Metabolic Acidosis

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Metabolic acidosis, the most common acid-base disorder, is associated with many life-threatening conditions. Metabolic acidosis is a state produced by excessive acid production, reduced acid excretion, or consumption or loss of body alkali. Arterial blood gas analysis typically shows the pH to be less than 7.35 and serum bicarbonate (HCO_3^-) to be less than 18 mEq/L. The signs and symptoms of metabolic acidosis are nonspecific, and its diagnosis relies on analysis of laboratory data. Delay in diagnosis is associated with increased mortality and morbidity.[1] Early recognition and prompt initiation of treatment are therefore critical. This article discusses the evaluation and management of this important acid-base disorder.

PATHOPHYSIOLOGY

Cellular metabolism produces carbon dioxide. By a reversible intracellular process, CO_2 combines with water to form carbonic acid ($H_2CO_3^-$). Carbonic acid is able to dissociate into hydrogen ions and HCO_3^- ions in a reversible manner. *Acidemia* is the state of elevated H^+ concentration and is measured in units of pH. Cells have a narrow pH range within which they function optimally.

There are 2 major mechanisms whereby cells maintain a constant H^+ concentration. The CO_2–HCO_3^- buffering system is the most important. The primary response to a metabolic acidosis is an increase in ventilation, resulting in increased CO_2 excretion by diffusion in the lungs. This results in a drop in the blood pH. Additionally, an excess of H^+ can be excreted by conversion to CO_2. The formula representing this buffering system is: $H^+ + HCO_3^- \leftrightarrow H_2CO_3^- \leftrightarrow CO_2 + H_2O$. The second mechanism for maintaining pH is a 2-tiered response by the kidneys. First, H^+ ions are excreted in the proximal tubules, where they combine with HCO_3^- to form carbonic acid ($H_2CO_3^-$). In the brush borders of the tubular cells, carbonic acid is converted to CO_2 and water, and these are reabsorbed. Second, bicarbonate can be regenerated by a reverse process of the buffering system in the lungs ($CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$). A metabolic acidosis can result when either or both of these compensatory responses fails or is overwhelmed.

CLINICAL SIGNS AND SYMPTOMS

Metabolic acidosis may be asymptomatic. If present, the signs and symptoms of metabolic acidosis are relatively nonspecific and may include fatigue, anorexia, confusion, tachycardia, tachypnea, and dehydration. Other manifestations depend on the underlying cause of the disorder.

The adverse hemodynamic effects of a deteriorating metabolic acidosis are profound and, if untreated, can be life threatening. An increase in acidity causes pulmonary vasoconstriction and an increase in pulmonary vascular pressures. These developments can lead to right ventricular failure. At an arterial pH less than 7.2, generalized myocardial depression eventually occurs.[2] In arteriolar smooth muscle, a decrease in pH leads to systemic vasodilation, which can cause hypotension and circulatory failure. In patients with underlying lung disease, the burden imposed by the compensatory increase in minute ventilation will progress to respiratory muscle fatigue and failure. The metabolic consequences include hyperkalemia, hypercalcemia, and hypercalciuria, a catabolic state caused by accelerated amino acid oxidation.

BLOOD GAS ANALYSIS AND INTERPRETATION

Metabolic acidosis can be identified by following the 5 steps below, using information from arterial blood gas analysis and serum electrolyte concentrations. The **Figure** provides an algorithm for assessing metabolic acidosis.

