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A stepwise approach to acid-base disorders

Practical patient evaluation for metabolic acidosis and other conditions

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PREVIEW

Acid-base disorders are often encountered in hospital and outpatient settings in association with severe diarrhea or vomiting, pregnancy, and other circumstances. Physicians need an organized method of evaluating these disorders to facilitate diagnosis and appropriate treatment. In this article, Dr Fall outlines a step-by-step approach to acid-base disorders, with emphasis on metabolic acidosis. An illustrative case is analyzed at applicable points throughout the article to depict salient features of this approach.

The normal daily diet generates volatile acid (CO_2), primarily from carbohydrate metabolism, and nonvolatile acid (hydrogen ion, H^+) from protein metabolism.[1,2] Both the lungs and kidneys are responsible for maintaining acid-base homeostasis by excreting these acids. Alveolar ventilation allows for excretion of CO_2. The kidneys must reclaim all filtered bicarbonate (HCO_3^-), because any urinary loss leads to net gain of H^+. In addition, the kidneys must excrete the daily acid load generated from dietary protein intake.

Less than half of this acid load is excreted as titratable acids (ie, phosphoric and sulfuric acids); the remaining acid load is excreted as ammonium. This process can increase markedly in the presence of metabolic acidosis. Hence, blood pH is determined by occurrence of these physiologic processes and by buffer systems present in the body.

The carbonic acid–bicarbonate system is the principal extracellular buffer in the body and the most clinically important. The relationship between pH and this buffer system is seen in the Henderson-Hasselbalch equation (discussed later), and a modification of this equation can be used in interpreting acid-base disorders. Primary changes in $PaCO_2$ lead to respiratory acidosis or alkalosis, and primary changes in HCO_3^- level lead to metabolic acidosis or alkalosis. In simple acid-base disorders, $PaCO_2$ and HCO_3^- change in the same direction (eg, a primary increase in $PaCO_2$ induces a compensatory increase in HCO_3^-).

Patient evaluation

The presence of an acid-base disturbance may be suspected on the basis of clinical presentation or by results of laboratory data (eg, a low HCO_3^-). Evaluation of any acid-base disorder can then be approached in a stepwise manner.

Step 1. Do comprehensive history taking and physical examination

Comprehensive history taking and physical examination can often give clues as to the underlying acid-base disorder (table 1). For example, patients who present with gastroenteritis manifested as diarrhea typically have non–anion gap metabolic acidosis from loss of fluid containing HCO_3^-. Patients who present with chronic obstructive lung disease usually have underlying chronic respiratory acidosis from retention of CO_2.

Illustrative case report: *Paramedics brought a 42-year-old man to the emergency department after he was found lying in an alley with an empty liquor bottle nearby. Physical examination revealed blood pressure of 120/80 mm Hg, pulse rate of 110/min, respiration rate of 28/min, and temperature of 37°C*

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Table 1. Common clinical states and associated acid-base disorders

Clinical state	Acid-base disorder
Pulmonary embolus	Respiratory alkalosis
Hypotension	Metabolic acidosis
Vomiting	Metabolic alkalosis
Severe diarrhea	Metabolic acidosis
Cirrhosis	Respiratory alkalosis
Renal failure	Metabolic acidosis
Sepsis	Respiratory alkalosis, metabolic acidosis
Pregnancy	Respiratory alkalosis
Diuretic use	Metabolic alkalosis
Chronic obstructive pulmonary disease	Respiratory acidosis

(98.6°F). The patient was unresponsive. His pupils were minimally reactive to light, and results of funduscopic examination were normal. Bibasilar crackles were noted on auscultation. His deep tendon reflexes were brisk and symmetric, and plantar reflexes were normal. His history suggested ingestion of a toxin, some of which are associated with acid-base disorders.

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Step 2. Order simultaneous arterial blood gas measurement and chemistry profile

The next step is to simultaneously obtain an arterial blood gas measurement for pH and $PaCO_2$ and a chemistry profile for total CO_2 in the serum. The HCO_3^- concentration accounts for the vast proportion of total CO_2, so these two findings are usually considered interchangeable.

