

Toxicologic Acid-Base Disorders

Sage W. Wiener, MD^{a,b,c,*}

KEYWORDS

• Acid-base • Acidemia • Alkalemia • Anion gap • Delta gap • Osmol gap • Toxicity

KEY POINTS

- Draw a blood gas with lactate and a chemistry panel in patients presenting after poisoning of unknown etiology.
- The toxicologic differential diagnosis of respiratory alkalosis, respiratory acidosis, metabolic alkalosis, and nonanion gap metabolic acidosis is fairly narrow.
- When approaching the patient with an anion gap metabolic acidosis, check for lactate first and ketones second, as these account for the vast majority of patients with anion gap metabolic acidosis.
- Patients with alcoholic ketoacidosis rapidly improve with fluids, dextrose, and thiamine.
- The osmol gap can sometimes be an important clue, but a normal osmol gap never excludes toxic alcohol poisoning.

INTRODUCTION

Interpretation of a patient's acid-base status can be critical to the evaluation of the poisoned patient. Many toxins will lead to a characteristic acid-base changes, and a blood gas analysis helps to establish a differential diagnosis that can be instrumental in narrowing down the potential cause of toxicity.

BASIC ACID-BASE PHYSIOLOGY

Human respiration is regulated by the brainstem to attempt to maintain a constant partial pressure of carbon dioxide (P_{CO_2}) of approximately 40 mm Hg. Carbonic anhydrase converts carbon dioxide and water to carbonic acid, with a concentration of carbonic acid linearly related to the P_{CO_2} . Carbonic acid can dissociate to

Disclosures: Nothing to disclose.

^a Department of Emergency Medicine, SUNY Downstate Medical Center, 450 Clarkson Avenue, Box 1228, Brooklyn, NY 11203, USA; ^b Department of Emergency Medicine, Kings County Hospital Center, 451 Clarkson Avenue, Brooklyn, NY 11203, USA; ^c New York City Department of Health and Mental Hygiene, New York City Poison Control Center, 455 First Avenue, New York, NY 10016, USA

* Department of Emergency Medicine, SUNY Downstate Medical Center, 450 Clarkson Avenue, Box 1228, Brooklyn, NY 11203.

E-mail address: sagewiener-em@yahoo.com

Emerg Med Clin N Am 32 (2014) 149–165
<http://dx.doi.org/10.1016/j.emc.2013.09.011>

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bicarbonate and hydrogen ion (a proton). This equilibrium is the primary buffering system of the body, and it is governed by the Henderson-Hasselbalch equation (Fig. 1). Acidemia (pH <7.35) results from either excess carbon dioxide (acid) or a paucity of bicarbonate (base). Alkalemia (pH >7.45) results from either a low P_{CO_2} or an excess of bicarbonate.

INTERPRETATION OF THE ARTERIAL BLOOD GAS

Identifying the Primary Acid Base Disorder

Interpretation of the arterial blood gas (ABG) starts with an assessment of the pH for acidemia or alkalemia. Most typically, a blood gas will have been drawn because of a suspicion of metabolic acidosis due to a low bicarbonate on a serum chemistry analysis. When this occurs, the pH can be used to distinguish metabolic acidosis from respiratory alkalosis as the primary process. If the serum bicarbonate is low and the pH is low, the primary process is a metabolic acidosis. If the pH is high, then the primary process must be a respiratory alkalosis. When the serum bicarbonate is high, a low pH indicates a respiratory acidosis, whereas a high pH indicates a metabolic alkalosis.

Determining Whether a Respiratory Disorder is Chronic or Acute

If there is a respiratory acidosis or alkalosis, the next step is to determine whether the process is acute or chronic. In an acute respiratory acidosis or alkalosis, for every 10 mm Hg change from 40 mm Hg in the P_{CO_2} , the pH should change from 7.40 by 0.08. If the process is chronic, the pH should change by approximately 0.03 for every 10 mm Hg change in the P_{CO_2} .

Determining Whether Compensation is Appropriate

If the primary process is a metabolic acidosis or alkalosis, it must next be determined whether respiratory compensation is appropriate. For a metabolic acidosis, this can be calculated using Winter's formula. The expected P_{CO_2} when compensation is appropriate should be approximately 1.5 times the serum bicarbonate concentration plus 8.

$$\text{Predicted } P_{CO_2} = (1.5 \times [\text{observed } HCO_3^-]) + 8 \pm 2$$

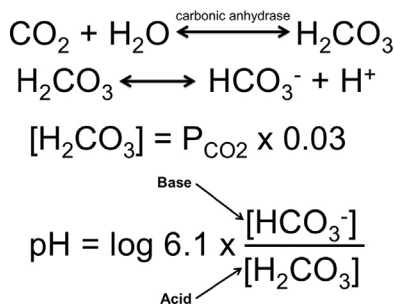


Fig. 1. Relationship among carbon dioxide, carbonic acid, and bicarbonate. Carbon dioxide and water are converted to carbonic acid by carbonic anhydrase. Carbonic acid is in equilibrium with bicarbonate, a relationship governed by the Henderson-Hasselbalch equation. The concentration of carbonic acid is a linear function of the partial pressure of carbon dioxide.

