otherwise, his physical examination is unremarkable, and his vital signs are normal. His laboratory values on arrival are SUN, 20 mg/dL; creatinine, 1.0 mg/dL; glucose, 100 mg/100 mL; [Na^+], 138 mEq/L; [Cl^-], 105 mEq/L; [HCO_3^-], 24 mEq/L; and [K^+] 4.0 mEq/L. His ABG values are pH 7.40; pO_2, 100 mm Hg; and pCO_2, 40 mm Hg. The urine analysis is unremarkable. His ethanol level is 110 mg/100 mL, and blood osmolality is 350 mOsm/L.*

Question 5: Which of the following is most likely correct?

a) He is inebriated with a high blood ethanol level and will likely improve as the ethanol is metabolized.
b) He has ingested ethanol but also has evidence of one/or several other alcohols or glycols.
c) The absence of a high anion gap metabolic acidosis makes ingestion of methanol or ethylene glycol unlikely.
d) He has ingested a toxic dose of salicylate together with the ethanol.

Before discussing the correct answer let us assume that the ED physician incorrectly believed that answer (a) was correct: the patient is inebriated with ethanol, and he will improve. He is observed in the ED for several hours.

Case 3, continued (hypothetical scenario): *After 3 hours the patient remains confused and has become increasingly combative. His serum chemistries are repeated, and now they reveal SUN, 30 mg/dL; creatinine, 1.2 mg/dL; glucose, 120 mg/100 mL; [Na^+], 140 mEq/L; [Cl^-], 105 mEq/L; [HCO_3^-], 16 mEq/L; and [K^+], 4.5 mEq/L. His ABG values are pH 7.32; pO_2, 100 mm Hg; and pCO_2, 30 mm Hg. The blood osmolality is measured again and has fallen from 350 to 310 mOsm/L. Urine analysis is also repeated and now reveals many crystals consistent with calcium oxalate.*

Question 6: What is the most likely cause of the patient's change in status?

a) He has developed lactic acidosis.
b) He has developed metabolic acidosis secondary to accumulation of glyoxylic and oxalic acid.
c) He has developed ethanol withdrawal syndrome.
d) He ingested salicylate in addition to ethanol and now has a salicylate-induced HAGMA.

For the answer to the questions, see the following text.

Although the ED physician attributed the patient's clinical and chemical findings to ethanol intoxication, an ethanol level of 110 mg/dL would only have increased his serum osmolality (ie, created an osmolal gap) by about

24 mOsm/L (divide the ethanol level [in mg/100 mL] by 4.6 to estimate its osmolality contribution). But this man's osmolal gap was 57: 350 − [(138 × 2) + (30/2.8) + (120/18)] = 57. Therefore 33 mOsm/L of the osmolal gap was not accounted for by the ethanol level in his blood (Table 2).

Consequently, there should have been a very high level of suspicion that he also ingested another, possibly toxic, alcohol or glycol. When a toxic alcohol, such as methanol, isopropanol, or ethylene glycol, is ingested, ethanol co-ingestion is common. Co-ingested ethanol will slow the oxidation of many toxic chemicals that are oxidized by the enzyme alcohol dehydrogenase

The oxidation of the ethanol generates acetyl CoA, which is metabolized by the liver. As the ethanol levels fall, accelerated oxidation of the co-ingested toxic chemical will generate toxic organic acids (Fig 2). This metabolic sequence can simultaneously reduce the osmolal gap and generate a HAGMA. In this particular case the finding of calcium oxalate crystals in the urine (Fig 3) strongly suggested that he had ingested ethylene glycol. Therefore, for both questions 5 and 6, answer (b) is correct, and the accumulating organic acids are probably mainly glyoxylic and oxalic acid. Note that one commonly ingested toxic alcohol, isopropanol (rubbing alcohol), is metabolized to acetone. Neither isopropanol nor acetone is an acid. Therefore, isopropanol ingestion will raise the osmolal gap but not generate a HAGMA.