1. Determine whether the patient is alkalemic or acidemic on the basis of arterial pH (normal,

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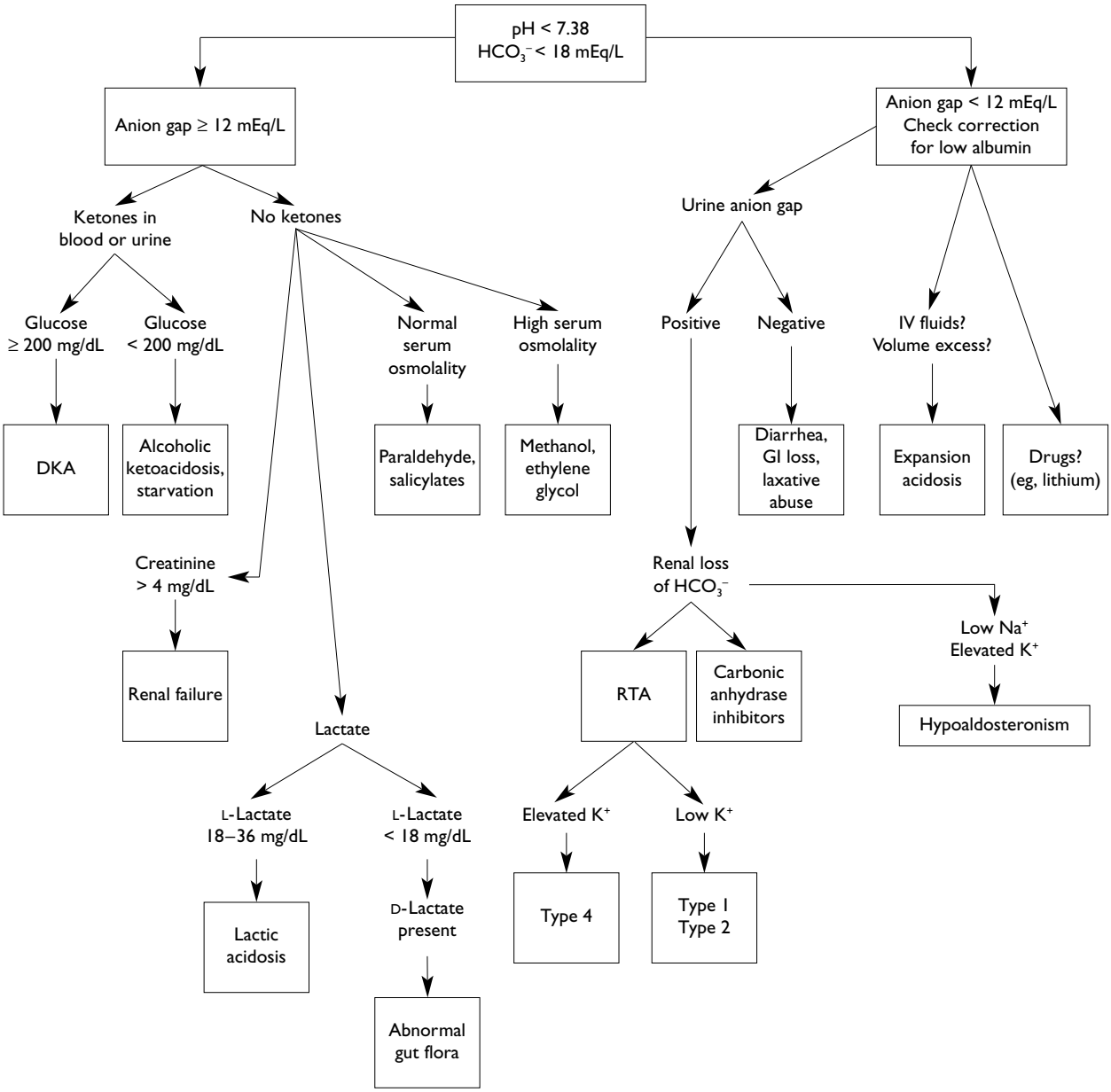

Figure. Algorithm for assessing metabolic acidosis. DKA = diabetic ketoacidosis; GI = gastrointestinal; IV = intravenous; RTA = renal tubular acidosis.

7.38–7.42). Blood with pH less than 7.38 is acidemic.

2. Determine whether the primary disorder causing acidemia is metabolic or respiratory. The normal serum level of HCO_3^- is 18 to 22 mEq/L. A serum HCO_3^- level of less than 18 mEq/L indicates a primary metabolic acidosis.

3. Determine whether gap or nongap acidosis is present. The anion gap is calculated as $Na^+ - (HCO_3^- + Cl^-)$, and the normal anion gap is 12 ± 2 mEq/L.[3]

4. Determine whether the respiratory system is appropriately compensating by excreting and lowering CO_2 (normal P_{CO_2}, 36–44 mm Hg). Winter's formula, $(HCO_3^- \times 1.5) + 8 \pm 2 = P_{CO_2}$, is an accurate way to calculate the expected P_{CO_2}. The last 2 digits of the pH should roughly equal the P_{CO_2} (the "quick look" method).[4]

Table 1. Causes of Increased Anion Gap Metabolic Acidosis

Increased acid production
Alcoholic ketoacidosis
Diabetic ketoacidosis
Starvation ketoacidosis (mild acidosis only)
Lactic acidosis
Type A (with tissue hypoxia)
Circulatory and respiratory failure
Sepsis
Myocardial infarction
Severe anemia
Massive hemorrhage
Carbon monoxide poisoning
Ischemia of large and small bowels
Ascites and other third-spacing of fluids
Type B (without tissue hypoxia)
Liver failure
Enzyme defects of childhood
Leukemia, lymphoma, solid tumors
Seizures
Poorly controlled diabetes mellitus
Severe burns
Parenteral nutrition
Epinephrine and norepinephrine infusions
Idiopathic
Bronchodilator
Drugs and toxins (aspirin, ethylene glycol, methanol, paraldehyde)
Renal failure
Dilutional (large volume of intravenous fluid replacement)

