Chapter 3
Etiologic Causes of Metabolic Acidosis I: The High Anion Gap Acidoses

Thomas D. DuBose Jr.

High Anion Gap Acidoses

The anion gap (AG) should always be corrected for the prevailing albumin concentration (for each g/dL decrease in albumin below the normal value of 4 g/dL, add 2.5 mEq/L to the traditionally calculated AG to obtain the corrected AG). A normal AG in patients with a normal serum albumin concentration and otherwise normal metabolic status is 10 ± 2 mEq/L. Corrected AG values above 10 ± 2 mEq/L represent a high AG metabolic acidosis. When corrected in this manner, the anion gap [1] serves a useful tool in the initial differentiation of the types of metabolic acidoses and should always be considered as an important component of understanding the pathophysiology of the specific defect. A high AG acidosis denotes addition of an acid other than hydrochloric acid or its equivalent to the ECF and is caused by the accumulation of organic acids. This may occur if the anion does not undergo glomerular filtration (e.g., uremic acid anions), or if, because of alteration in metabolic pathways (ketoacidosis, L-lactic acidosis), the anion cannot be utilized immediately. Theoretically, with a pure AG acidosis, the increment in the AG above the normal value of 10 ± 3 mEq/L (ΔAG), should equal the decrease in bicarbonate concentration below the normal value of 25 mEq/L (ΔHCO_3^-). When this relationship is considered, circumstances in which the increment in the AG exceeds the decrement in bicarbonate ($\Delta AG > \Delta HCO_3^-$) suggest the coexistence of a metabolic alkalosis. By contrast, circumstances in which the increment in the AG is less than the decrement in bicarbonate ($\Delta AG < \Delta HCO_3^-$) suggest the coexistence of a non-AG metabolic acidosis.

Common causes of a high gap acidosis include (1) lactic acidosis, (2) ketoacidosis, (3) toxin- or poison-induced acidosis, and (4) uremic acidosis. Clinical examples are summarized in Table 3.1.

T.D. DuBose Jr., M.D., M.A.C.P., F.A.S.N. (✉)
Section on General Internal Medicine, Wake Forest School of Medicine,
Medical Center Boulevard, Winston Salem, NC 27157, USA
e-mail: tdubose@wakehealth.edu

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Table 3.1 Causes of high anion gap metabolic acidosis

Lactic acidosis	Toxins
Ketoacidosis	Ethylene glycol
Diabetic	Methanol
Alcoholic	Salicylates
Starvation	Propylene glycol
	Pyroglutamic acid
	Kidney failure (acute and chronic)

Lactic Acidosis

Pathophysiology

Lactic acid can exist in two forms: L (levorotatory)-lactic acid and D (dextrorotatory)-lactic acid. In mammals, only the levorotatory form is a product of mammalian metabolism. D-Lactate can accumulate in humans only as a by-product of metabolism of carbohydrate by bacteria which abnormally accumulate and overgrow in the gastrointestinal tract as might occur with a "blind loop" in bowel, with jejunal bypass, or short bowel syndrome. L-Lactic acidosis is one of the most common forms of a high AG acidosis, and hospital chemical laboratories routinely measure L-lactic acid levels, not D-lactic acid levels. Consequently, the clinician who suspects D-lactic acidosis must ask the clinical laboratory to specifically measure D-lactic acid.

Lactic acid metabolism, although similar to that of pyruvate, is in a metabolic cul-de-sac with pyruvate as its only outlet [2]. In most cells, the major metabolic pathway for pyruvate is oxidation in the mitochondria to acetyl–coenzyme A by the enzyme pyruvate dehydrogenase within the mitochondria. The overall reaction may be expressed as in Eq. (3.1):

$$\text{Pyruvate}^- + \text{NADH} \Leftrightarrow \text{lactate}^- + \text{NAD} + \text{H}^+ \tag{3.1}$$

Normally, this cytosolic reaction catalyzed by the enzyme lactate dehydrogenase (LDH) is close to equilibrium, so that the law of mass action applies and the equation is rearranged as (3.2):

$$[\text{Lactate}^-] = K_{\text{eq}}[\text{H}^+]\frac{\text{NADH}}{\text{NAD}^+} \tag{3.2}$$

The concentration of lactate is a function of the equilibrium constant (K_{eq}), the pyruvate concentration, the cytosolic pH, and the intracellular redox state represented by the concentration ratio of reduced to oxidized nicotinamide adenine dinucleotide or [NADH]/[NAD^+] [2].