Additional Readings

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Other Toxins

Case 4: *A 20-year-old woman with a history of schizophrenia and a mood disorder has presented to the ED after taking a "small bottle full of aspirin pills," stating she had wanted to kill herself. Her psychiatrist has prescribed oral haloperidol in the past, but she denies taking any other medications and denies alcohol ingestion. She vomited several times after the aspirin ingestion and developed dyspnea and tinnitus. She has no previous history of suicide attempts. Physical examination reveals an anxious young woman who is alert and oriented × 3. Her vital signs are blood pressure, 118/70 mm Hg; pulse, 100 beats per minute and regular; respiratory rate, 26 breaths per minute; temperature 37.2 °C. The examination is only notable for deep ventilation and dry mucous membranes. The laboratory findings are [Na^+], 141 mEq/L; [K^+], 3.8 mEq/L; [Cl^-], 95 mEq/L [HCO_3^-], 25 mEq/L; [AG], 21 mEq/L; albumin, 4.0 g/dL; SUN, 10 mg/dL; creatinine, 1.06 mg/dL; and glucose, 116 mg/100 mL. Her ABG (room air) values are pH 7.63; pCO_2, 24 mm Hg; [HCO_3] 24 mEq/l and pO_2, 90 mm Hg. Her salicylate level is 71.8 mg/dL (therapeutic level is less than 20), and her urine pH was 5.5. A toxicology screen is negative except for salicylate.*

Question 7: What is this patient's acid-base disturbance?

a) HAGMA
b) HAGMA and respiratory alkalosis
c) HAGMA, metabolic alkalosis and respiratory alkalosis
d) Metabolic alkalosis, respiratory alkalosis, and an artifactual elevation of the anion gap (pseudohypochloremia)

For the answer to the question, see the following text.

Table 2. Effect of Alcohols, Acetone and Glycols on Serum Osmolality

	Molecular Weight (mg/mmol)	Osmolal Gap Produced by 100 mg%
Ethanol	46	22
Isopropanol	60	17
Acetone	58	17
Methanol	32	31
Ethylene glycol	62	16
Propylene glycol	76	13
Diethylene glycol	106	9

This patient probably ingested a large amount of aspirin in a suicide attempt. Her serum salicylate level is in the toxic range. The most characteristic acid-base disorder generated by salicylate intoxication is mixed HAGMA and respiratory alkalosis. Toxic salicylate levels directly stimulate the medullary respiratory center, increasing both the rate and depth of respirations; this generates the respiratory alkalosis. Salicylate toxicity also uncouples oxidative phosphorylation, inhibits citric acid cycle dehydrogenases, accelerates glycolysis (generating lactic acid), and stimulates lipolysis and hepatic ketogenesis. These actions combine to generate the HAGMA. A small component of the HAGMA is the salicylic acid itself.

This patient's [AG] was 21 mEq/L ($\Delta AG = 11$), and this degree of metabolic acidosis would be expected to reduce her [HCO_3^-] reciprocally by about 11 mEq/L. But her [HCO_3^-] is 23 mEq/L. These results are consistent with HAGMA due to the salicylate poisoning and metabolic alkalosis due to vomiting. The resulting normal [HCO_3^-] of 23 mEq/L should not generate any respiratory compensatory response. However, the ABG reveals an alkaline pH (7.63 [whenever the pCO_2 and HCO_3 equal one another the pH must be 7.63]) and a markedly reduced $PaCO_2$ (24 mm Hg). This is due to respiratory alkalosis generated by the salicylate toxicity. Thus, the correct answer to question 7 is (c): HAGMA, metabolic alkalosis, and respiratory alkalosis.

