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How to work up an adult patient with metabolic acidosis

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Abstract

Metabolic acidosis is a common complication among acutely unwell hospitalised patients. Untreated, it can result in undesirable cardiovascular, respiratory and neurological consequences. Metabolic acidosis can occur as an isolated entity or coexist with other acid–base disorders, making diagnosing the aetiology difficult. Accurate identification of the underlying cause is imperative for proper and timely management. A systematic approach can help simplify the assessment of patients and can aid in establishing the correct diagnosis, even in more complex cases. This article provides a practical, step-by-step guide for the assessment of adult patients with metabolic acidosis.

Key words: Acid–base disorders; Acidosis; Anion gap; Compensation; Metabolic acidosis; Respiratory

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Introduction

In healthy individuals, the systemic arterial pH (negative log of hydrogen ion (H^+) concentration) is generally maintained between 7.35 and 7.45 (corresponding H^+ concentration 35–45 nmol/litre). Different disease processes can cause the disruption of normal acid–base regulatory pathways. Accumulation of excess acids can lead to the development of acidosis, which can either be of primary respiratory or metabolic origin. Metabolic acidosis is commonly encountered by hospital doctors caring for acutely ill patients. The diagnosis can often be challenging, especially in more complex cases. Understanding the underlying processes causing the development of metabolic acidosis and rationale for appropriate investigations can help treating physicians properly work up patients and make a precise diagnosis. This article provides a practical, step-by-step guide for assessing adults with metabolic acidosis (Figure 1), explaining the basic pathophysiology and reasoning for the investigative process.

An overview of acid–base balance

A normal adult diet contains 70–100 mmol of acid (H^+) per day. Moreover, a large amount of acid is generated daily, including carbon dioxide (CO_2), organic acids (lactic acid and citric acid) and non-volatile acid (mostly sulphuric acid) resulting from the metabolism of sulphur-containing amino acids. Acid–base balance is tightly regulated in a healthy state, maintaining pH within physiological limits.

Intracellular and extracellular buffers (haemoglobin, calcium carbonate, calcium phosphate, bicarbonate (HCO_3)), elimination of excess CO_2 by the respiratory system, metabolism of the organic acids to neutral molecules, and reabsorption of HCO_3 and excretion of H^+ by the kidneys (combining it with urinary buffers such as phosphate or with ammonia to form ammonium) all play a crucial role in maintaining the normal acid–base balance.

Acidosis and alkalosis

The basic concept of acidosis and alkalosis can be understood by the equation $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3$. All sections of this equation exist in equilibrium, and changes to one section lead to corresponding changes in the others. H^+ and HCO_3 combine to form