Table 2. Causes of Normal Anion Gap Metabolic Acidosis

Hypokalemia-associated causes
Diarrhea
Renal tubular acidosis types 1 and 2
Carbonic anhydrase inhibitors (eg, acetazolamide)
Ureteral diversions
Post-hypocapnic conditions
Laxative abuse
Hyperkalemia-associated causes
Acid loads and total parenteral nutrition
Obstructive uropathy
Cholestyramine
Addison disease (hypoaldosteronism)
Renal tubular acidosis type 4
Sulfur toxicity
21-Hydroxylase deficiency
Potassium-sparing diuretics (eg, triamterene)
Chlorine gas exposure

5. Determine whether another metabolic disorder is present in patients with a high anion gap acidosis. Calculate the delta anion gap[5] as follows: delta gap = (anion gap – 10)/(24 – HCO_3^-). The normal value is between 1 and 1.6. A low delta gap suggests the presence of a concomitant nongap acidosis, whereas a delta gap greater than 1.6 suggests the presence of a concomitant metabolic alkalosis.

DIFFERENTIAL DIAGNOSIS

Metabolic acidoses can be classified clinically as an increased anion gap acidosis or a normal anion gap acidosis (hyperchloremic metabolic acidosis). As a concept, the anion gap has shortcomings; nonetheless, it is a useful clinical tool in developing a differential diagnosis of metabolic acidosis.[6] The concept of the anion gap is derived from the law of electrical neutrality. The sum of the positively charged cations in the serum must equal the sum of the negatively charged anions. The cations are primarily sodium and potassium. The major anions are chlorine and bicarbonate. Increased anion gap acidosis is generally more severe (in terms of potentially fatal outcome) than normal anion gap acidosis. The causes of increased and normal anion gap metabolic acidosis are summarized in **Tables 1** and **2**.

Gastrointestinal loss can be differentiated from renal pathologies as a cause of normal gap acidosis by using the urinary anion gap ([urine Na^+ + urine K^+] – urine Cl^-), an indirect measure of ammonium secretion.[7,8] A negative urinary anion gap (< 0) suggests appropriate renal excretion of ammonium and points to gastrointestinal loss as the cause of the acidosis. Conversely, a zero or positive anion gap suggests impaired ammonia production and a renal etiology for the acidosis.

Calculation of an osmolar gap in a patient with a metabolic acidosis is essential if the clinical scenario suggests ingestion or poisoning. Osmolality is a measure of solute particles in a solution. Plasma osmolality reflects both the intracellular and extracellular compartments because they are in osmotic equilibrium. Osmolality can be measured or calculated as follows: 2 × Na^+ (mEq/L) + (blood urea nitrogen [mg/dL]/2.8) + (glucose [mg/dL]/18). This formula reflects the major solutes in extracellular fluid. The calculated plasma osmolality should be within 10 mOsm/L water of the measured plasma osmolality. If unmeasured solutes are present in

the plasma, the measured osmolality will be much higher than the calculated osmolality; this is called an osmolar gap. An osmolar gap in metabolic acidosis should raise suspicion for ethylene glycol or methanol poisoning.

If the anion gap is being used to assess a metabolic acidosis, the anion gap must be adjusted if the patient has hypoalbuminemia. Albumin is a negatively charged protein, and thus hypoalbuminemia falsely lowers the anion gap. The adjustment is made by adding 2.5 to the gap for every 1 g/dL that the albumin is below normal.[9]

BICARBONATE THERAPY

Treatment strategies for metabolic acidosis are primarily directed toward the underlying cause. Bicarbonate therapy is a temporary measure used for severe acidosis (pH < 7.1). The rationale for bicarbonate therapy is that at extracellular pH levels lower than 7.1, small decreases in the level of HCO_3^- or increases in P_{CO_2} are poorly tolerated.

The use of bicarbonate therapy continues to be controversial.[4,10] Risks associated with bicarbonate therapy include hypernatremia, hyperosmolality, volume overload, and overshoot alkalosis. Also, bicarbonate paradoxically shifts the hemoglobin-oxygen dissociation curve unfavorably, potentially resulting in a worsened cerebral metabolic acidosis.