Because K_{eq} and intracellular H^+ concentration are relatively constant, the normal lactate/pyruvate concentration ratio (1.0/0.1 mEq/L) is proportional to the

NADH/NAD⁺ concentration ratio. Therefore the lactate/pyruvate ratio and the ratio of reduced to the oxidized forms of these molecules is a function of the cellular redox potential (3.3):

$$\frac{[\text{NADH}]}{[\text{NAD}^+]^+} \propto \frac{[\text{Lactate}]}{[\text{Pyruvate}]} \propto \frac{[\beta \quad \text{hydroxybutyrate}]}{[\text{acetoacetate}]} \propto \frac{[\text{ethanol}]}{\text{acetaldehyde}} \tag{3.3}$$

If the lactate concentration is high compared with that of pyruvate, NAD⁺ will be depleted, and the NADH/NAD⁺ ratio will increase. The production of lactic acid has been estimated to be about 15–20 mEq/kg/day in normal humans [3], but can be increased by ischemia, seizures, extreme exercise, leukemia, and alkalosis [2]. The increase in production occurs principally through enhanced phosphofructokinase activity.

Decreased lactate consumption may also lead to L-lactic acidosis. The principal organs for lactate removal include the liver, kidneys, and skeletal muscle [4]. Hepatic utilization of lactate can be impeded by: poor perfusion of the liver; defective active transport of lactate into cells; and inadequate metabolic conversion of lactate into pyruvate because of altered intracellular pH, redox state, or enzyme activity. Examples of states causing impaired hepatic lactate removal include primary diseases of the liver, enzymatic defects, tissue anoxia or ischemia, severe acidosis, and altered redox states, as occurs with alcohol intoxication, fructose consumption by fructose-intolerant individuals, or administration of nucleoside reverse transcriptase inhibitors [2, 5, 6] or biguanides such as metformin [2, 7, 8]. Since thiamine is a cofactor for pyruvate dehydrogenase that catalyzes the oxidative decarboxylation of pyruvate to acetyl–coenzyme A under aerobic conditions, it is not surprising that deaths have been reported due to refractory lactic acidosis secondary to thiamine deficiency [9]. When pyruvate cannot be metabolized with thiamine deficiency, excess pyruvate is converted to hydrogen ions and lactate.

Pathogenesis and Clinical Spectrum

According to the historical classification of the L-lactic acidoses, type A L-lactic acidosis is due to tissue hypoperfusion or acute hypoxia, whereas type B L-lactic acidosis is associated with common diseases, drugs and toxins, and hereditary and miscellaneous disorders [2]. Lactate concentrations are mildly increased in various nonpathologic states (e.g., exercise), but the magnitude of the elevation is generally small. A lactate concentration greater than 4 mmol/L (normal is 0.67–1.8 mmol/L) is taken as evidence that the metabolic acidosis is the result of lactic acid acidosis.

Tissue underperfusion and acute underoxygenation at the tissue level (tissue hypoxia) are the most common causes of type A lactic acidosis. Inadequate cardiac output, of either the low-output or the high-output variety, is the most frequent cause, but severe arterial hypoxemia can also generate L-lactic acidosis. The prognosis is related to the increment in plasma L-lactate and the severity of the acidemia [2, 8, 10].

A number of medical disorders (without tissue hypoxia) may cause type B L-lactic acidosis. Hepatic failure reduces hepatic lactate metabolism, and leukemia increases lactate production. Severe anemia, especially as a result of iron deficiency or methemoglobulinemia, may cause lactic acidosis. Among patients in the critical care unit the most common cause of L-lactic acidosis is bowel ischemia and infarction. Malignant cells produce more lactate than normal cells even under aerobic conditions. This phenomenon is magnified if the tumor expands rapidly and outstrips its blood supply. Therefore, exceptionally large tumors may be associated with severe L-lactic acidosis. Seizures, extreme exertion, heat stroke, and tumor lysis syndrome may all cause L-lactic acidosis.

Several drugs and toxins predispose to L-lactic acidosis. Of these, metformin is the most widely reported to have this effect [2, 7, 8], but metformin-induced lactic acidosis is at higher risk in patients with chronic kidney disease (and is contraindicated when the serum creatinine exceeds 1.4 mg/dL), or whenever there is hypoperfusion or hypotension, including severe volume depletion (especially in the elderly), shock, septicemia, CHF, or a recent AMI.

In patients with HIV infection, nucleoside analogs predispose to toxic effects on mitochondria by inhibiting DNA polymerase-γ. Therefore, hyperlactatemia is common with anti-HIV therapy, but the serum L-lactate level is usually only mildly elevated [2, 5, 6, 11]. However, with severe concurrent illness pronounced lactic acidosis may occur in association with hepatic steatosis [2, 6] and a high mortality.

Translational Approach

The overall mortality of patients with L-lactic acidosis is approximately 60 %, but approaches 100 % in those with coexisting hypotension or multiorgan dysfunction [2]. The only effective form of therapy for L-lactic acidosis is to correct the underlying condition initiating the disruption in normal lactate metabolism. Cessation of acid production by improvement of tissue oxygenation, restoration of the circulating fluid volume, improvement or augmentation of cardiac function, resection of ischemic tissue, and antibiotics is necessary for type A L-lactic acidosis.