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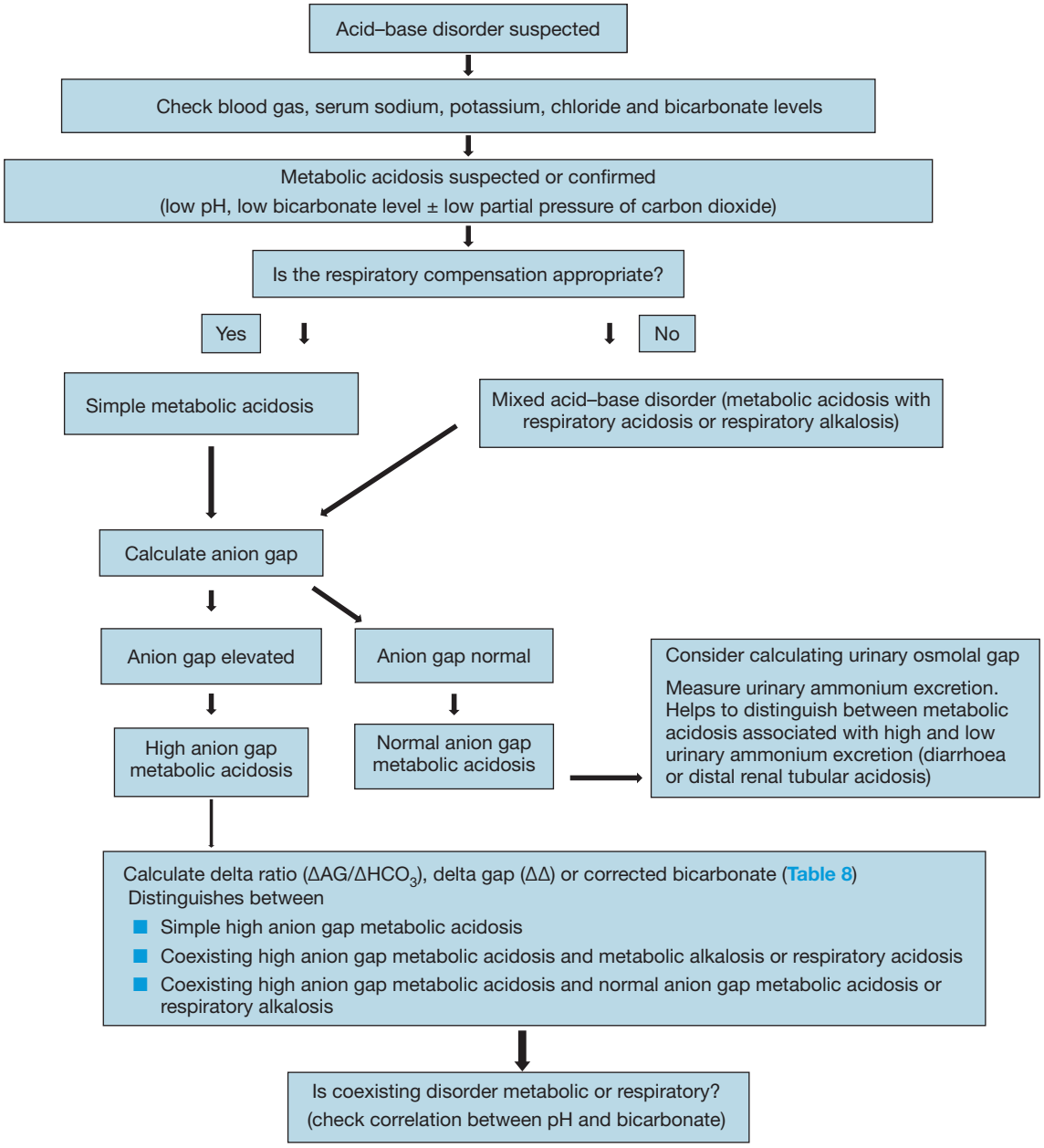

Figure 1. Overview of assessment of a patient with metabolic acidosis.

carbonic acid (H_2CO_3), which in the presence of enzyme carbonic anhydrase converts to CO_2 and water (H_2O). Similarly, hydration of CO_2 forms H_2CO_3 which subsequently generates H^+ and HCO_3.

Increased CO_2 concentration (mainly as a result of hypoventilation) shifts the equation to the right, leading to a rise in the concentration of H^+ and a fall in the pH, causing respiratory acidosis. Conversely, a fall in CO_2 concentration (primarily as a result of hyperventilation) leads to a corresponding fall in H^+ concentration, causing respiratory alkalosis.

The addition of H^+ leads to a corresponding fall in HCO_3 concentration and pH, leading to metabolic acidosis. Loss of HCO_3 leads to a rise in H^+ concentration with the same result. A decrease in H^+ concentration or accumulation of HCO_3 has corresponding inverse effects on HCO_3 and H^+ concentrations: the pH rises, resulting in metabolic alkalosis.

Respiratory and metabolic compensation

In states of acid–base abnormalities, regulation of pCO_2 by the respiratory system and HCO_3 concentration by the kidneys is the fundamental compensatory process that attempts to return the pH back towards the normal level. Primary respiratory disorders stimulate a

compensatory metabolic response and primary metabolic disorders invoke a compensatory respiratory response. The relationship between pH, CO_2, and HCO_3 can be depicted by the Henderson–Hasselbach equation pH=6.10 + log ([HCO_3] ÷ [0.03 x PCO_2]). PCO_2 is the partial pressure of CO_2 in arterial blood.

Considering the equation $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3$ again, a rise in pCO_2 will shift the equation towards the right, resulting in a rise in HCO_3 concentration. A fall in pCO_2 will lead to a fall in HCO_3 concentration. Changes in HCO_3 will improve the pH towards normal values (metabolic compensation).

