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Understanding Acid-Base Disorders

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<i>Case for consideration</i>			
<i>A 25 year old mechanic is admitted in a very confused and drowsy state. His initial laboratory results are listed below. What diagnoses should be considered?</i>			
	<i>Reference Range</i>		<i>Reference Range</i>
<i>pH 7.1</i>	<i>7.35-7.45</i>	<i>Na⁺ 136 mmol/L</i>	<i>136-145</i>
<i>PaO₂ 13.4 kPa</i>	<i>11.0-14.0</i>	<i>K⁺ 3.8 mmol/L</i>	<i>3.5-5.3</i>
<i>PaCO₂ 2.5 kPa</i>	<i>4.5-6.0</i>	<i>Cl⁻ 95 mmol/L</i>	<i>95-108</i>
<i>Bicarbonate 5.3 mmol/L</i>	<i>22-29</i>	<i>Total CO₂ 6 mmol/L</i>	<i>22-29</i>
<i>Lactate 1.2 mmol/L</i>	<i>0.6-2.4</i>	<i>Urea 4.2 mmol/L</i>	<i>2.5-7.8</i>
<i>Ketones <1 mmol/L</i>	<i>Depends on context</i>	<i>Creatinine 92 µmol/L</i>	<i>40-110</i>
		<i>eGFR >60 mL/min/1.73m²</i>	<i>>60</i>

INTRODUCTION

The accurate interpretation of laboratory tests in patients with acid-base disorders is critical for understanding pathophysiology, making a diagnosis, planning effective treatment and monitoring progress. This is an important topic particularly for junior medical staff who may encounter acid-base problems outside normal working hours when patients become acutely unwell. These clinical situations may be a source of confusion particularly because of the variety of terms used to describe and classify acid-base disorders. In this article, we aim to provide the reader with an overview of the key concepts necessary for developing a good working understanding of acid-base disorders that commonly present in clinical medicine. We start with some acid-base disorder definitions and then provide a series of case vignettes to illustrate the key points.

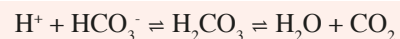
DEFINITIONS

- Acidaemia** An arterial pH below the normal range (pH<7.35).
- Alkalaemia** An arterial pH above the normal range (pH>7.45).
- Acidosis** A process lowering pH. This may be caused by a fall in serum bicarbonate and/or a rise in the partial pressure of carbon dioxide (PaCO₂).
- Alkalosis** A process raising pH. This may be caused by a rise in serum bicarbonate and/or a fall in PaCO₂.

ACID-BASE HOMEOSTASIS

Like temperature, blood pressure, osmolality and many other physiological parameters, the human body strives to keep its acid-base balance within tightly controlled limits. It is not the aim of this article to review in detail the physiology of acid-base homeostasis, but to provide a working knowledge of some key concepts that will help in the interpretation of results encountered commonly in clinical practice. More detailed free text reviews of acid-base homeostasis are available¹⁻⁵.

A buffer is a solution that resists a change in pH. There are many different buffer systems in the body, but the key one for understanding most acid-base disorders is the bicarbonate system present in the extracellular fluid. Like any buffer, this system comprises a weak acid (in this case carbonic acid, H₂CO₃) and its conjugate base (the bicarbonate ion, HCO₃⁻), which exist in a dynamic equilibrium as shown in Equation 1⁶:



Equation 1

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The acidity of a solution is governed by the concentration of hydrogen ions (H^+) present. If a disease process results in an increase in the concentration of hydrogen ions, one would expect the body to become more acidic. However, the bicarbonate buffer system resists this change because the excess of hydrogen ions drives the reaction in Equation 1 to the right: hydrogen ions react with and “consume” bicarbonate ions and any change in acidity is minimised. This process requires an adequate supply of bicarbonate ions. The kidneys are vital organs in acid-base balance as they can both generate “new” bicarbonate buffer and reclaim filtered bicarbonate in the proximal tubules (Figure 1).

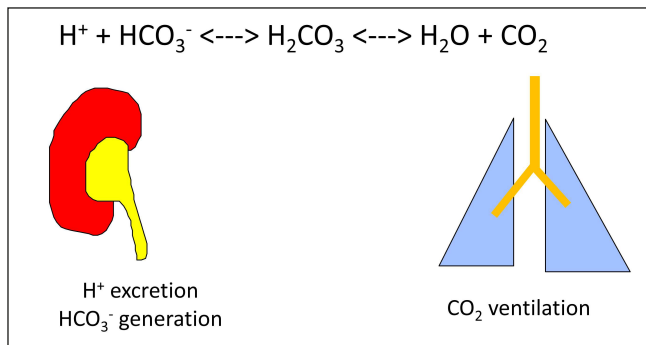


Fig 1. Acid-base balance is maintained by effective renal and respiratory homeostatic mechanisms

By rearranging and simplifying the above acid-base reaction, it is possible to derive the useful relationship shown in Equation 2:

$$H^+ \text{ is proportional to } \frac{PaCO_2}{HCO_3^-}$$

Equation 2

Equation 2 helps to illustrate how the body’s hydrogen ion concentration can be regulated by altering the ratio of CO_2 to bicarbonate. Ventilation controls the $PaCO_2$ level and the kidneys regulate the bicarbonate level (Figure 1).