Alkali therapy is generally advocated for acute, severe acidemia (pH of <7.0) to improve myocardial inotropy and lactate utilization. However, $NaHCO_3$ therapy in large amounts can depress cardiac performance and exacerbate the acidemia. Paradoxically, bicarbonate therapy activates phosphofructokinase, which is regulated by intracellular pH, thereby increasing lactate production. For all of these reasons, $NaHCO_3$ should be used cautiously with the goal of increasing the plasma [HCO_3^-] to no more than 5–8 mmol/L.

If the underlying cause of the L-lactic acidosis can be remedied, blood lactate will be reconverted to HCO_3^-. The bicarbonate derived metabolically from lactate conversion is additive to any new HCO_3^- generated by kidney mechanisms during acidosis and from exogenous alkali therapy might lead to an "overshoot" alkalosis.

D-Lactic Acidosis

The typical manifestations of D-lactate acidosis are episodic encephalopathy and high AG acidosis in association with short bowel syndrome. D-Lactic acidosis has been described in patients with bowel obstruction, jejunal bypass, short bowel, or ischemic bowel disease. Ileus or stasis is associated with overgrowth of flora in the gastrointestinal tract, which is exacerbated by a high-carbohydrate diet [2]. D-Lactate acidosis occurs when fermentation by colonic bacteria in the intestine causes D-lactate to accumulate so that it can be absorbed into the circulation. Serum D-lactate levels of greater than 3 mmol/L confirm the diagnosis. Treatment with a low-carbohydrate diet and antibiotics (neomycin, vancomycin, or metronidazole) is often effective [12–15].

Ketoacidosis

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is due to increased fatty acid metabolism and accumulation of ketoacids (acetoacetate and β-hydroxybutyrate) as a result of insulin deficiency or resistance and elevated glucagon levels. DKA is usually seen in insulin-dependent diabetes mellitus upon cessation of insulin therapy or during an illness, such as an infection, gastroenteritis, pancreatitis, or myocardial infarction, which increases insulin requirements acutely. The accumulation of ketoacids accounts for the increment in the AG, which is accompanied, most often, by hyperglycemia (glucose level of >300 mg/dL) [15–17].

Alcoholic Ketoacidosis

Some patients with chronic alcoholism, especially binge drinkers, who discontinue food intake while continuing alcohol consumption, may develop the alcoholic form of ketoacidosis [12, 13, 18]. Often the onset of vomiting and abdominal pain with volume depletion leads to cessation of alcohol consumption [16, 17]. The metabolic acidosis may be severe but is accompanied by only modestly deranged glucose levels, which are usually low but may be slightly elevated [15, 18]. The net result of the deranged metabolic state is ketosis. The acidosis is primarily due to elevated levels of ketones, which exist predominantly in the form of β-hydroxybutyrate because of the altered redox state induced by the metabolism of alcohol. Compared with patients with DKA, patients with AKA have lower plasma glucose concentrations and higher β-hydroxybutyrate/acetoacetate and lactate/pyruvate ratios [16, 17]. Because the standard clinical tests for ketone bodies do not detect the reduced

ketoacid β-hydroxybutyrate, AKA patients with severe ketoacidosis comprised mostly of β-hydroxybutyrate might escape detection in the setting of a negative test for ketones if the clinician does not have a high index of suspicion. The typical high AG acidosis is often mixed with metabolic alkalosis (vomiting), respiratory alkalosis (alcoholic liver disease), lactic acidosis (hypoperfusion), and/or hyperchloremic acidosis (kidney excretion of ketoacids). Finally, elevation in the osmolar gap is usually accounted for by an increased blood alcohol level, but the differential diagnosis should always include ethylene glycol and/or methanol intoxication [16, 17].

Drug- and Toxin-Induced Acidosis

Salicylate

Intoxication with salicylates, although more common in children than in adults, may result in the development of a high AG metabolic acidosis, but [15] adult patients with salicylate intoxication usually have pure respiratory alkalosis or mixed respiratory alkalosis–metabolic acidosis [15]. A portion of the increase in the AG is due to the increase in plasma salicylate concentration, and the remainder is due to high ketone concentrations, present in as many as 40 % of adult salicylate-intoxicated patients in combination with increased L-lactic acid production, due to a direct drug effect and the result of the salicylate-induced decrease in PCO_2 [15, 19].