For a metabolic alkalosis, the appropriate compensation can be estimated using the formula:

$$\text{Predicted } P_{\text{CO}_2} = 15 + (\text{observed } \text{HCO}_3^-)$$

If the P_{CO_2} does not fall within the predicted range, there is a second acid-base disorder, respiratory acidosis or respiratory alkalosis depending on whether the P_{CO_2} is above or below the predicted P_{CO_2} , respectively. This generally indicates a problem with ventilation, and must be addressed immediately.

Determining Whether a Metabolic Acidosis is Associated with an Anion Gap

If a metabolic acidosis is present, the next step is to calculate the anion gap. The anion gap is the difference between the serum sodium concentration (the primary cation in the body) and the sum of the chloride and bicarbonate concentrations (the primary anions in the body).

$$\text{Anion gap} = (\text{Na}^+) - ([\text{Cl}^-] + [\text{HCO}_3^-])$$

Normally, the difference is 8 to 12 because there are more unmeasured anions (eg, phosphates, sulfates, albumin, organic acids) than unmeasured cations (magnesium, potassium). When there is an excess of an organic acid, the anion gap rises because the sum of all anions and the sum of all cations must always be equal, and the amount of unmeasured anions rises. When there is a metabolic acidosis, distinguishing between acidosis with an elevated anion gap from acidosis with a normal anion gap is critical, because they suggest different underlying etiologies. The anion gap may be elevated by toxins that produce deficiencies in calcium, potassium, or magnesium. Conversely, it may be lowered by cationic toxins such as lithium, or halides other than chlorine such as bromine or iodine.

Distinguishing a Mixed Acid-Base Disorder from an Isolated Anion Gap Acidosis

When a metabolic acidosis with an elevated anion gap is present, the next step is to calculate the *delta gap*. The delta gap allows the distinction between a pure anion gap metabolic acidosis and a mixed acid base disorder with both anion gap and non-anion gap acidosis. The delta gap is calculated as follows:

$$\text{delta gap} = \text{delta anion gap} - \text{delta bicarbonate}$$

The delta anion gap is the rise in the anion gap from 12, whereas the delta bicarbonate is the fall in bicarbonate from 24. For a pure anion gap metabolic acidosis, the delta gap should approximate zero. If the delta gap is significantly positive, there is a metabolic alkalosis in addition to the anion gap metabolic acidosis. If the delta gap is significantly negative, there is a concomitant non-anion gap metabolic acidosis.¹

The Stewart Strong Ion Difference

The Stewart strong ion theory is another approach to acid-base problems that takes into account all of the major ions that are normally in the plasma, and separates them into dependent and independent variables. The independent variables are P_{CO_2} , the total weak nonvolatile acids, such as phosphate and proteins (A_{TOT}) and the strong ion difference (SID). The SID is defined as follows:

$$(\text{SID}) = (\text{Na}^+) + (\text{K}^+) + (\text{Ca}^{2+}) + (\text{Mg}^{2+}) - (\text{Cl}^-) - (\text{Other Strong Anions})$$

In a sense, this is similar in concept to the anion gap, in that it is based on the law of electroneutrality, which is that the sum of all anions must equal the sum of all cations in the body. The strong ion theory is useful because it explains some concepts, such as dilutional acidosis and contraction alkalosis, which are more difficult to explain using a standard approach to acid-base problems, and because it includes the effects of changes in other buffers, such as albumin and phosphate, all in one master equation.^{2,3} However, it is more complicated to calculate and proportionately more affected by small errors in measurement, and thus less commonly used in the clinical setting. Additionally, although it is mathematically correct, it does not correspond to actual physiology, in that the body regulates pH and bicarbonate, not strong ion difference.^{2,4,5}

RESPIRATORY ALKALOSIS

The most common reason for respiratory alkalosis is compensation for a metabolic acidosis, but compensatory respiratory alkalosis cannot be the primary disorder, because compensation does not overcorrect (does not change the pH past 7.40). The major toxicologic causes of respiratory alkalosis include salicylate toxicity and hyperventilation compensating for impaired oxygenation from pulmonary toxins.

Salicylates

Salicylates are complex metabolic toxins that cause a characteristic acid-base pattern that changes somewhat depending on how far along the course of illness the patient presents. Early in poisoning, patients will have a respiratory alkalosis. This is because of direct stimulation of the medulla, where salicylates increase respiratory rate and tidal volume.⁶ This stage may be missed in younger children, because of the lack the ventilatory reserve that adults are able to mobilize.⁷ As toxicity progresses, patients may display double, or even triple, acid-base disorders as they develop metabolic alkalosis from vomiting and metabolic acidosis through multiple mechanisms (see later in this article).

Hyperventilation due to Impaired Oxygenation

Patients with impaired gas exchange compensate by increasing their ventilation, becoming tachypneic and hyperpneic. Several toxins may cause impaired gas exchange by causing pulmonary edema or pulmonary fibrosis, or interstitial lung disease (**Table 1**). Some of these patients may also have a concomitant metabolic acidosis due to lactate from anaerobic metabolism if oxygenation is severely impaired.

RESPIRATORY ACIDOSIS

Respiratory acidosis is a marker of hypoventilation. Hopefully, by the time a blood gas result demonstrates respiratory acidosis, the hypoventilation will have already been recognized based on the physical examination, and addressed. However, it is important to be aware that hypoventilation may occur even with a normal respiratory rate if the tidal volume is decreased. When this occurs, not only is there a resulting diminished minute ventilation, proportionally more dead space ventilation occurs, and this poor gas exchange leads to CO₂ accumulation and respiratory acidosis. The major toxicologic causes of primary respiratory acidosis are opioid intoxication and sedative-hypnotic intoxication.