Step 3. Assess accuracy of data

A modified Henderson-Hasselbalch equation (see equation 1 in box on page 257) can be used to check the validity of the laboratory values obtained. $PaCO_2$ is obtained from the arterial blood gas measurement, and HCO_3^- is derived from the chemistry profile. There is a direct correlation (an inverse relationship) between measured pH and calculated H^+. At a normal pH of 7.4, H^+ is 40 nEq/L. When pH is between 7.2 and 7.55, there is a 0.01 change from 7.4 pH in the opposite direction for every 1 nEq/L change in H^+ from 40 nEq/L. This inverse relationship allows verification of internal consistency of the data obtained. If the H^+ and pH do not correspond, one of the variables has been measured incorrectly, data have been recorded erroneously, or samples were obtained at different times.

Illustrative case report: *The patient's laboratory findings were as follows: arterial blood gas pH, 7.1; $PaCO_2$, 35 mm Hg; PaO_2, 90 mm Hg at room air; sodium (Na^+), 145 mEq/L; potassium (K^+), 5 mEq/L; chloride (Cl^-), 97 mEq/L; HCO_3^-, 12 mEq/L; blood urea nitrogen, 30 mg/dL; creatinine, 1.5 mg/dL; and glucose, 110 mg/dL.*

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When equation 1 was applied, H^+ was found to be 70 nEq/L (24 × 35 ÷ 12). This represented an increase of 30 nEq/L in the normal H^+ concentration of 40 nEq/L and corresponded to a 0.3 change in pH. Therefore, the calculated pH equaled 7.1 (7.4 – 0.3), which corresponded to the measured pH, indicating that data were internally consistent.

Step 4. Identify the primary disturbance

The next step is to determine whether the patient is acidemic (pH < 7.35) or alkalemic (pH > 7.45) and whether the primary process is metabolic (initiated by a change in HCO_3^-) or respiratory (initiated by a change in $PaCO_2$).

Table 2. Compensation formulas for simple acid-base disorders

Acid-base disorder	Compensation formula*
Metabolic acidosis	Change in $Paco_2$ = 1.2 × change in HCO_3^-
Metabolic alkalosis	Change in $Paco_2$ = 0.6 × change in HCO_3^-
Acute respiratory acidosis	Change in HCO_3^- = 0.1 × change in $Paco_2$
Chronic respiratory acidosis	Change in HCO_3^- = 0.35 × change in $Paco_2$
Acute respiratory alkalosis	Change in HCO_3^- = 0.2 × change in $Paco_2$
Chronic respiratory alkalosis	Change in HCO_3^- = 0.5 × change in $Paco_2$

*A positive or negative change represents an increase or decrease, respectively, from the normal value of 40 mm Hg for $Paco_2$ or 24 mEq/L for HCO_3^-.

Adapted from Narins and Emmett.[2]

Step 5. Calculate the expected compensation

Any alteration in acid-base equilibrium sets into motion a compensatory response by either the lungs or the kidneys. The compensatory response attempts to return the ratio between $PaCO_2$ and HCO_3^- to normal and thereby normalize pH. Compensation is predictable, and adaptive responses for the simple acid-base disorders have been quantified experimentally[2] (table 2).

Illustrative case report: *The patient was acidemic, and because both HCO_3^- and $PaCO_2$ had decreased, the primary disorder was metabolic. According to table 2, compensation for metabolic acidosis should result in a change in $PaCO_2$ equal to 1.2 times the change in HCO_3^-. Because HCO_3^- had decreased from 24 to 12, the change in $PaCO_2$ equaled about 14 mm Hg (ie, 1.2 × 12). Therefore, the expected $PaCO_2$ was 26 mm Hg (ie, 40 mm Hg – 14 mm Hg). Since the measured $PaCO_2$ of 35 mm Hg was much higher than expected, concomitant respiratory acidosis was also present.*

Step 6. Calculate the "gaps"

Calculating the various gaps can be useful in evaluation of acid-base disorders. Usually, differential diagnosis of metabolic acidosis is approached by consideration of the anion gap.