This makes it easy to see that the concentration of hydrogen ions increases in two settings: an increase in $PaCO_2$ or a reduction in plasma bicarbonate. One of the functions of ventilation is the elimination of CO_2 during exhalation. If a patient is tachypnoeic, they will tend to lose CO_2 , while patients with a reduced respiratory drive will retain CO_2 . An increased concentration of hydrogen ions (an acidosis) stimulates the respiratory centre to increase the rate of breathing (exhaling more CO_2). This mechanism is another key physiological response that helps to maintain acid-base balance.

Acid-base disorders are broadly classified into problems involving metabolic and/or respiratory processes. Metabolic processes primarily direct change in the level of bicarbonate and respiratory processes primarily direct changes in $PaCO_2$ (Figure 2).

The body adapts, or compensates where there is an acid-base disturbance in an attempt to maintain homeostasis⁷.

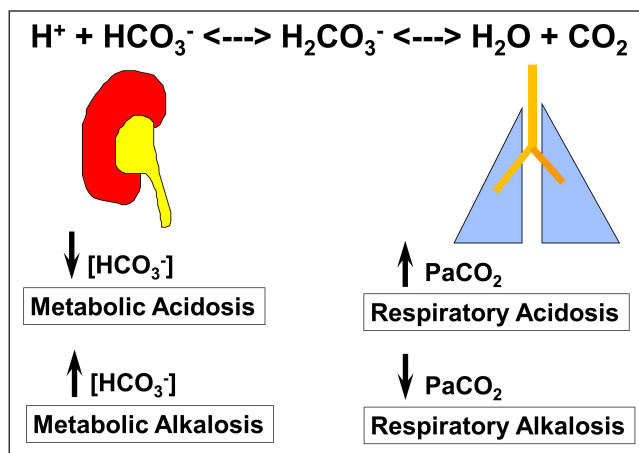


Fig 2. Changes in $PaCO_2$ level and bicarbonate concentration $[HCO_3^-]$ can help identify the nature of the acid-base disorder.

If the primary acid-base problem is metabolic, then the compensatory mechanism is respiratory. The respiratory rate is altered, usually within minutes, in an attempt to keep the hydrogen ion concentration normal. If the primary acid-base problem is respiratory, then the kidneys adapt to counteract the change by altering their handling of hydrogen ions. This process in the kidneys usually takes place over several days.

CAUSES OF ACID-BASE DISORDERS

Acid-base disorders are classified according to whether there is acidosis or alkalosis present (see pH section for details), and whether the primary problem is metabolic or respiratory (Figure 2). Bear in mind that there may be more than one problem occurring simultaneously and that the body may be compensating for the derangement. Table 1 outlines, with some clinical examples, acid-base disorders that are commonly encountered.

TABLE 1

Definitions and main causes of acid-base disorders

Metabolic acidosis	Process that primarily reduces bicarbonate: Excessive H^+ formation e.g. lactic acidosis, ketoacidosis Reduced H^+ excretion e.g. renal failure Excessive HCO_3^- loss e.g. diarrhoea
Metabolic alkalosis	Process that primarily raises bicarbonate: Extracellular fluid volume loss e.g. due to vomiting or diuretics Excessive potassium loss with subsequent hyperaldosteronism
Respiratory acidosis	Process that primarily causes elevation in $PaCO_2$: Reduced effective ventilation e.g. many chronic respiratory diseases or drugs depressing the respiratory centre
Respiratory alkalosis	Process that primarily causes reduction in $PaCO_2$: Increased ventilation e.g. in response to hypoxia or secondary to a metabolic acidosis

Remember, metabolic processes primarily direct changes in bicarbonate and respiratory processes primarily direct changes in $PaCO_2$ (Figure 2).

MEASURED AND DERIVED INDICES

Some potentially confusing terminology is often used when discussing acid-base disorders. These terms include $PaCO_2$,



total bicarbonate, total CO_2 , standard bicarbonate and base excess⁸. It is useful to know what these terms mean and how they are derived. Most blood gas analysis is carried out on point-of-care blood gas analysers, and these generally only measure two substances when it comes to acid-base reports: hydrogen ions (from which pH is calculated – see below) and PaCO_2 . The ‘bicarbonate’ results that are given from such analysers are generally calculated using Equation 2.