The Osmolar Gap and Toxin-Induced Metabolic Acidosis

Under most physiologic conditions, Na^+, urea, and glucose generate the osmotic pressure of blood. Serum osmolality is calculated according to the following expression (3.4):

$$\text{Osmolality} = 2[Na^+] + \frac{[\text{BUN}]}{2.8} + \frac{[\text{Glucose(mg / dL)}]}{18} \tag{3.4}$$

The calculated and determined osmolality should agree within 10 mOsm/kg. When the measured osmolality exceeds the calculated osmolality by more than 10 mOsm/kg, one of two circumstances prevails. First, the serum Na^+ may be spuriously low, as occurs with hyperlipidemia or hyperproteinemia (pseudohyponatremia). Second, osmolytes other than sodium salts, glucose, or urea may have accumulated in plasma. Examples are infused mannitol, radiocontrast media, or other solutes, including the alcohols, ethylene glycol, and acetone, which can increase the osmolality in plasma. For these examples, the difference between the osmolality calculated from Eq. (3.4) and the measured osmolality is proportional to the concentration of the unmeasured solute. This difference, is known as the *osmo-*

lar gap, and becomes a very reliable and helpful screening tool in assessing for toxin-associated high AG acidosis.

Ethylene Glycol

Ingestion of ethylene glycol (EG), used in antifreeze, leads to a high AG metabolic [15, 20, 21] acidosis in addition to severe central nervous system, cardiopulmonary, and kidney damage. Disparity between the measured and calculated blood osmolality (high osmolar gap) is usually noted, especially in the first few hours after ingestion. Typically over time, as the EG is metabolized, the osmolar gap begins to fall and the anion gap begins to rise so that in advanced EG intoxication, the AG will be very high but the osmolar gap will narrow. The high AG is attributable to ethylene glycol metabolites, especially oxalic acid, glycolic acid, and other incompletely identified organic acids [21]. L-Lactic acid production also increases as a result of a toxic depression in the reaction rates of the citric acid cycle and altered intracellular redox state [21].

Methanol

Methanol has wide application in commercially available solvents and is used for industrial and automotive purposes. Sources include windshield wiper fluid, paint remover or thinner, deicing fluid, canned heating sources, varnish, and shellac. Ingestion of methanol (wood alcohol) causes metabolic acidosis in addition to severe optic nerve and central nervous system manifestations resulting from its metabolism to formic acid from formaldehyde [15, 20]. Lactic acids and ketoacids as well as other unidentified organic acids may contribute to the acidosis. Because of the low molecular mass of methanol (32 Da), an osmolar gap is usually present early in the course but declines as the anion gap increases, the latter reflecting the metabolism of methanol. Therapy for both methanol and ethylene glycol intoxication includes general supportive measures, fomepizole administration, and hemodialysis [22].

Pyroglutamic Acid

Pyroglutamic acid, or 5-oxoproline, is an intermediate in the γ-glutamyl cycle for the synthesis of glutathione. Acetaminophen ingestion can in rare cases deplete glutathione, which results in increased formation of γ-glutamyl cysteine, which is metabolized to pyroglutamic acid [23]. Accumulation of this intermediate has been reported in critically ill patients taking acetaminophen, usually with sepsis. Such patients have severe high AG acidosis and alterations in mental status [23].

Propylene Glycol

Propylene glycol is used as a vehicle for intravenous medications and some cosmetics and is metabolized to lactic acid by hepatic alcohol dehydrogenase. Numerous intravenous preparations contain propylene glycol as the vehicle (lorazepam, diazepam, pentobarbital, phenytoin, nitroglycerin, and TMP-SMX), and may accumulate and cause a high AG, high osmolar gap acidosis in patients receiving continuous infusion or higher dosages of these agents, especially in the presence of chronic kidney disease, chronic liver disease, alcohol abuse, or pregnancy [24, 25]. The acidosis is the result of accumulation of L-lactic acid, D-lactic acid, and L-acetaldehyde, but typically abates with cessation of the offending agent [26].

Uremia

Advanced chronic kidney disease eventually converts the non-gap metabolic acidosis of Stage 3–4 CKD to the typical high AG acidosis, or "uremic acidosis" of Stage 5 CKD [27]. Poor filtration plus continued reabsorption of poorly identified uremic organic anions contributes to the pathogenesis of this metabolic disturbance.

Classical uremic acidosis is characterized by a reduced rate of NH_4^+ production and excretion because of cumulative and significant loss of kidney mass [27–29]. Usually, acidosis does not occur until a major portion of the total functional nephron population has been compromised, because of the adaptation by surviving nephrons to increase ammoniagenesis.

Pathophysiological Basis of Correction of Acidosis of Chronic Kidney Failure

The uremic acidosis of advanced CKD requires oral alkali replacement to maintain the HCO_3^- concentration above 22 mEq/L. This can be accomplished with relatively modest amounts of alkali (1.0–1.5 mEq/kg/day of $NaHCO_3$ tablets). Alkali replacement serves to prevent the harmful effects of prolonged positive H^+ balance, especially progressive catabolism of muscle and loss of bone.

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