Table 1
Some toxins and toxicants that cause respiratory alkalosis by inducing tachypnea due to impaired gas exchange^a

Toxicologic Causes of Respiratory Alkalosis	
Pulmonary Edema	Pulmonary Fibrosis
Calcium channel antagonists	Amiodarone
Deferoxamine	Bleomycin
Glyphosate	Busulfan
Meprobamate, ethchlorvynol	Cyclophosphamide
Nonsteroidal anti-inflammatory drugs	Environmental (bird and animal droppings)
Opioids	Methotrexate
Phenobarbital	Nitrofurantoin
Pulmonary irritant inhalants	Occupational (silica, asbestos, coal, beryllium, grain)
Salicylates	Propranolol
Scorpion envenomation	Sulfasalazine

^a Selected data elements contained in reference.⁸

Opioids

Opioids lead to hypoventilation through mu-opioid receptor-mediated blockade of specialized respiratory neurons in the brainstem.⁹ These lead to tolerance of hypercapnea, suppressing the normal drive for respiration. In fact, hypoventilation is the best predictor of response to naloxone (an opioid antagonist) in the prehospital setting.¹⁰ Other signs may provide clues to opioid intoxication, including miosis, hypoactive bowel sounds, “track marks” on the forearms, or drug paraphernalia found on the scene, but the absence of these signs do not exclude opioid intoxication as the cause of hypoventilation. A history of opioid abuse or chronic pain may also suggest the diagnosis. In patients with chronic pain with opioid overdose, it is important to perform a careful skin examination to exclude adherent opioid analgesic patches. If found, these should be immediately removed from the skin to prevent further absorption.

Most cases of opioid intoxication are readily reversed by the opioid antagonist naloxone. However, if a patient has a respiratory acidosis due to an opioid, the patient should be ventilated by bag valve mask before administering the antidote. Abrupt reversal of opioid effect in a patient who is still hypercapneic may precipitate acute lung injury (ALI),¹¹ although ALI may also result from opioid overdose alone. Rapid reversal of opioid effect on the brainstem in a patient who is still hypercapneic leads to release of catecholamines that increase the permeability of the vascular bed in the lungs. If the patient is ventilated before administration of naloxone, the P_{CO_2} will be normalized once the opioid effect on the brain is reversed, so the catecholamine surge should not occur.

Sedatives/Hypnotics

Sedatives/hypnotics classically cause coma with normal vital signs. However, some sedative/hypnotic agents may be associated with hypoventilation and respiratory acidosis, particularly barbiturates, GHB (gamma-hydroxybutyrate) and its congeners, and propofol. Additionally, combinations of sedative hypnotics (eg, ethanol and benzodiazepines) can cause respiratory depression. Although a competitive antagonist for benzodiazepines exists (flumazenil), it should not be used in patients who may

be benzodiazepine tolerant or dependent, because it may induce seizures and life-threatening withdrawal.¹² There is no reversal agent for other sedative/hypnotics. If hypoventilation and respiratory acidosis occur, they can be treated with intubation and mechanical ventilation.

METABOLIC ALKALOSIS

The underlying mechanisms for metabolic alkalosis can be separated into five basic categories:

- Compensation for respiratory acidosis (never a primary process)
- Addition of bicarbonate
- Loss of chloride
- Appropriate mineralocorticoid excess
- Inappropriate mineralocorticoid excess (renin, aldosterone-producing tumors, renal artery stenosis, Bartter syndrome)

The urine chloride can help distinguish between causes of metabolic alkalosis (Table 2).

Vomiting

Vomiting is a common adverse effect of many toxins. When vomiting is severe, metabolic alkalosis may occur due to the loss of hydrochloric acid in emesis. Additionally, patients with severe vomiting can become volume depleted and develop a contraction alkalosis (from appropriate mineralocorticoid excess). Although recent data suggest that the chloride loss may be the underlying factor causing acidosis, not the volume depletion (see contraction alkalosis/chloride depletion/acidosis later in this article),³ there is not yet universal consensus on this point.⁵

Increased Bicarbonate Intake

Patients who ingest too much bicarbonate (antacid abuse/milk-alkali syndrome) may develop metabolic alkalosis directly due to absorption of the bicarbonate. This most commonly occurs in people who take excessive antacids for symptoms of dyspepsia. Milk-alkali syndrome, a triad of metabolic alkalosis, hypercalcemia, and renal insufficiency results from excess calcium and alkali intake.¹³ Calcium carbonate taken as an antacid (with or without milk intake) is the most common cause, although it may also occur in people taking calcium carbonate as a calcium

Table 2
Distinguishing causes of metabolic alkalosis by urinary chloride

Differential Diagnosis of Metabolic Alkalosis by Urinary Chloride	
[Urine Cl ⁻] <25 mEq/L	[Urine Cl ⁻] >45 mEq/L
Vomiting or nasogastric suction ^a	Mineralocorticoid excess ^a
Diuretics (late) ^a	Diuretics (early) ^a
Posthypercapnea	Alkali load (bicarbonate overdose) ^a
Cystic fibrosis	Severe hypokalemia (<2.0 mEq/L) ^a
Low chloride intake	—
Refeeding	—