The law of electrical neutrality dictates that the number of positively charged ions (cations) in the serum must equal the number of negatively charged ions (anions) (see equation 2 in box on page 257). Serum cations include Na^+ and several unmeasured cations, such as calcium, potassium, and magnesium. Serum anions include Cl^-, HCO_3^-, and several unmeasured anions, such as phosphates, sulfates, organic anions, and proteins. Under typical

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The anion gap should be calculated in all cases of suspected acid-base disorder, because it may identify metabolic acidosis even when pH is normal or alkalemic.

circumstances, unmeasured anions exceed unmeasured cations. This difference is referred to as the anion gap,[3] which is normally 10 ± 4 mEq/L (see equation 3 in box on page 257).

In high-anion-gap metabolic acidosis, acid dissociates into H^+ and an unmeasured anion. H^+ is buffered by HCO_3^-, and the unmeasured anion accumulates in the serum, resulting in an increase in the anion gap. In non–anion gap metabolic acidosis, H^+ is accompanied by Cl^- (a measured anion); therefore, there is no change in the anion gap.

Illustrative case report: *With use of equation 3, the anion gap was found to be 36 mEq/L (145 – 97 – 12). This significant elevation indicated the presence of high-anion-gap metabolic acidosis.*

The anion gap should be calculated in all cases of suspected acid-base disorder because it may identify metabolic acidosis even when pH is normal or alkalemic. However, the anion gap does have limitations, and the distinction between high-anion-gap and non–anion gap metabolic acidosis is not always clear.[4] In addition, a normal anion gap does not exclude the presence of an unmeasured anion (eg, lactate).[5] Nevertheless, significant elevation in the anion gap should prompt investigation for underlying metabolic acidosis.[6] Major causes of metabolic acidosis according to anion gap are discussed later.

The delta anion gap can be used to detect the presence of additional acid-base disorders in patients who present with high-anion-gap metabolic acidosis.[7] This measurement (see equation 4 in box on page 257) assesses elevation of the anion gap relative to the decrease in HCO_3^-. Normally, the delta anion gap averages between 1 and 1.6. A value of less than 1 indicates that HCO_3^- has decreased out of proportion to elevation of the anion gap and suggests the presence of non–anion gap metabolic acidosis. A delta anion gap value exceeding 1.6 indicates the anion gap has increased out of proportion to the rise in HCO_3^- and suggests the presence of a concomitant metabolic alkalosis.

Illustrative case report: *With use of equation 4, the delta anion gap was found to be about 2.2 ([36 – 10] ÷ [24 – 12]). This value exceeded 1.6, indicating the presence of an additional metabolic alkalosis.*

Other gaps that can be useful in evaluating acid-base disorders are the osmole gap and the urine anion gap, both of which are discussed in the following text.

Metabolic acidosis

Metabolic acidosis is characterized by a decrease in serum HCO_3^- and pH. In general, this decrease occurs through either accumulation of acid in or loss of alkali from the body. Major causes of metabolic acidosis fall into two general categories: high anion gap and non–anion gap.

High anion gap

Causes of high-anion-gap metabolic acidosis can be further divided into (1) acidosis with an organic source (ie, lactic acidosis, ketoacidosis [whether diabetic, alcoholic, or starvation], and renal failure) and (2) acidosis resulting from ingestion of a toxin (eg, methanol, ethylene glycol, salicylate).

Organic acidosis: Lactic acidosis is believed to be the most common cause of metabolic acidosis among hospitalized patients.[8,9] It is defined by a serum lactate concentration of at least

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5 mEq/L in the presence of metabolic acidosis and represents disruption of the normal balance between lactate production and utilization. Tissue hypoxia, resulting from either increased oxygen demand or decreased oxygen delivery, is the most common cause of clinically significant lactic acidosis. Clinical features include signs of shock and organ hypoperfusion (eg, tachycardia, tachypnea, hypotension, decreased urine output, decreased mentation).