If bicarbonate is used, it should be given cautiously, with frequent acid-base monitoring and a goal of returning the pH to approximately 7.2. It should be given as a slow infusion to lessen the effect of CO_2 generation during buffering. The goal is to adjust the serum HCO_3^- level to 8 to 10 mEq/L. A useful formula for calculating the bicarbonate requirement is: dose of bicarbonate = (desired HCO_3^- – serum HCO_3^-)(mEq/L) × weight (kg) × 0.5.[11] Intravenous bicarbonate is the main alkalinizing agent.

Although the controversy surrounding bicarbonate therapy in metabolic acidosis probably overstates its risks, it has led to a search for alternative agents with fewer adverse effects. Such agents include carbicarb, which consists of equimolar concentrations of sodium bicarbonate and sodium carbonate; tris-hydroxymethyl aminomethane (THAM); and Tribonat, a mixture of THAM, acetate, bicarbonate, and phosphate. Only THAM, however, is currently available in the United States, and the benefits of these agents have not been confirmed.[12–14]

MANAGEMENT OF SPECIFIC CONDITIONS

Renal Failure

When renal failure progresses to the point that uremia is present, metabolic acidosis results. Studies suggest that this leads to protein malnutrition, depressed myocardial contractility, increased bone resorption, and decreased thyroid hormone secretion.[15] Correcting the acidosis improves the nutritional status by preventing muscle protein breakdown.[16] This correction can be achieved by the oral administration of either sodium bicarbonate or sodium citrate 10% solution. Sodium citrate has fewer gastrointestinal adverse effects than sodium bicarbonate; however, caution is required with long-term use of oral citrate in patients with advanced chronic renal failure because it has been shown to increase intestinal absorption of aluminum, which can result in chronic bone toxicity. In short-term situations in which serum HCO_3^- is less than 15 mEq/L, it can be slowly corrected with intravenous bicarbonate. Too-rapid correction of acidosis can lead to tetany and arrhythmias. In addition, hypernatremia, hypertension, and edema may occur.

Hyperkalemia is sometimes present in patients with some degree of renal failure or a disturbance of tubular secretion of potassium. Management depends on the degree of hyperkalemia present.

Renal Tubular Acidoses

Hyperkalemic hyperchloremic metabolic acidosis (type 4 renal tubular acidosis) results from either aldosterone deficiency or renal tubules not responding to aldosterone. In cases caused by drug-related nephrotoxicity, removal of the offending agent is indicated. A decrease in serum potassium concentrations often improves the acidosis; the decision to treat is based on the degree of hyperkalemia. A cation exchange resin (sodium polystyrene sulfonate) with restriction of dietary potassium is effective. Hypovolemia should be corrected. Oral bicarbonate may be beneficial. Cases caused by mineralocorticoid deficiency may require replacement therapy.

Type 1 (distal) renal tubular acidosis is frequently associated with renal stone formation and hypokalemia. The goal of treatment is to eliminate acidosis, which will decrease the hypercalciuria. Alkalinization with oral sodium bicarbonate or Shohl's solution (sodium and potassium citrate) is effective. Potassium supplementation is usually not required.

Type 2 (proximal) renal tubular acidosis is caused by defective HCO_3^- resorption in the proximal renal tubules. Treatment with oral bicarbonate or citrate salts is beneficial. Potassium supplementation is required in the rare severely acidotic cases that require alkali therapy.

Ketoacidosis

Ketoacidosis is caused by increased acid production resulting from increased fatty acid metabolism. Alcoholic ketoacidosis is a syndrome characterized by a high anion gap acidosis and malnutrition in the setting of binge drinking and chronic alcoholism. The pathophysiology is complex.[17] The metabolic acidosis is often complicated by acid-base abnormalities caused by coexisting disorders. Treatment with intravenous saline and glucose rapidly corrects the metabolic acidosis by facilitating the metabolism of the ketoacids. Volume replacement to correct dehydration is important early in the course of treatment.

Fasting and starvation also induce a ketoacidosis. Treatment is directed toward correcting nutritional deficiencies and hypovolemia. The metabolic acidosis is always mild and does not require treatment with bicarbonate.

Patients with diabetic ketoacidosis present with hyperglycemia, ketonemia, and acidosis. The metabolic acidosis is usually severe owing to coexistent uremic acidosis and lactic acidosis. Dehydration and hyperosmolarity are usually present. Treatment with intravenous insulin and fluids rapidly reverses the acidosis and ketonemia. With fluids and insulin, the liver rapidly metabolizes the ketoacids in the liver to bicarbonate, with prompt improvement in the metabolic acidosis. Although studies have not shown a benefit to treating patients with severe diabetic ketoacidosis with bicarbonate,[18] in practice, it is frequently administered to those with a pH of less than 7.1 and HCO_3^- below 8 mEq/L.