^a Toxicologic or potentially toxicologic causes.

supplement or as a phosphate binder in chronic renal insufficiency. In one series, milk-alkali syndrome was responsible for 12% of patients presenting with hypercalcemia.¹⁴

Licorice Abuse

Ingestion of natural licorice can lead to acidosis among other effects due to the *glycyrrhizin* in natural licorice (not the candy typically sold as “licorice” in the United States). Glycyrrhizin and related compounds are inhibitors of 11-beta-hydroxysteroid dehydrogenase in the kidney. This enzyme normally inactivates cortisol, which has significant mineralocorticoid activity, by converting it to cortisone, which does not. When this enzyme is inhibited, cortisol in the kidney leads to excess sodium retention and excess potassium and hydrogen ion excretion.¹⁵ Inhibition of the enzyme is reversible, and discontinuing exposure will resolve the problem.

Contraction Alkalosis/Chloride Depletion Alkalosis

Patients with volume depletion characteristically develop what has traditionally been termed “contraction alkalosis.” If patients lose water without losing bicarbonate (typically due to diuretics), the concentration of bicarbonate rises. Because the P_{CO_2} is regulated by ventilation to remain constant, alkalosis results.¹⁶ Additionally, volume depletion stimulates the renin-angiotensin-aldosterone system, which leads to increased sodium and bicarbonate reabsorption in the proximal tubule and increased proton and potassium secretion in the distal tubule.

A newer understanding of the process suggests that the underlying problem is not volume depletion (contraction), but chloride depletion, and it has been suggested that the condition be renamed “chloride depletion alkalosis.” A chloride/bicarbonate exchanger called pendrin has been identified as being key to the process. In both a rat model and in healthy human volunteers with acidosis induced by furosemide and dietary chloride restriction, repletion of chloride corrects the acidosis even when volume depletion and sodium depletion persist.³

METABOLIC ACIDOSIS

There are five common mechanisms by which a metabolic acidosis is generated:

- Compensation for a respiratory alkalosis (never a primary process)
- Addition of acid (eg, HCl)
- Increase in the generation of H^+ from endogenous (eg, lactate, ketones) or exogenous acids (eg, salicylate, ethylene glycol, methanol)
- Inability of the kidneys to excrete the hydrogen from dietary protein intake (types 1 and 4 renal tubular acidosis [RTA])
- The loss of bicarbonate due to wasting through the kidney (type 2 RTA) or the gastrointestinal tract (diarrhea)

As described previously, calculating the anion gap is the first step to distinguishing between causes of metabolic acidosis.

Non-Anion Gap Metabolic Acidosis

There are a limited number of mechanisms whereby a non-anion gap metabolic acidosis is generated (**Table 3**). These include the following:

- RTA-inducing toxins (**Table 4**)
- Diarrhea-inducing toxins (**Table 5**)
- Ingestion of an absorbable acid

Table 3
Distinguishing underlying mechanisms of non-anion gap acidosis based on serum potassium concentration, urine pH, and urine ammonia

Hyperchloremic (Non-Anion Gap) Metabolic Acidosis					
Disease	Renal Defect	Plasma [K ⁺]	Proximal Acidification	Distal Acidification	
			HCO ₃ ⁻ Reabsorption	Urine pH	Urine NH ₃
Recovery DKA	None	↓	normal or ↑	<5.5	↑
Diarrhea	None	↓	normal or ↑	<5.5	↑
Proximal RTA (Type 2)	↓ proximal acidification	↓	↓	<5.5	normal or ↑
Classic distal RTA (Type 1)	↓ distal acidification	↓	normal or ↑	>5.5	↓
Generalized distal RTA (Type 4)	↓ aldosterone action	↑	normal or ↑	<5.5	↓
Renal failure	↓ ammonia production	normal or ↑	normal or ↑	<5.5	↓

Abbreviations: ↑, increased; ↓, decreased; DKA, diabetic ketoacidosis; RTA, renal tubular acidosis.

- Carbonic anhydrase inhibition
- Toluene, ethylene glycol
- Dilutional acidosis

Toxins that Cause RTA

There are three types of RTA: type 1 (defect of distal tubule bicarbonate absorption), type 2 (defect of proximal tubule bicarbonate absorption), and type 4 (hypo-reninemic hypoaldosteroneism). Any of the three may be caused by toxins. Examples are provided in [Table 4](#). Metabolic acidosis due to RTA, unlike anion gap acidosis, should be treated with bicarbonate, because the underlying problem is loss of bicarbonate.