Treatment is started in the ED with intravenous saline and potassium chloride. An alkaline diuresis, which would

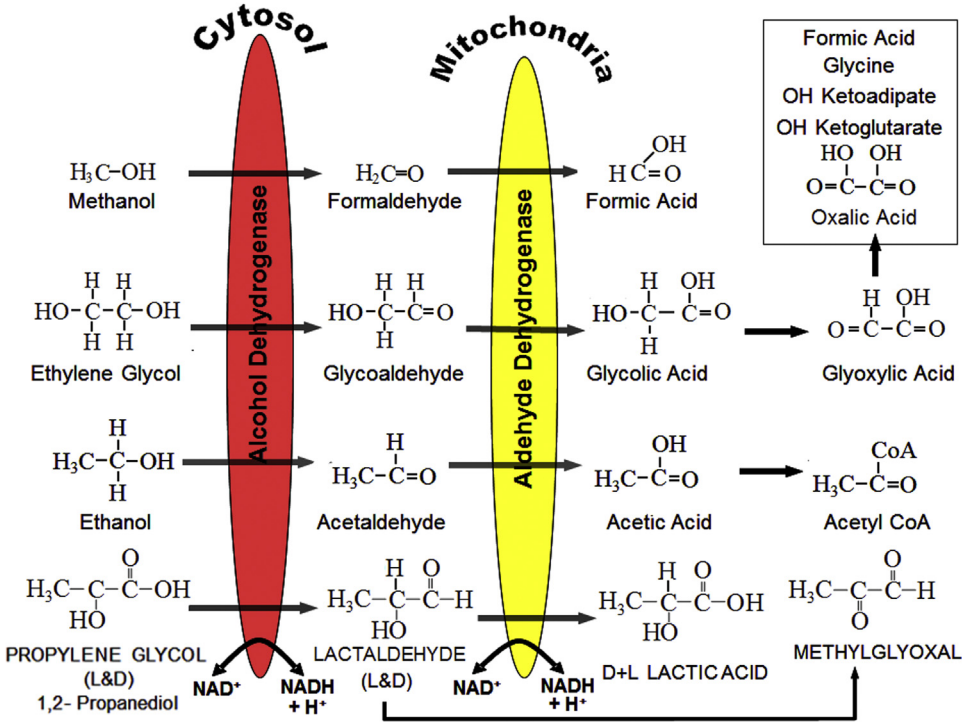

Figure 2. Hepatic oxidation of methanol, ethanol, ethylene glycol, and propylene glycol. A number of aldehydes, strong acids, and other metabolites, many of which are toxic, are generated. The metabolites in the box are downstream products of glyoxylic acid.

enhance renal salicylate excretion, is considered, but bicarbonate salts are not infused due to the patient's marked alkalemia. With this conservative therapy her condition improved.

Case 4, continued: *After 3 hours, the patient's blood chemistries are repeated and reveal [Na^+], 140 mEq/L; [K^+], 3.5 mEq/L; [Cl^-], 135 mEq/L; [HCO_3^-], 24 mEq/L; SUN, 9 mg/dL; creatinine, 0.92 mg/dL; glucose, 115 mg/100 mL; and [AG], −19 mEq/L.*

Question 8: How do you explain these electrolyte values?

a) The patient also ingested bromide salts.
b) This represents pseudohyperchloremia related to the salicylate.
c) This represents pseudohyperbicarbonatemia related to the salicylate.
d) The sodium concentration is spuriously decreased.

For the answer to the question, see the following text.