Likewise, increased H^+ concentration will shift the equation to the left, leading to increased pCO_2. This will stimulate hyperventilation leading to the elimination of excess CO_2 and thus move the pH towards normal. On the other hand, reduced H^+ concentration leads to the reduction of pCO_2. This will cause hypoventilation leading to retention of CO_2 and reducing the pH towards the upper normal value (respiratory compensation).

Respiratory compensation occurs quickly (minutes to hours), while metabolic compensation takes time to develop (hours to days). It is important to remember that the compensation is never complete, except for prolonged chronic respiratory acidosis, and the pH never normalises or goes in the opposite direction as a result of the compensatory processes alone (Thomas and DuBose, 2018). In such a situation, the possibility of a mixed acid–base disorder should be considered.

Simple and mixed acid–base disorders

An acid–base disorder is considered simple when a single primary disturbance (respiratory acidosis or alkalosis, or metabolic acidosis or alkalosis) occurs as a standalone entity. Acid–base disorders are considered mixed or complex when two or more independent primary disorders coexist simultaneously (not just as a result of compensatory responses), for example, coexisting respiratory acidosis and metabolic acidosis in a patient with chronic obstructive pulmonary disease and diabetic ketoacidosis.

When to suspect the presence of a mixed disorder

Table 1 shows the relationship between pH, H^+, and PCO_2 in simple acid–base disorders. The compensatory response will move the HCO_3 in the same direction as PCO_2 in primary respiratory disorders, and the compensatory response will move PCO_2 in the same direction as HCO_3 in primary metabolic disorders. Changes in HCO_3 and PCO_2 in the opposite direction usually indicate the presence of a mixed disorder (Thomas and DuBose, 2018).

Simple bedside guide for estimating the expected compensation

The degree of metabolic and respiratory compensations is predictable. Any change outside the expected values indicates the presence of a mixed disorder. Table 2 shows the expected compensatory changes in HCO_3 or PCO_2 in simple acid–base disorders. It can help clinicians make a quick bedside decision while dealing with an acutely unwell patient with acid–base disorder.

Metabolic acidosis

Definition and classification

Metabolic acidosis is a pathological process characterised by the accumulation of hydrogen ions (H^+) in conjunction with reduced serum bicarbonate (HCO_3) concentration. Base excess on blood–gas analysis is typically low (≤2 mmol/litre), accounting for the loss of HCO_3. Respiratory compensation, when established, usually leads to a fall in PCO_2 (Tables 1 and 2).

Metabolic acidosis can exist as an isolated condition (simple metabolic acidosis) or in combination with other acid–base abnormalities (mixed metabolic acidosis). Furthermore, it can be acute or chronic and can also be categorised based on the anion gap into high anion gap metabolic acidosis and normal anion gap metabolic acidosis (Thomas and DuBose, 2018).

Pathogenesis

Metabolic acidosis can occur because of increased acid production (eg ketoacidosis and lactic acidosis), ingestion or infusion (eg salicylate poisoning), loss of bicarbonate (eg

Table 1. Relationship between pH, bicarbonate and partial pressure of carbon dioxide in acid–base disorders

	pH	Bicarbonate (HCO_3)	Partial pressure of carbon dioxide (PCO_2)	
Metabolic acidosis	↑	↓	N or ↓	In primary metabolic disorders pH and PCO_2 move in the same direction
Metabolic alkalosis	↓	↑	N or ↑	
Respiratory acidosis	↓	N or ↑	↑	In primary respiratory disorders pH and PCO_2 move in opposite directions
Respiratory alkalosis	N or ↑	N or ↓	↓	

Table 2. Bedside guide for expected metabolic and respiratory compensation

	Bicarbonate (HCO_3)	Partial pressure of carbon dioxide (PCO_2)
Metabolic acidosis	↓1 unit (mmol/litre)	↓ 0.13 units kPa (1 unit mmHg)
Metabolic alkalosis	↑ 2 units (mmol/litre)	↑ 0.13 units kPa (1 unit mmHg)
Acute respiratory acidosis	↑ 1 unit (mmol/litre)	↑ 1.3 units kPa (10 units mmHg)
Chronic respiratory acidosis	↑ 4 units (mmol/litre)	↑ 1.3 units kPa (10 units mmHg)
Acute respiratory alkalosis	↓ 2 units (mmol/litre)	↓1.3 units kPa (10 units mmHg)
Chronic respiratory alkalosis	↓ 4 units (mmol/litre)	↓1.3 units kPa (10 units mmHg)

1 kPa=7.5 mmHg

diarrhoea and renal tubular acidosis), or reduced renal acid excretion (eg acute and chronic renal failure).