Toxins that Cause Diarrhea

Toxins may cause diarrhea through several mechanisms (see [Table 5](#)). Osmotic agents, like most laxatives, draw fluid into the gastrointestinal (GI) tract by introducing

Table 4
Selected toxins causing renal tubular acidosis

Distal (Type 1)	Proximal (Type 2)	Hypoaldosterone (Type 4)
Amphotericin B	Cadmium	Angiotensin-converting enzyme inhibitors
Ifosfamide	Antiretroviral therapy	Angiotensin receptor antagonists
Lithium carbonate	Ifosfamide	Eplerenone
Toluene	Lead	Nonsteroidal anti-inflammatory drugs
Zoledronate	—	Pentamidine
—	—	Spirolactone
—	—	Trimethoprim

Mechanism	Examples
Malabsorption	Cholestyramine, olestra, tetrahydrolipstatin, alpha-glucosidase inhibitors
Motility	Erythromycin, metoclopramide
Mucosal necrosis	Colchicine, methotrexate, antineoplastics
Osmotic	Sorbitol, magnesium citrate, lactose, mannitol, sodium polystyrene sulfonate, polyethylene glycol (some formulations)
Secretory	Stimulant laxatives

molecules that cannot be absorbed into the lumen. Secretory diarrhea occurs from toxins that irritate the GI mucosa. Other toxins interfere with absorption in the gut. Motility agents may cause diarrhea by speeding transit through the GI tract. Finally, some chemotherapeutic drugs cause necrosis of the GI mucosa. Severe diarrhea may also cause a contraction alkalosis.

Ingestion of an Absorbable Acid

Unlike ingestion of alkalis, ingestion of some strong acids leads to systemic absorption of those acids. For example, when sulfuric acid is absorbed, the sulfate becomes an unmeasured anion, leading to an elevated anion gap. However, when hydrochloric acid is absorbed, the excess chloride is accounted for in the measured anions, so an anion gap elevation does not occur. This is generally not clinically occult, because hydrochloric acid has significant caustic effects; signs and symptoms of the caustic effect are often present.

Carbonic Anhydrase Inhibition

Carbonic anhydrase inhibitors (acetazolamide, topiramate) can induce non-anion gap metabolic acidosis, particularly in patients with impaired renal function.^{17,18} The underlying mechanism is increased renal bicarbonate loss due to inability to absorb protons with bicarbonate in the kidney.¹⁹ The protons are instead absorbed with chloride, leading to a hyperchloremic acidosis.

Non-anion Gap Metabolic Acidosis from Toluene and Ethylene Glycol

Although non-gap acidosis from toluene has been attributed to distal RTA in the past, this has recently been called into question. The acidosis may in fact be due to toluene's metabolism to hippuric acid. Although hippurate is an unmeasured anion, and could cause anion gap acidosis, it is postulated that the presence or absence of an anion gap elevation is dependent on the kidney's ability to excrete that anion.²⁰ Similarly, patients have been identified that develop non-gap acidosis after ethylene glycol poisoning, presumably for similar reasons.²¹

Dilutional Acidosis

It seems counterintuitive that the addition of a neutral solution such as saline could acidify the blood. The reason this occurs is that respiration is regulated to maintain a constant P_{CO_2} . When saline is administered, the bicarbonate buffer gets diluted while the P_{CO_2} remains constant, thus the pH drops.² This is conceptually the exact opposite of what happens in contraction alkalosis.

Anion Gap Metabolic Acidosis

Basic approach to anion gap acidosis

Most medical students are familiar with the mnemonic “MUDPILES” or its extension “CAT-MUDPILES” for the differential diagnosis of metabolic acidosis with an elevated anion gap. This stands for the following:

- C = cyanide
- A = alcoholic ketoacidosis
- T = toluene
- M = methanol, metformin
- U = uremia
- D = DKA (diabetic ketoacidosis)
- P = phenformin, paraldehyde
- I = iron, INH (isoniazid), ibuprofen
- L = lactate
- E = ethylene glycol
- S = salicylates, SKA (starvation ketoacidosis)

Although this is an easy way to remember most of the common causes of anion gap elevation, it is not exhaustive, nor does it provide a rational approach to the evaluation of the patient with an anion gap acidosis. For example, numerous mitochondrial poisons, vasoactive agents, systemic toxins (aluminum phosphide) and nonsteroidal anti-inflammatory drugs are excluded from this list. It is highly inefficient to take a “shotgun” approach to anion gap metabolic acidosis, sending tests to rule out all of the “CAT-MUDPILES” causes when the acid-base disorder is recognized. In most centers, tests for methanol and ethylene glycol are not done on-site, so results may take several days. If toxic alcohols are suspected, treatment should not be delayed for these results, and an alcohol dehydrogenase (ADH) inhibitor, ethanol or fomepizole, should be administered. This is potentially expensive, unnecessary, and can lead to other complications, particularly if ethanol is used as the ADH inhibitor.

A more rational approach to the patient with an elevated anion gap is to rule out the most common causes before considering more rare causes (Fig. 2). The vast majority of patients with anion gap acidosis have an elevated lactate as the cause. Thus, when sending a sample for blood gas analysis, it is critical to also request a lactate concentration. Ketoacidosis is also common, so serum and/or urine should be analyzed for ketones. Uremia is also a common cause of anion gap acidosis, but it is typically apparent whether a patient is uremic by the time it is determined that there is an anion gap elevation. It is also rare for the metabolic acidosis to occur from uremia unless the serum creatinine approaches 5 to 6 mg/dL. Once these common causes have been evaluated, the diagnosis of toxic alcohols may be pursued, unless the diagnosis is suspected based on the history or other clues.



Fig. 2. Metabolic acidosis. A rational approach to the differential diagnosis of metabolic acidosis with an elevated anion gap focuses on what causes are most common.