Ketoacidosis, from either uncontrolled diabetes mellitus[10] or alcohol ingestion in conjunction with poor dietary intake,[11] can cause high-anion-gap metabolic acidosis. Insulin deficiency and glucagon excess enable release of free fatty acids from fat cells, which are then metabolized to the ketoacids acetoacetate and ß-hydroxybutyrate. These ketones serve as an alternative source of energy. They also cause an increase in the anion gap because they are unmeasured anions. Both alcoholic ketoacidosis and diabetic ketoacidosis can cause profound elevation in the anion gap, whereas starvation ketoacidosis usually does not raise the anion gap above 18 mEq/L.[12]

A clinical feature of ketoacidosis is a sweet odor to the breath, which is caused by acetone. In addition, patients who have diabetic ketoacidosis can present with polyuria, polydipsia, weight loss, volume depletion secondary to osmotic diuresis, and altered mental status secondary to the hyperosmolar state.

Diagnosis is aided by means of the nitroprusside ketone reaction (Acetest), which detects acetone and acetoacetate in the serum. However, the nitroprusside ketone reaction does not detect ß-hydroxybutyrate, which makes

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Formulas for calculating laboratory values in acid-base disorders

Equation 1. Modified Henderson-Hasselbalch equation, to check validity of laboratory measurements obtained

$H^+ = 24 \times PaCO_2 \div HCO_3^- = 40$ nEq/L

Equation 2. Law of electrical neutrality (ie, number of cations in serum must equal number of anions)

$Cl^- + HCO_3^-$ + unmeasured anions = Na^+ + unmeasured cations

Equation 3. Anion gap: difference between unmeasured anions and unmeasured cations (normal = 10 ± 4 mEq/L)

Anion gap = $Na^+ - Cl^- - HCO_3^-$

Equation 4. Delta anion gap: elevation of anion gap relative to decrease in HCO_3^- (normal = 1 to 1.6)

Delta anion gap = (anion gap – 10) ÷ (24 – HCO_3^-)

Equation 5. Osmole gap: difference between measured serum osmolarity and calculated osmolarity (normal = 10 to 20 mOsm/L)

Osmole gap = measured serum osm – calculated osm

Equation 6. Calculated osmolarity

Calculated osm (mOsm/L) = (2 × Na^+) + (glucose ÷ 18) + (blood urea nitrogen ÷ 2.8) = 275 to 290 mOsm/L

Equation 7. Law of electrical neutrality for urine anion gap (ie, number of anions in urine must equal number of cations)

Unmeasured anions + Cl^- = unmeasured cations + Na^+ + K^+

Equation 8. Urine anion gap: unmeasured anions – unmeasured cations (normal = –20 to 0 mEq/L)

Urine anion gap = $Na^+ + K^+ - Cl^-$

up 75% of the ketones in diabetic ketoacidosis and 90% of the ketones in alcoholic ketoacidosis. Therefore, nitroprusside testing may underestimate the degree of ketosis.

Toxin ingestion: A variety of toxins can lead to high-anion-gap metabolic acidosis. One such toxin is methanol (wood alcohol), which is a component of several common household products (eg, shellac, varnish, automotive fluids).[13] Methanol is metabolized to formaldehyde and formic acid, the latter dissociating into H^+ and an unmeasured anion (formate). Clinical features of methanol intoxication include weakness, nausea, vomiting, decreased vision, and altered mental status.

Ethylene glycol is a component of antifreeze and some solvents. Its toxic metabolites include glycolic acid and oxalic acid, both of which dissociate to H^+ and unmeasured anions. Clinical features of ethylene glycol intoxication vary depending on the timing after ingestion. Neurologic symptoms predominate early on, followed by cardiopulmonary symptoms and then acute renal failure. In patients with ethylene glycol intoxication, urine may exhibit fluorescence under Wood's light, and urinalysis may reveal characteristic envelope-shaped calcium oxalate crystals.

Serum levels of both methanol and ethylene glycol should be measured in patients who present with high-anion-gap metabolic acidosis and suspected toxin ingestion. However, depending on the turnaround time for results, other laboratory clues may have to be used for initial diagnosis.

Clinical features of intoxication from ethylene glycol (a component of antifreeze) vary depending on the timing after ingestion.