Clinical consequences

Untreated metabolic acidosis can lead to several cardiovascular, musculoskeletal and endocrine complications. It also suppresses immunity, worsens systemic inflammation and increases mortality (Table 3).

Initial workup and role of blood–gas analysis

Measurement of pH, PCO_2, HCO_3 and other electrolytes is essential for proper evaluation of patients suspected to have metabolic acidosis (Table 4). A blood gas sample is a crucial initial investigation, especially in critically ill patients with mixed disorders. In patients with simple metabolic acidosis, pH and HCO_3 are low. PCO_2 can be normal initially but usually falls subsequently as a result of respiratory compensation.

Arterial vs venous blood gas analysis

Arterial blood gas analysis is preferable but is not always possible. When an arterial sample cannot be acquired safely, a venous blood gas might also be appropriate for evaluations, but it is important to remember that venous blood gas values do not correspond to arterial blood gas values. The venous pH is approximately 0.03–0.05 units lower than the arterial pH, venous HCO_3 concentration is usually 2–3 mmol/litre higher and the venous PCO_2 is approximately 0.5–1 kPa (4–8 mmHg) more than the arterial value (Brandenburg and Dire, 1998; Gokel et al, 2000). These relationships should be considered while using venous blood gas for assessment of metabolic acidosis.

Pitfalls of arterial blood gas analysis

The HCO_3 value obtained from arterial blood–gas analysis is calculated using the Henderson–Hasselbach equation from the measured pH and PCO_2. Care should be taken to compare the calculated value with measured HCO_3 on laboratory electrolyte analysis of a venous blood sample. The two values should not vary more than 2 mmol/litre (Thomas and DuBose, 2018). Both arterial and venous samples should be obtained simultaneously. Heparinisation required to

Table 3. Complications of metabolic acidosis	
System	**Complications**
Cardiovascular	Myocardial depression
	Vasodilatation
	Cardiac arrhythmias
	Hypotension
Musculoskeletal	Muscle protein catabolism and muscle wasting
	Increased bone resorption
	Osteoporosis and increased fracture risk
Endocrine	Insulin resistance
Others	Suppressed immunity
	Worsened systemic inflammation
	Increased mortality risk
	Progression of kidney disease

Table 4. Normal values of parameters involved in acid–base assessment	
Parameter	**Normal range**
pH	7.35–7.45
Partial pressure of carbon dioxide	4.7–6 kPa (35–45 mmHg)
Bicarbonate	22–26 mmol/litre
Hydrogen ions	35–45 nmol/litre

analyse blood samples in an arterial blood gas machine may dilute the sample and affect results. Therefore, use of excessive heparin should be avoided while taking the arterial blood sample.

Identification of underlying aetiology: role of the anion gap

Measuring the anion gap is the key to identifying the underlying cause and should be calculated in all patients with metabolic acidosis. Both high anion gap and normal anion gap metabolic acidosis have specific aetiologies, which helps narrow the differential diagnosis and plan further management.

The anion gap

Generally, in healthy individuals, the total amount of cations (positively charged ions) is equal to the total amount of anions (negatively charged ions), and electroneutrality is maintained. However, not all cations and anions are measured by routine laboratory tests. The number of unmeasured anions far exceeds the unmeasured cations, and this is the basis of the anion gap (Figure 2).

Typically, measured cations present in the plasma are sodium (Na), potassium (K), calcium (Ca) and magnesium (Mg). Na is by far the most abundant cation, and for anion gap calculation purposes, all non-Na cations (except for K in some countries) are considered unmeasured.

The measured anions are chloride (Cl) and HCO_3. The negative charges on albumin, lactate, sulphate, phosphate and other organic acids are unmeasured anions (Yaqoob and McCafferty, 2017).