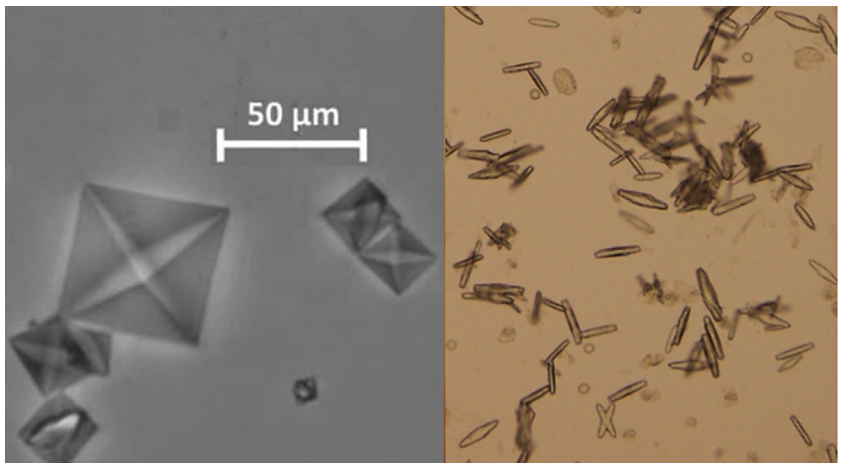

Figure 3. Photomicrographs of typical calcium oxalate crystals in urine. Left: classic-appearing "back of envelope" calcium oxalate crystals. Right: less pathognomonic, but more common, thick needle-shaped calcium oxalate crystals. Left photomicrograph reproduced from Daudon and Frochot 2015 (*Clin Chem Lab Med.* https://doi.org/10.1515/cclm-2015-0860) with permission of the copyright holder; original image © 2015 Walter de Gruyter and Company.

Several clinical conditions can reduce the AG to a level near 0 or even generate a slightly negative AG. The 2 most common conditions that can cause this to occur are hypoalbuminemia (reduced "unmeasured" anions) and multiple myeloma (increased "unmeasured" cations with IgG myeloma, but usually not with IgA myeloma). However, when the AG is found to be extremely negative (more negative than −5 mEq/L) this is usually due to an electrolyte measurement artifact (pseudohyponatremia, pseudohyperchloremia, or pseudohyperbicarbonatemia).

Pseudohyperchloremia can be generated by several clinical disorders. Historically the most common cause of pseudohyperchloremia was chronic bromide ingestion. Bromide ions in the specimen can generate very high artifactual chloride concentrations. More recently, it has been discovered that salicylate can also generate marked pseudohyperchloremia.

The development of pseudohyperchloremia with salicylate poisoning is dependent on the specific technique used to measure chloride. Chloride measurements are now almost always performed with various types of chloride ion–selective electrodes (Cl-ISE). Several unusual anions, which are not normally present in clinical specimens, can alter the Cl-ISE permeability and thereby generate pseudohyperchloremia. Bromide, thiocyanate, and salicylate can all generate pseudohyperchloremia.

Salicylate-related pseudohyperchloremia has unusual properties. Its severity is dependent on the salicylate level, the specific Cl-ISE used, and also the "age" of the Cl-ISE electrode. Many laboratory analyzers use the same ISEs for a large number of measurements over several weeks. The chloride measurement artifact generated by salicylate may be minor with a new "fresh" Cl-ISE but becomes increasingly more severe as the electrode ages. Therefore, the correct answer to question 8 is (b). It is likely that the first reported measurement in this patient was carried out with a device using a fresh Cl-ISE and the second measurement was run on a different analytical instrument with an older Cl-ISE.

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High Anion Gap Metabolic Acidosis: Unusual Acid No. 1