Toxin-Related Acidosis

Ethylene glycol intoxication produces a severe metabolic acidosis. It should be suspected in an intoxicated patient with an increased anion gap acidosis, oxylate crystals in the urine sediment, and an osmolar gap greater than 10 mOsm/L. Early correction of the acidosis improves the chance of survival, and bicarbonate replacement is required.

Methanol, like ethylene glycol, is metabolized to toxic products by the enzyme alcohol dehydrogenase. It likewise produces an osmolar gap. It results in much more severe anion gap metabolic acidosis. Visual symptoms are more prominent in its presentation compared with the ataxia and seizures associated with ethylene glycol poisoning. Intravenous ethanol is effective in preventing this metabolic action because the ethanol competes for the enzyme. If marked acidosis is present, bicarbonate therapy should be given.

Patients with aspirin toxicity present initially with respiratory alkalosis caused by hyperventilation as a result of direct stimulation of the respiratory center by salicylate. Most commonly, a mixed metabolic acidosis and respiratory alkalosis are seen at presentation. Therapy is directed at reducing drug absorption and promoting renal excretion. The latter is achieved by alkalinization with sodium bicarbonate and promotion of diuresis with adequate intravenous fluid therapy. Hemodialysis may be needed in cases of severe intoxication.

Glue sniffing and inhalant abuse involving toluene causes toluene toxicity, characterized by a severe metabolic acidosis that is a mixture of increased anion gap and nongap acidosis. Toluene toxicity frequently causes a type I renal tubular acidosis and can result in renal failure. The mainstay of therapy is intravenous fluids and potassium replacement.[19]

Lactic Acidosis

L-Lactic acidosis is caused by the overproduction or impaired breakdown of lactate. It is characterized by a high anion gap, serum lactate level higher than 5 mmol/L, and pH less than 7.3. In the absence of renal failure, an increased phosphorus level with an increased gap acidosis is a strong clue to the presence of lactic acidosis. Lactic acidosis is classically divided into 2 types: type A is associated with impaired tissue oxygenation; type B is not (Table 1). In practice, the distinction between the 2 types is often not clear. Severe cases of lactic acidosis may be fatal.

Management of lactic acidosis depends on its causes. Therapy should focus on adequate oxygenation, correction of extracellular fluid deficits, and treatment specific to the underlying causes. Transient lactic acidosis, such as that resulting from seizure, is frequently of little consequence.

Judicious use of bicarbonate as a temporary measure in patients whose pH is less than 7.1 and whose serum bicarbonate level is less than 8 mEq/L is generally recommended.[20] Results in experimental studies of the use of dichloroacetate in lactic acidosis have been encouraging[21] but were not replicated in a large controlled clinical trial.[22] D-Lactic acidosis has been reported in patients with short-bowel syndrome. It is usually treated with antibiotics to suppress pathogenic flora.

Cardiac Arrest

The exact mechanism by which metabolic acidosis is generated in myocardial cells is unclear.[23] Lactic acidosis and the rapid onset of hypercarbia play a role. Bicarbonate is generally used in prolonged attempts at resuscitation and when severe acidosis results. However, the role of bicarbonate during cardiopulmonary resuscitation is unclear. Studies provide little evidence of

benefit.[23,24] Coronary perfusion pressure, not myocardial pH, seems to determine the success of resuscitation. Efforts are best directed at establishing adequate oxygenation and effective circulation.

Dilutional Acidosis

In patients receiving intravenous solutions of lactate, acetate, or citrate in large volumes, an increased gap acidosis can develop as a result of incomplete conversion to bicarbonate. The addition of bicarbonate to the infusion prevents this. By a similar mechanism, the negatively charged salts of some antibiotics (eg, carbenicillin) given in large quantities can cause a metabolic acidosis.

CONCLUSION

Metabolic acidosis may be the result of a transient and easily reversible condition such as a seizure. More severe metabolic acidoses require precise diagnosis and timely treatment of the underlying condition. The focus of any treatment plan is the underlying disease process; however, if the pH is lower than 7.2, the effects of acidemia can dominate clinical decision making. The goal of alkali therapy is to reverse severe acidemia and protect against the detrimental effects on the cardiovascular system. Intravenous sodium bicarbonate is the mainstay of alkali therapy and is given as a continuous infusion to prevent the effects of "overshoot" alkalosis. Alternative alkalizing agents such as sodium lactate and citrate are not as reliable because their effects depend on oxygenation to bicarbonate. Research efforts aimed at finding alternatives to bicarbonate therapy continue, as do studies to better identify those subgroups of metabolic acidosis that benefit from alkalinization therapy. **HP**

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