LACTATE

Metabolic acidosis with an elevated lactate is typically classified as Type A (associated with underlying tissue hypoxemia or hypoperfusion) or Type B (associated with inborn errors of metabolism, toxins, or underlying diseases). However, this is generally less useful from a toxicologic perspective, as some toxins lead to lactate excess because of underlying tissue hypoxemia or hypoperfusion. Toxins such as iron can cause both a Type A and Type B lactic acidosis. It is more useful to consider which of two basic mechanisms is the underlying cause of an elevated lactate: excess production of lactate or inability to clear lactate. Most toxin-associated lactic acidosis is due to excess production of lactate. Production of excess lactate is generally due to one of the several underlying mechanisms (Table 6):

- Seizure-inducing toxins: seizures cause excess motor activity, causing a basic imbalance between oxygen supply and demand, particularly in generalized seizures, during which ventilation may be impaired. In this situation, skeletal muscle tissue turns to anaerobic metabolism for energy, generating lactate (Fig. 3).
- Toxins causing oxygen demand to exceed oxygen supply: lactate is a nonspecific marker of severe illness and hypovolemia in many disease states, from sepsis to trauma. Some toxins can also cause lactate elevation by causing hypovolemia and/or mismatch of oxygen supply and demand. This is characteristic of iron toxicity (the “I” in MUDPILES). Lactate is also a marker of poor prognosis after acetaminophen poisoning, likely for similar reasons.²² Another example is the lactate elevation that may occur after beta-agonist poisoning.^{23,24}
- Tissue ischemia due to vasoconstriction and local hypoperfusion: toxins that cause vasoconstriction, primarily alpha-adrenergic agonists and ergot derivatives, lead to local tissue hypoperfusion and resultant anaerobic metabolism in that tissue, producing lactate (see Fig. 3).
- Interference with oxygen utilization: toxins may interfere with oxygen utilization either by directly interfering with the electron transport chain and oxidative phosphorylation (eg, carbon monoxide, cyanide, or hydrogen sulfide binding to

Mechanism of Lactic Acidosis		Examples
Seizures ^a		INH, bupropion, camphor, theophylline
Oxygen demand exceeds supply		Iron, acetaminophen, beta-agonists
Interference with oxygen utilization	Oxidative phosphorylation inhibitors Mitochondrial toxins	Carbon monoxide, cyanide, hydrogen sulfide, rotenone Nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, propofol
Local ischemia		Cocaine, ergots, amphetamines, cathinones
Metabolism to lactate		Propylene glycol
Inability to clear lactate		Metformin/phenformin, ethanol

Abbreviation: INH, isoniazid.

^a Seizures are themselves an example in which oxygen demand exceeds oxygen supply, but because toxins that cause acidosis by this mechanism have a clinically apparent manifestation, they are listed as a separate category.

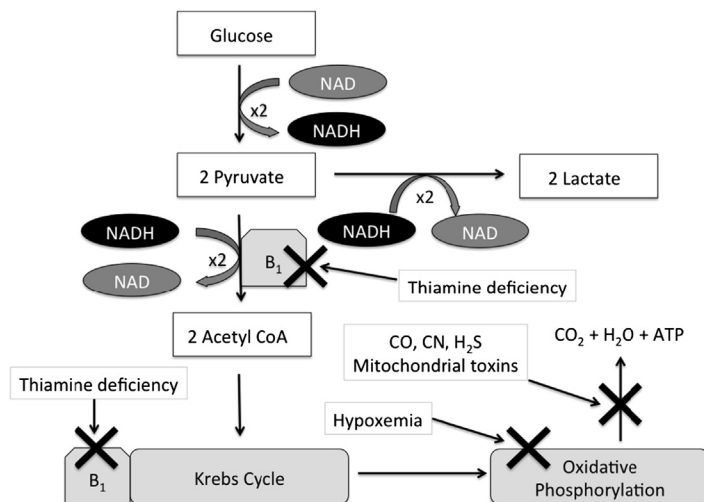


Fig. 3. Effects of hypoxemia, thiamine deficiency, and mitochondrial toxins on glucose metabolism. Ultimately, by blocking different stages of metabolism after glycolysis, all of these mechanisms prevent aerobic metabolism. When pyruvate cannot enter into the Krebs cycle by conversion to acetyl CoA, the only way to maintain glycolysis is to convert pyruvate to lactate, regenerating oxidized NAD.

cytochrome aa3 oxidase) or by poisoning mitochondria. These include nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors which interfere with mitochondrial DNA chlordecone and amphotericin induced changes in mitochondrial permeability, and mitochondrial uncoupling agents such as dinitrophenol and pentachlorophenol). In either case, when oxidative phosphorylation cannot proceed, NADH must be cleared by converting pyruvate to lactate to permit continued glycolysis (see **Fig. 3**). There is some evidence that metformin-associated lactic acidosis may also involve inhibition of oxidative phosphorylation.²⁵

- Direct metabolism of a toxin to lactate: propylene glycol, a diol, is metabolized successively by ADH and aldehyde dehydrogenase to lactate. Patients who ingest propylene glycol can have markedly elevated serum lactate concentrations to values that would in most circumstances be incompatible with life. These values are well tolerated in propylene glycol cases because the excess lactate is not reflective of underlying pathology.

Some toxin-associated lactic acidosis is due to an inability to clear lactate. Extensive metabolism of ethanol leads to a reduced redox state of the body (excess NADH relative to NAD). This shifts the lactate/pyruvate equilibrium toward lactate, preventing its metabolism (**Fig. 4**). Metformin-associated lactic acidosis may involve inhibition of pyruvate dehydrogenase, preventing pyruvate metabolism to acetyl CoA and further metabolism.²⁶ This also shifts the pyruvate/lactate equilibrium toward lactate.