Case 5: *A 38-year-old woman with a history of severe restrictive lung disease had a bilateral lung transplant 4 months ago. She has had a complex posttransplant course with several episodes of successfully treated acute lung rejections. She also had 2 episodes of AKI, and now has a persistently reduced GFR. Her poor oral intake required placement of a gastric feeding tube. She is very depressed and reports persistent pain at the site of her G-tube. She has been taking acetaminophen, 650 mg 3 times a day, for the past 3 weeks. She denies use of any other medications and said she would not try to harm herself. Physical examination shows normal vital signs and malnutrition, with temporal wasting and diffuse muscle wasting. The G-tube exit site is erythematous but without drainage. Her serum chemistries are glucose, 90 mg/100 mL; SUN, 10 mg/dL; creatinine, 0.7 mg/dL; [Na^+], 140 mEq/L; [K^+], 4.2 mEq/L; [Cl^-], 106 mEq/L; [HCO_3^-], 12 mEq/L. Her ABG values are pH 7.21; $paCO_2$ 26 mm Hg; [HCO_3^-], 10 mEq/L. Her albumin is 3.0 g/dL, and L-lactate is 0.8 mmol/L. Her urine is negative for ketones, and her serum β-hydroxybutyrate is normal at 0.5 mEq/L. Serum osmolality (by freezing point depression) is 290 mOsm/L. Serum salicylate is undetectable. Acetaminophen level is in the therapeutic range.*

Question 9: The most likely cause of the patient's HAGMA is:

a) Ethylene glycol ingestion/instillation
b) 5-Oxoproline (pyroglutamic acid)
c) Starvation ketoacidosis
d) D-Lactic acidosis

For the answer to the question, see the following text.

This patient has a HAGMA with no readily apparent etiology. There is no biochemical evidence for lactic or keto acidosis. Although a D-lactate level was not measured, there is no history to suggest that she would be susceptible to this disorder (D-lactic acidosis typically develops in patients with short gut syndromes). If D-lactic acidosis is suspected, a specific serum D-lactate level should be measured because D-lactate is not detected by routine "lactic acid" assays, which measures only the L optical isomer of lactate.

The patient has a history of depression, but there was no history of a toxin or poison ingestion (or infusion into her feeding tube). If she had ingested/infused a toxic alcohol, such as methanol, or a glycol such as ethylene glycol, these compounds should increase her measured osmolality and would generate an osmolal gap. Her measured osmolality was normal at 290 mOsm/L and consistent with a [Na^+] = 140 mEq/L (which generates about 280 mOsm/L) and a normal glucose and SUN (accounting for about 9 mOsm/L).

Salicylate poisoning will often produce an HAGMA due to the combination of salicylic acid itself and other endogenous intermediary organic acids that accumulate. However, salicylate-generated HAGMA only occurs with toxic salicylate levels, and no salicylate was detected on admission. All these normal or negative laboratory results together with her clinical story strongly suggest that the most likely cause of her HAGMA is a disorder related to chronic acetaminophen ingestion.

Chronic ingestion of acetaminophen, especially by ill and malnourished women, has become increasingly

recognized as a cause of HAGMA due to the accumulation of 5-oxoproline, also called pyroglutamic acid. Detoxification of acetaminophen is accomplished by converting the native compound to several sulfated metabolites, including acetaminophen sulfate, acetaminophen glutathione, and acetaminophen mercapturate, which are then excreted in the urine. These reactions deplete glutathione, cysteine, and other sulfated intermediary molecules, especially when the patient is malnourished. The combination of glutathione and cysteine deficiency accelerates generation and accumulation of 5-oxoproline. Thus, the correct answer to question 9 is (b).

It is not surprising that malnourished and chronically ill individuals would be especially susceptible to this disorder, but it remains unclear why the vast majority of patients are women. This disorder is distinct from the toxicity generated by acute acetaminophen poisoning. High levels of acetaminophen can generate acute severe liver toxicity as well as acute kidney injury. That form of acute acetaminophen poisoning sometimes generates lactic acidosis. By contrast, the HAGMA due to chronic acetaminophen ingestion is a result of the accumulation of 5-oxoproline and develops in patients with therapeutic or even subtherapeutic acetaminophen levels.

The HAGMA due to acetaminophen related 5-oxoproline accumulation typically resolves quickly after acetaminophen is discontinued and the patient's overall medical status has been improved with general supportive measures. Although the administration of N-acetyl-cysteine seems reasonable and has little apparent downside, there is no clear evidence that it is necessary or that it accelerates recovery.