The osmole gap (see equation 5 in box on page 257) may be helpful in diagnosing suspected toxin ingestion. It is defined as the difference between measured serum osmolarity and calculated osmolarity (see equation 6 in box on page 257). The osmole gap represents the presence of an unmeasured solute. Substances with a low molecular weight that can achieve high serum concentrations without causing death (eg, methanol, ethylene glycol, ethanol, isopropyl alcohol) can increase serum osmolarity. Both methanol and ethylene glycol can cause high-anion-gap metabolic acidosis in conjunction with an increased osmole gap.

Illustrative case report: *Further laboratory findings in the patient were as follows: measured serum osmolarity, 350 mOsm/L; lactate, 1 mEq/L; ketones, negative; and salicylate, negative. Measurements of methanol and ethylene glycol levels had not been received. Urinalysis showed calcium oxalate crystals. With use of equation 6, calculated osmolarity was found to be about 307 mOsm/L ([2 × 145] + [110 ÷ 18] + [30 ÷ 2.8]). With use of equation 5, the osmole gap was found to be 43 mOsm/L (350 – 307). The elevated osmole gap in the presence of high-anion-gap metabolic acidosis suggested ingestion of methanol or ethylene glycol. A clue to support ingestion of ethylene glycol was the presence of calcium oxalate crystals in the urine.*

In summary, this patient had a complex triple acid-base disorder: high-anion-gap metabolic acidosis secondary to ethylene glycol intoxication, respiratory acidosis, and metabolic alkalosis, probably as a result of vomiting.

Non–anion gap

Common causes of non–anion gap metabolic acidosis include diarrhea, renal tubular acidosis, and hyperalimentation. The urine anion gap can be useful in evaluation of these disorders.[14,15] As with the anion gap, the law of electrical neutrality applies to the urine anion gap, so anions must equal cations in the urine (see equation 7 in box on page 257).

Under normal circumstances,

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urine is virtually free of HCO_3^-, and the major ionic constituents are as follows:

- Cations: Na^+, K^+, Ca^{++}, Mg^{++}, NH_4^+
- Anions: Cl^-, $H_2PO_4^-$, $SO_4^=$

Of these, the measurable constituents are Na^+, K^+, and Cl^-. The levels of Ca^{++}, Mg^{++}, $H_2PO_4^-$, and $SO_4^=$ change little during an acid-base disorder and therefore do not contribute much to changes in the urine anion gap.

The urine anion gap is defined as the difference between the unmeasured anions and the unmeasured cations (see equation 8 in box on page 257). NH_4^+ is the predominant unmeasured cation, and its excretion is usually accompanied by Cl^-. Under normal circumstances, 20 to 40 mEq/L of NH_4^+ is excreted each day, and the urine anion gap has a negative value (ranging from –20 to 0 mEq/L). The normal renal response to an acid load (or loss of alkali) is an increase in renal generation of ammonia, with an increase in urine NH_4^+ excretion.

In metabolic acidosis, NH_4^+ excretion should increase dramatically if renal acidification is intact (as in diarrhea), resulting in a large negative urine anion gap (ie, –20 to –50 mEq/L). However, if a defect in renal acidification is present (eg, renal tubular acidosis), NH_4^+ excretion is impaired, and the urine anion gap is positive.

Summary

Acid-base disorders can usually be approached by following the steps outlined in the text and doing the calculations shown in the box on page 257. Clues about the underlying disorder can be obtained from history taking and physical examination. Assessment of pH, $PaCO_2$, and HCO_3^- allows determination of whether a primary metabolic or respiratory disorder is present. Calculation of the predicted compensatory response for simple acid-base disorders might suggest the presence of an additional disease process if compensation is not appropriate. Calculation of the various gaps can be helpful in differential diagnosis (ie, anion gap for diagnosis of metabolic acidosis, delta anion gap for diagnosis of high-anion-gap metabolic acidosis, and urine anion gap for diagnosis of a non–anion gap metabolic acidosis). Most acid-base problems can be solved with use of the stepwise approach described. **PGM**

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