Calculation of anion gap

The anion gap can be calculated using the following formula $AG = Na - (Cl + HCO_3)$ (Winter et al, 1990). The normal anion gap range is 4–12 mmol/litre. For example, if a

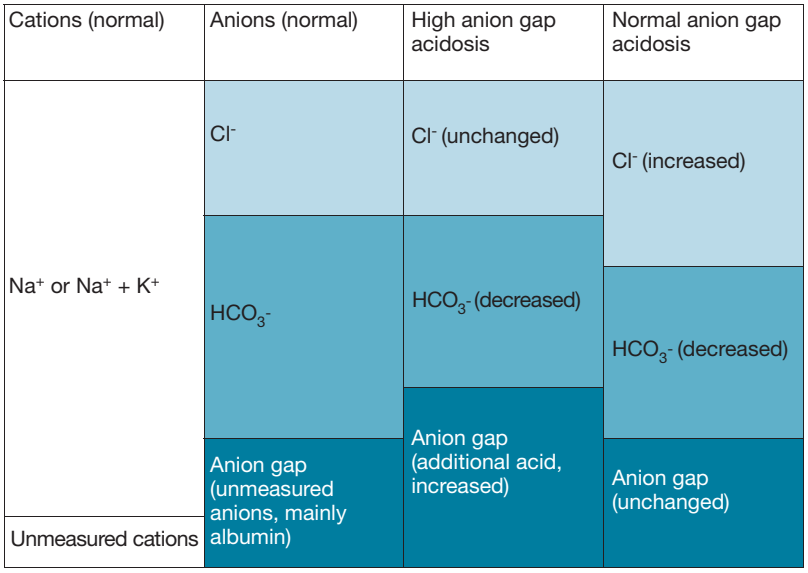

Figure 2. Measured ionic composition of plasma and anion gap. Total positive charge = total negative charge (electroneutrality).

patient has Na 144 mmol/litre, K 3.9 mmol/litre, Cl 102 mmol/litre and HCO_3 16 mmol/litre the anion gap would be 26 mmol/litre (144 – [102 + 16]). The calculated anion gap in this case is higher than the normal upper limit of 12 mmol/litre, thus the patient has a high anion gap.

In certain centres, K is added to the formula (AG = [Na + K] – [Cl+$HC0_3$]). The normal anion gap range using this formula will increase by 4 mmol/litre (normal range 8–16 mmol/litre).

Correction of calculated anion gap for albumin

Albumin makes up the largest portion of all unmeasured anions. A fall in the plasma albumin concentration from the normal value of 40 g/litre to 20 g/litre may reduce the anion gap by 6 mmol/litre because each 1 g/litre of albumin has a negative charge of 0.2–0.28 mmol/litre (Winter et al, 1990). Generally, a fall in serum albumin by 1 g/litre from a normal value of 45 g/litre reduces anion gap by 0.25 mmol/litre (corrected anion gap = measured anion gap + 0.25 × (45 − measured albumin (g/litre)).

For example, if the measured anion gap in a patient with serum albumin of 20 g/litre is 10 mmol/litre, the corrected anion gap will be 16.25 mmol/litre (10 + 2.5 x [45–20]). This patient has a high anion gap (>12 mmol/litre). Similarly, the anion gap must be adjusted using the same correction factor in patients with hyperalbuminaemia (Feldman et al, 2005).

Causes of high anion gap

High anion gap metabolic acidosis most often suggests the accumulation of non-Cl acids such as phosphates, sulphates, lactate, ketoacids and salicylate (Table 5). The HCO_3 level falls, but Cl remains unchanged. The additional acids usually have a negative charge and contribute to unmeasured anions, increasing the anion gap (Figure 2). High anion gap almost always indicates the presence of metabolic acidosis, even when the HCO_3 level remains normal or increases as a result of a coexisting acid–base disorder such as respiratory acidosis or metabolic alkalosis.

Diarrhoea commonly causes normal anion gap metabolic acidosis. However, in rare cases of severe diarrhoea, the patient can develop high anion gap metabolic acidosis as a result of severe dehydration leading to increased lactate production, hyperphosphatasaemia, hyperproteinaemia and reduced kidney function (Wang et al, 1986).

The anion gap also increases if non-acid unmeasured anions such as phosphate and IgA paraproteins accumulate in excess (Kraut and Madias, 2007). Moreover, a severe reduction in unmeasured cations (K, Ca and Mg) might increase the anion gap without metabolic acidosis.