Although the large majority of cases of HAGMA due to 5-oxoproline are generated by the use of acetaminophen, several other causes have been identified. The disorder was first reported as a complication of very rare inherited disorders of either 5-oxoprolinase or glutathione synthetase. In addition, some patients treated with the antibiotics flucloxacillin or netilmicin and others treated with the anticonvulsant vigabatrin have developed HAGMA due to 5-oxoproline. However, most often 5-oxoproline acidosis is generated by chronic use of acetaminophen, especially in malnourished women.

Additional Readings

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High Anion Gap Metabolic Acidosis: Unusual Acid No. 2

Case 6: *A 45-year-old man presents with increasing confusion, ataxia, and slurred speech for the prior 5 days. His past medical history is notable for an abdominal stab wound 3 years ago that required multiple abdominal surgeries with extensive small-bowel resections. Subsequently he developed chronic intermittent diarrhea, lost weight, and appeared malnourished. His family reports several prior episodes of milder confusion. His only medication is a daily multivitamin. He denies ingestion of any illicit drugs or alcohols. Physical examination reveals normal vital signs. He is lethargic, confused, has slurred speech, nystagmus, and a staggering gait. His laboratory values are* $[Na^+]$, *140 mEq/L;* K^+, *3.8 mEq/L;* $[Cl^-]$, *105 mEq/L;* $[HCO_3^-]$, *10 mEq/L; SUN, 12 mg/dL; creatinine, 0.9 mg/dL; glucose, 96 mg/100 mL; albumin, 3.9 g/dL; and serum lactate, 1.1 mEq/L. His ABG values are pH 7.20;* pCO_2, *21 mm Hg; and* pO_2, *98 mm Hg. The urine analysis is unremarkable and negative for ketones.*

Question 10: The most likely acid-base diagnosis is:

a) Hyperchloremic metabolic acidosis due to chronic diarrhea
b) Ingestion of a toxic alcohol
c) D-Lactic acidosis
d) 5-Oxoproline (pyroglutamic) acidosis

For the answer to the question, see the following text.

This patient has an anion gap metabolic acidosis, with appropriate respiratory compensation. The [AG] is 25 mEq/L, which is 15 mEq/L above an assumed baseline level of 10 mEq/L. This matches the reduction in $[HCO_3^-]$ from 25 to 10 mEq/L. Thus, the Δ[AG] increase = Δ$[HCO_3^-]$ decrease. The pCO_2 is appropriately reduced, so he does not have a respiratory acid-base disorder. The clinical presentation did not suggest sepsis, and his L-lactate level is normal. Chronic diarrhea will often produce a normal AG (hyperchloremic) metabolic acidosis. There was no history of toxic alcohol or glycol ingestion, but measurement of an osmolal gap should be strongly considered in this case because a definitive diagnosis may take several days. However, given his surgical and clinical history, the disorder of D-lactic acidosis should rise to the very top of the differential diagnosis list; thus, the correct answer to question 10 is (c).

D-Lactic acidosis is a rare (but likely underdiagnosed) form of metabolic acidosis that can affect some patients with short bowel clinical syndrome or other types of gastrointestinal malabsorption. In these patients, intestinal bacteria metabolize (ferment) unabsorbed glucose and starch to multiple organic acids, including the D-optical isomer of lactic acid, which is metabolized very slowly by humans. Hence, when this lactic acid isomer is systemically absorbed from the bowel, D-lactate acidosis develops.

It is important to know that most laboratories do not measure D-lactate when a "lactate" level is ordered. Quantitation of D-lactate levels requires special analytic

techniques, and this test must be specifically ordered. D-Lactic acid levels can also increase in patients who receive or ingest large amounts of propylene glycol and in many patients with diabetic ketoacidosis. In these patients, D-lactic acid is a metabolic product of lactaldehyde with propylene glycol intoxication and methylglyoxal in diabetic ketoacidosis. In diabetic ketoacidosis, the concentration of D-lactic acid may reach the 8 to 10 mEq/L range and hence significantly contribute to the HAGMA.