One non-physiological reason for an elevated lactate is ethylene glycol poisoning. Ethylene glycol may interfere with some lactate assays, yielding a high false-positive lactate reading, typically on blood gas analyzers. To help decipher true elevations from spurious values, both serum and blood gas sample lactates can be obtained to determine if a “lactate gap” (a difference between the two samples) exists.

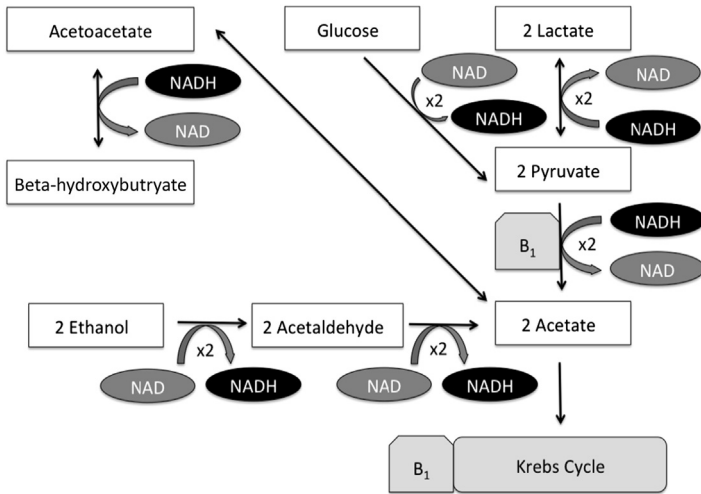


Fig. 4. Relationship between pyruvate and lactate, acetoacetate and beta-hydroxybutyrate, and ethanol and acetate. When NADH is abundant, the equilibrium between pyruvate and lactate shifts to favor lactate and the equilibrium between acetoacetate and beta-hydroxybutyrate shifts to favor beta-hydroxybutyrate. States that lead to abundance of NADH include glucose metabolism when aerobic metabolism is not possible (due to relative hypoxemia, inhibition of the Krebs cycle or oxidative phosphorylation by toxins, or absence of thiamine preventing conversion of pyruvate to acetyl CoA), and extensive metabolism of ethanol. The shift from pyruvate to lactate in chronic drinkers also makes pyruvate unavailable as a starting point for gluconeogenesis.

KETONES

From a toxicologic perspective, the main causes of ketosis are isopropanol or acetone intoxication and alcoholic ketoacidosis (AKA). Salicylates and valproate poisoning may also be associated with ketosis. However, of these, only AKA and salicylates cause a metabolic acidosis. When isopropanol is metabolized by alcohol dehydrogenase, the end product is acetone. Acetone is a ketone, but not an acid, so it is not associated with acidemia. Further, because it is a ketone, not an aldehyde, it cannot be further metabolized to an acid by aldehyde dehydrogenase. This is why acute and isolated isopropanol ingestions may present with “ketosis without acidosis.”

Alcoholic ketoacidosis typically occurs in chronic drinkers during a period of abstinence after a binge. Chronic drinkers have depleted glycogen stores, and usually have depleted thiamine as well. This scenario leads to fatty acid breakdown, and generation of acetyl CoA. The absence of thiamine inhibits the Krebs cycle (as it is a cofactor for alpha-ketoglutarate dehydrogenase), so the excess acetyl CoA is converted to acetoacetate (Fig. 5). Because of the excess NADH from ethanol metabolism, the equilibrium between acetoacetate and beta-hydroxybutyrate shifts toward mostly beta-hydroxybutyrate (see Fig. 4); thus, there may be only trace serum ketones even when there is extensive acidosis (because beta-hydroxybutyrate is a carboxylic acid and not a ketone).²⁷

It is common for patients with a history of alcoholism to present with anion gap acidosis of unclear etiology, and trace ketones. Although toxic alcohols may be considered in the differential diagnosis in this setting, it is reasonable to attempt treatment of AKA first. If thiamine, dextrose, and fluids are administered, the anion gap

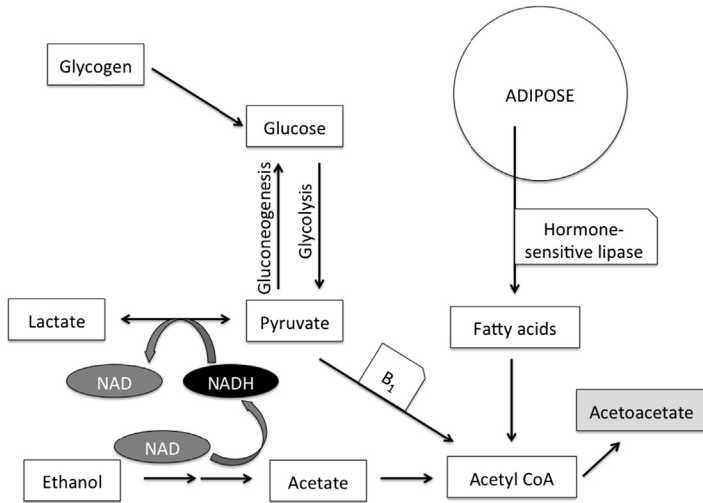


Fig. 5. Starvation, thiamine deficiency, and ethanol metabolism lead to ketoacidosis. Glycogen reserves are quickly exhausted, and glucose intake is low. Existing pyruvate is converted to lactate because of excess NADH from ethanol metabolism, and becomes relatively unavailable for gluconeogenesis. Low glucose impairs insulin release, and hormone-sensitive lipase is activated, liberating fatty acids from fat. These fatty acids are broken down to acetyl CoA in the liver. Absence of thiamine inhibits the Krebs cycle, and the excess acetyl CoA is converted to acetoacetate.

generally improves rapidly if due to AKA, which is not expected in toxic alcohol poisoning without specific antidotal therapy or concurrent ingestion of ethanol.