Table 5. Cause of metabolic acidosis with a high anion gap	
Increased acid production	Lactic acidosis (type A, type B, D-lactate)
	Ketoacidosis (diabetic, alcoholic, starvation)
Decreased renal excretion	Renal failure (acute and chronic)
Drugs and toxins	Salicylates
	Ethylene glycol
	Propylene glycol
	Methanol
Others	Severe diarrhoea (cholera)

Causes of normal anion gap

Normal anion gap metabolic acidosis suggests renal or gastrointestinal HCO_3 loss or reduced renal acid excretion in the setting of normal kidney function (Table 6). Plasma HCO_3 decreases, Cl increases and the anion gap remains unchanged (Figure 2). Consequently, these disorders are also referred to as hyperchloraemic metabolic acidosis.

Rarely, infusion of a large volume of chloride-rich fluids such as 0.9% saline or ingestion or infusion of compounds that can generate hydrogen chloride can also lead to the development of normal anion gap metabolic acidosis. The equal amount of Cl replaces HCO_3 with no effect on the anion gap, leading to hyperchloraemic metabolic acidosis (Eisenhut, 2006).

Loss of potential HCO_3 (ketoacids) in the urine in response to fluid treatment with 0.9% saline in diabetic ketoacidosis can also convert the initial high anion gap metabolic acidosis into normal anion gap metabolic acidosis during the recovery phase (Oh et al, 1978).

Causes of low anion gap

Low anion gap can be caused by hypoalbuminaemia, marked hypercalcaemia, hypermagnesaemia, hyperkalaemia or hyponatraemia. Dilutional states, IgG paraproteinemia, or bromide, lithium or iodide intoxication may also cause a low anion gap (Emmett and Narins, 1977).

Further assessment and investigations to reach a precise diagnosis

The approach mentioned above will help narrow down the possible differential diagnosis, and further assessment to reach the precise diagnosis is relatively straightforward. Usually,

Table 6. Cause of metabolic acidosis with a normal anion gap	
Increased gastrointestinal HCO_3 loss	Diarrhoea
	External pancreatic or small bowel drainage
	Ureteral diversion (jejunal loop, ileal loop)
Increased renal HCO_3 loss	Proximal (type 2) renal tubular acidosis
	Acetazolamide therapy
	Tubular damage (drugs, heavy metals, paraproteins)
	Post-treatment ketoacidosis
Decreased renal H+ excretion	Distal (type 1) renal tubular acidosis
	Type 4 renal tubular acidosis (aldosterone deficiency)
	Moderate kidney dysfunction (estimated glomerular filtration rate >15–20 ml/min/1.73m^2)
Others	Ingestion of ammonium chloride
	Hyperalimentation
	Rapid administration of saline (expansion acidosis)

a thorough history and clinical examination will be enough to determine the possible aetiology. Measurement of renal function, urinary pH, blood glucose level, serum lactate, blood or urinary ketones, salicylate level, serum ethanol level, serum osmolality, and plasma osmolal gap (large osmolal gap suggests recent methanol, ethylene glycol, or isopropyl alcohol exposure) can be considered in appropriate clinical setting.

Mixed metabolic acidosis and respiratory disorder

As discussed, respiratory compensation in metabolic acidosis is predictable, and any unexpected change in PCO_2 points towards a possible mixed disorder (metabolic acidosis plus respiratory acidosis or respiratory alkalosis). Typically, a fall in HCO_3 in metabolic acidosis is compensated by a compensatory fall in PCO_2 (Table 1). An elevated PCO_2 in this setting will indicate coexisting metabolic acidosis and respiratory acidosis.

Moreover, the expected degree of compensatory fall in PCO_2 for the degree of reduction in HCO_3 concentration in metabolic acidosis can be estimated with fair certainty different using formulas (Tables 2 and 7). As a general rule, in simple metabolic acidosis, each unit fall in HCO_3 below the normal is expected to be compensated by 0.13 units kPa (1 unit mmHg) fall in PCO_2. A greater than expected fall points towards mixed metabolic acidosis with respiratory alkalosis.

Similarly, if the patient has an HCO_3 of 14, the expected PCO_2 using the Winter's formula ($PCO_2 = [1.5 \times HCO_3] + 8 \pm 2$) would be 27–31 mmHg. Values below 27 or above 31 point towards mixed metabolic acidosis and respiratory alkalosis and mixed metabolic acidosis and respiratory acidosis respectively (Fulop, 1997; Thomas and DuBose, 2018).