Patients with short bowel syndrome may have chronic, low-grade elevations that are insufficient to generate significant acidosis or symptomatology. However, carbohydrate loading can lead to severe and symptomatic D-lactic acidosis. In addition, if kidney function declines, a similar clinical picture may emerge.

Patients with D-lactic acidosis typically present with an AG metabolic acidosis and characteristic neurological abnormalities, such as confusion, cerebellar ataxia, slurred speech, incontinence, and nystagmus. The renal tubule reabsorption of D-lactate is not as efficient as the reabsorption of L-lactate. Therefore, large renal losses of D-lactate can convert this HAGMA to a hyperchloremic acidosis. If D-lactic acidosis is strongly suspected, measurements of urine D-lactate levels are commercially available and may be very helpful.

Treatment for D-lactic acidosis must be tailored to each patient. When severe metabolic acidosis develops, sodium bicarbonate can be administered. When the syndrome develops in patients with short bowel syndrome, oral antimicrobial agents (such as neomycin or metronidazole) can be helpful. They probably act by decreasing the density of D-lactate-producing organisms. Preventive strategies include a low-carbohydrate diet, which reduces colonic carbohydrate delivery and D-lactate production. Some patients with frequent episodes of D-lactic acidosis have been successfully treated with fecal transplantation.

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Summary

The AG is a mathematical "virtual" construct because a true anion gap cannot exist in any solution. Nonetheless, this artificial construct is a very helpful clinical tool for assessing acid base disorders and for categorizing the metabolic acidoses. The metabolic acidoses are readily subdivided into those with a large AG (HAGMA) and those with a normal AG (by definition the hyperchloremic metabolic acidoses).

When HAGMA exists, the reciprocal relationship between the amount of increase of [AG] and decrease in $[HCO_3^-]$ (designated as the $\Delta[AG]/\Delta[HCO_3^-]$ can be a very helpful indicator of certain forms of mixed acid-base disorders. If the HAGMA had developed in a single fluid space without loss of any HCO_3^-, or anions of accumulating strong acids, then a perfect 1:1 $\Delta[AG]/\Delta[HCO_3^-]$ ratio should exist. However, strong acid anions and HCO_3^- actually have variable spaces of distributions and can be excreted by the kidneys at variable rates. Consequently, a perfect 1:1 $\Delta[AG]/\Delta[HCO_3^-]$ ratio does not always exist when HAGMA occurs. Nonetheless, in general, a 1:1 $\Delta[AG]/\Delta[HCO_3^-]$ relationship remains a very good starting point for interpreting the HAGMAs. When the increase of the AG ($\Delta[AG]$) markedly exceeds the fall in $[HCO_3^-]$ ($\Delta[HCO_3^-]$) an additional acid base disorder must be strongly considered – either metabolic alkalosis or chronic respiratory acidosis.

The AG should be calculated whenever electrolyte results are reported. A high, low, or negative AG is demands a clinical explanation.

Article Information

Authors' Full Names and Academic Degrees: Andrew Z. Fenves, MD, and Michael Emmett, MD.

Authors' Affiliations: Division of Nephrology, Department of Internal Medicine, Massachusetts General Hospital, and Medical School, Harvard University, Boston, Massachusetts (AZF); Internal Medicine, Baylor University Medical Center, Dallas, Texas (EM).

Address for Correspondence: Michael Emmett MD, MACP, Baylor University Medical Center, 3500 Gaston Ave, Rm H-102, Dallas, TX 75246-2096. Email: m.emmett@baylorhealth.edu

Support: This Core Curriculum was produced without any direct financial support.

Financial Disclosure: The authors declare that they have no have relevant financial interests.

Peer Review: Received November 23, 2020, in response to an invitation from the journal. Evaluated by 3 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form February 24, 2021.