SALICYLATES

In addition to the respiratory alkalosis (previously discussed in this article), salicylates characteristically cause an anion gap metabolic acidosis. Although early in poisoning it may not yet be present, eventually an acidosis is generated through several mechanisms:

- Lactate from anaerobic metabolism due to lack of oxidative phosphorylation²⁸
- Ketones due to inhibition of dehydrogenases in the Krebs cycle, leading to accumulation of acetyl CoA²⁹
- Salicylic acid
- Proton shifts due to uncoupling of oxidative phosphorylation
- Sulfuric and phosphorous-containing acids due to effects of salicylate on renal function

In fact, salicylate can cause even more complex acid-base disorders. Patients with severe toxicity may have respiratory alkalosis, anion gap metabolic acidosis by the mechanisms noted previously, and hypochloremic metabolic alkalosis/contraction alkalosis from vomiting and/or osmotic diuresis.

TOXIC ALCOHOLS

Toxic alcohols are “toxic” because they have toxic metabolites. Methanol, ethylene glycol, and other “toxic” alcohols (eg, diethylene glycol, benzyl alcohol) cause metabolic acidosis because they are converted to carboxylic acids through successive

metabolism by ADH and aldehyde dehydrogenase. These acids are unmeasured anions and thus cause an elevated anion gap. The formate metabolite of methanol is particularly toxic to the retina, and may cause blindness. The glycolate metabolite of ethylene glycol is responsible for metabolic acidosis, whereas the oxalate metabolite is responsible for nephrotoxicity. Blindness or renal failure may be clues to diagnosis in a patient who presents late after ingestion. As discussed previously, when evaluating a patient with an anion acidosis of unclear etiology, it is important to rule out the more common causes before pursuing toxic alcohols, unless the history or symptoms strongly suggest this etiology. When toxic alcohols are suspected, toxic alcohol concentrations should be obtained also. However, in most hospitals, these are “send-out” tests, and take several days for results to be available. Thus, in the absence of a clear history, decisions about therapy must be made based on collateral information, such as a serum ethanol concentration and serum osmolality, both of which should be obtained during the initial laboratory evaluation.

- Serum ethanol: ethanol is the preferred substrate for ADH, and if present, will prevent metabolism of other alcohols. Thus, if there is significant serum ethanol, an anion gap acidosis cannot have been due to a toxic alcohol, because the ethanol present would have precluded metabolism to the carboxylic acid metabolite that would generate an acidosis. The exception to this is if the patient ingested a toxic alcohol several hours before ingesting ethanol, but this scenario is exceedingly uncommon.
- Osm gap: The osm gap is the difference between the measured osmolality (commonly measured by freezing point depression), and the calculated osmolarity. It is unitless because of the unit differences in osmolality and osmolarity, although they are similar at low solute concentrations. The calculated osmolarity has traditionally been calculated using the formula:

$$\text{Osm}_{\text{calc}} = 2 \times (\text{Na}^+) + (\text{glucose})/18 + \text{BUN}/2.8 + (\text{ETOH})/4.6,$$

although a recent study found that it may be more accurate to use 4.25 as the denominator for ethanol.³⁰ The osm gap is useful to calculate, as long as one considers potential pitfalls. A normal osm gap ranges from -14 to 10 .³¹ Because of this, a “normal” osm gap cannot completely exclude toxic alcohol poisoning, because a potentially consequential concentration of methanol or ethylene glycol may still be present with an osm gap in this range (if an individual’s osm gap had changed from -14 to $+10$, for example). In addition, as the alcohol is metabolized, the osm gap decreases as the anion gap increases. If toxic alcohols are only being considered in the differential diagnosis because of an elevated anion gap, it may be too late to find an osm gap that may initially have been present. In contrast, a mildly elevated osm gap does not necessarily mean that a patient is poisoned by a toxic alcohol. Patients with either alcoholic ketoacidosis or lactic acidosis may have osm gap elevations significantly above the normal range.^{32,33} However, a markedly elevated osm gap (40 – 60 osms) is almost always a toxic alcohol.

SUMMARY

Understanding the interpretation of a patient’s acid-base status can be invaluable in caring for poisoned patients. Obtaining a few critical tests, including serum chemistry, blood gas with lactate, urine or serum ketones, and occasionally serum osmolality, serum ethanol concentration, or urine electrolytes, pH and ammonia can markedly narrow the differential diagnosis and guide therapy. The acid-base status

is closely tied to the underlying pathophysiology of many toxicologic processes, so understanding the acid-base status also means better understanding the disease.

ACKNOWLEDGMENTS

Special thanks to Dr Richard Sinert for his help with several of the tables in this article.

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