However, there is a limit to the maximum respiratory compensation attained, and the PCO_2 cannot be reduced below 1.06–1.6 kPa (8–12 mmHg) in severe metabolic acidosis (HCO_3 <6 mmol/litre).

Limitations of serum HCO_3 in mixed metabolic and respiratory disorders

While low HCO_3 indicates the presence of metabolic acidosis in simple cases, the HCO_3 level in more complex cases with mixed metabolic acidosis might be normal or even high, eg when metabolic acidosis coexists with respiratory acidosis or metabolic alkalosis. In such a situation, the HCO_3 level will usually be lower than the expected level for that scenario but might remain within normal limits. Consider a patient with chronic obstructive pulmonary disease, with a high baseline HCO_3 of 34 mmol/litre as a result of metabolic compensation, who develops diarrhoea and their HCO_3 level falls to 25 mmol/litre. Although the HCO_3 has stayed within normal limits, it is much lower than the baseline, and the patient has metabolic acidosis with chronic respiratory acidosis. Similarly, HCO_3 levels can be low as a result of metabolic compensation in cases of respiratory alkalosis. Hence HCO_3 level alone is not always enough to diagnose metabolic acidosis, and other criteria are needed to establish a clinical diagnosis.

Mixed metabolic disorders

Under certain situations, metabolic acidosis can coexist with metabolic alkalosis, or both high anion gap metabolic acidosis and normal anion gap metabolic acidosis can be present simultaneously in the same patient. The following sections explain how to make the distinction in such complex scenarios.

Table 7. Predicted partial pressure of carbon dioxide in metabolic acidosis

pCO_2 (mmHg) = 1.5 x HCO_3 + 8 ± 2 (Winter's formula)
pCO_2 (mmHg) is approximate the decimal digits of the arterial pH
pCO_2 (mmHg) = HCO_3 + 15
HCO_3 = bicarbonate, 1 kPa=7.5 mmHg

The concept of delta anion gap, delta HCO_3 and corrected HCO_3

In simple high anion gap metabolic acidosis, the change in anion gap (ΔAG) is usually proportional to the change in HCO_3 (ΔHCO_3). For example, if the anion gap increases by 5 units, the HCO_3 will reduce by 5 units. In other words, ΔAG (measured anion gap – normal anion gap mmol/litre) = ΔHCO_3 (normal HCO_3 [ie 24 mmol/litre] – measured HCO_3). Unequal results signify the presence of mixed metabolic disorders and can be described using the formulas given in Table 8 (Rastegar, 2007; Thomas and DuBose, 2018). Physicians should familiarise themselves with one of these equations and use it in the clinical setting. The relationship between pH and PCO_2 can clarify whether the primary problem is respiratory or metabolic (Figure 2).

Mixed high anion gap metabolic acidosis and metabolic alkalosis

Consider a patient with a pH 7.25, HCO_3 11 mmol/litre, PCO_2 25 mmHg, Na 142 mmol/litre and Cl 80 mmol/litre. The anion gap is 51 mmol/litre (142 – [11 + 80]), ΔAG is 39 (51 – 12) and ΔHCO3 is 13 (24–11). Using the formulas in Table 8, $\Delta AG:\Delta HCO_3$ is 3 (39/13), ΔΔ is 26 (39 – 13), and corrected HCO_3 is 50 (39 + 11). Using any of the equations, the patient has mixed high anion gap metabolic acidosis with metabolic alkalosis or respiratory acidosis. Both pH and PCO_2 are low (moving in the same direction), so the primary problem is metabolic, and the patient has simultaneous high anion gap metabolic acidosis and metabolic alkalosis.

Mixed high anion gap metabolic acidosis and normal anion gap metabolic acidosis

The patient has a pH 7.15, HCO_3 7 mmol/litre, PCO_2 16 mmHg, Na 142 mmol/litre, and Cl 115 mmol/litre. Anion gap is 20 mmol/litre (142 – [115 + 7]), ΔAG is 8 (20 – 12) and ΔHCO_3 is 17 (24 – 7).

Using the above-mentioned equations, $\Delta AG:\Delta HCO_3$ is 0.47 (8/17), ΔΔ is -9 (8 – 17) and corrected HCO_3 is 15 (8 + 7). The patient has mixed high anion gap metabolic acidosis with normal anion gap metabolic acidosis or respiratory alkalosis. Both pH and PCO_2 are low (moving in the same direction), so the primary problem is metabolic, and the patient has coexisting high anion gap metabolic acidosis and normal anion gap metabolic acidosis.

Differentiation between causes of normal anion gap metabolic acidosis

The concept of urinary osmolal gap

Calculation of urinary anion gap or urinary osmolal gap provides an indirect measure of urinary ammonium (NH_4) excretion and might be helpful in evaluating normal anion gap metabolic acidosis. Urinary anion gap has some limitations and, at times, might not correctly represent urinary NH_4 excretion. As a result, urinary osmolal gap is preferred and is discussed here.

Urinary osmolal gap is the difference between measured and calculated urine osmolality. Usually, urinary osmolality is a product of NH_4, Na, K, urea and glucose and can be measured in the laboratory using the osmometer. The urine osmolality is calculated using the following formula (Dyck et al, 1990).

Calculated urine osmolality (mosmol/kg) = 2 x [Na + K]) + urea + glucose

The Na and K concentrations are multiplied by 2 to account for the osmotic contributions of their dissociated anions. Urinary NH_4 is generally not measurable and does not form part of the equation to calculate urine osmolality. Hence the measured urine osmolality will be higher than the calculated urine osmolality, and the difference between the two (urinary osmolal gap) will provide an indirect estimate of urinary NH_4.

Patients with type 1 (distal) or type 4 renal tubular acidosis have reduced urinary NH_4 excretion and consequently will generally have a urinary osmolal gap of less than 150 mosmol/kg (suggestive but not diagnostic). On the other hand, normal anion gap metabolic acidosis caused by chronic diarrhoea will have increased urinary NH_4 excretion leading to increased urinary osmolal gap, usually more than 400 mosmol/kg. Metabolic acidosis caused by inhalation of toluene and other disorders in which the renal response to acidosis remains intact will have similar findings (Dyck et al, 1990).

Table 8. Formulas for evaluation high anion gap metabolic acidosis and interpretation of results

Formulas	Interpretation
Delta ratio ($\Delta AG:\Delta HCO_3$)	<1 = high anion gap metabolic acidosis + normal anion gap metabolic acidosis or respiratory alkalosis >1.6 = high anion gap metabolic acidosis + metabolic alkalosis or respiratory acidosis
Delta gap ($\Delta\Delta=\Delta AG - \Delta HCO_3$)	>0 [+ve value] = high anion gap metabolic acidosis + metabolic alkalosis or respiratory acidosis <0 [-ve value] = high anion gap metabolic acidosis +normal anion gap metabolic acidosis or respiratory alkalosis
Corrected HCO_3 (ΔAG + measured HCO_3	>24 = high anion gap metabolic acidosis + metabolic alkalosis or respiratory acidosis <24 = high anion gap metabolic acidosis + normal anion gap metabolic acidosis or respiratory alkalosis

Although in most cases, the differentiation between renal tubular acidosis and a non-renal tubular acidosis cause of normal anion gap metabolic acidosis can be made by clinical presentation and analysis of electrolytes and urinary pH, a distinction can be difficult in certain situations. For example, both distal renal tubular acidosis and severe diarrhoea can cause normal anion gap metabolic acidosis, hypokalaemia and urinary pH above 5.5. Calculation of urinary osmolal gap might be helpful in this case.

Conclusions

A systematic approach can help establish a correct diagnosis in patients with metabolic acidosis. This approach is instrumental in complex cases where multiple acid–base disorders coexist.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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Key points

- Simultaneous measurement of serum electrolytes and blood gas (arterial or venous) is needed to assess suspected metabolic acidosis properly.
- HCO_3 and electrolyte values obtained from blood gas analysis should be correlated with the formal laboratory values to ensure accuracy.
- The respiratory compensation should be checked to see if it is appropriate.
- Calculate the anion gap and ensure it is corrected for albumin.
- If the anion gap is high, calculate delta ratio, delta gap or corrected bicarbonate.
- If the patient has normal anion gap metabolic acidosis, consider calculating the urinary osmolal gap.

Curriculum checklist

This article addresses the following requirements from the general internal medicine curriculum:

- Managing an acute unselected take
- Managing an acute specialty-related take
- Managing medical problems in patients in other specialties and special cases.

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