Most laboratories measure total CO_2 concentration as part of the standard electrolyte profile. The reason behind this is that it is technically difficult to measure bicarbonate ions in isolation, but relatively straightforward to measure total CO_2 . Total CO_2 represents the total amount of bicarbonate ions, dissolved CO_2 and other CO_2 -containing substances in a solution. Since bicarbonate normally constitutes the majority of this, total CO_2 is normally used as a convenient surrogate measure of bicarbonate. The total CO_2 on the electrolyte profile may provide the first clue to the presence of an acid-base disturbance in a patient and should not be overlooked when reviewing electrolyte results. One cannot, however, diagnose acid-base disturbances from an isolated total CO_2 measurement. In order to characterise an acid-base disturbance, measures of pH, PaCO_2 , total CO_2 or bicarbonate are required, as well as measurement of the anion gap.

Standard bicarbonate is a calculated index that attempts to provide information on what the bicarbonate concentration would be if the respiratory components of the disorder were eliminated. Base excess is another calculated index which will be elevated in the setting of metabolic alkalosis and reduced in metabolic acidosis. We will not consider the use of these calculated indices further in this article.

UNDERSTANDING ACID-BASE DISORDERS – A FOUR STEP APPROACH

In order to understand the nature of an acid-base problem, we recommend a structured approach during which the following four questions should be asked.

Question 1: What is the pH?

The first step in interpreting an acid-base problem is to look at the pH (or $[\text{H}^+]$) and decide if you are dealing with acidosis, alkalosis or normality. The concept of pH as a measure of acidity will already be familiar. With most human enzymes favouring physiologically neutral conditions, acidaemia is deemed to be present when the pH is less than 7.35 and alkalaemia when the pH exceeds 7.45. It is becoming increasingly common to directly quote the concentration of hydrogen ions ($[\text{H}^+]$) present in a solution. pH and $[\text{H}^+]$ are directly related using Equation 3:

$$\text{pH} = -\log_{10} [\text{H}^+], \text{ where } [\text{H}^+] \text{ is in mol/L}$$

Equation 3

Thus, pH 6.8 corresponds to 1.6×10^{-7} mol/L $[\text{H}^+]$, pH 7.4 to 4.0×10^{-8} mol/L, and pH 7.6 to 2.5×10^{-8} mol/L, i.e. pH falls as $[\text{H}^+]$ rises.

Because the body compensates for acid-base disorders, it is possible that a disorder might be present even if the pH is normal. It should also be borne in mind that the body never over-compensates.

Question 2: What is the bicarbonate?

The second step in interpreting an acid-base disorder is to consider the bicarbonate concentration relative to the normal reference range (which will vary from laboratory to laboratory, but is typically in the range 22-29 mmol/L).

A reduced bicarbonate concentration could mean that the body’s main buffer is being used up buffering excess acid (hydrogen ion) production e.g. in lactic acidosis or ketoacidosis. Alternatively the reduced bicarbonate concentration could indicate a problem related to loss of bicarbonate from the gastrointestinal tract e.g. diarrhoea or a kidney problem i.e. failure to generate new bicarbonate or reclaim bicarbonate filtered into the renal tubules. **A reduced bicarbonate concentration is a hallmark of metabolic acidosis.**

An increased bicarbonate concentration may indicate that there have been substantial losses of acidic fluid e.g. loss of gastric fluid from persistent vomiting or prolonged nasogastric aspiration. Alternatively an increased bicarbonate concentration may be a chronic adaptation by the kidney to high PaCO_2 levels in persons with chronic respiratory diseases associated with CO_2 retention (see Equation 1 where elevated CO_2 levels drives the equation to the left producing more bicarbonate). **An elevated bicarbonate concentration is a feature of metabolic alkalosis.**

Question 3: What is the PaCO_2 ?

The third step in assessing an acid-base problem is to measure the PaCO_2 . This is helpful in determining whether the respiratory system is responding normally to an acid load and reducing the PaCO_2 to compensate for an acidosis i.e. the primary acid-base disturbance is a metabolic acidosis and this is compensated by an increased respiratory rate resulting in a secondary respiratory alkalosis. **A decreased PaCO_2 is a feature of respiratory alkalosis.**

Alternatively, if there is a primary respiratory problem, e.g. respiratory failure associated with chronic obstructive pulmonary disease, the retained CO_2 results in an elevated PaCO_2 (and will drive Equation 1 to the left) and produce a respiratory acidosis. It is also possible to develop a respiratory acidosis if drugs, such as opiate analgesics, depress the respiratory centre resulting in a critical reduction in the rate of ventilation resulting in CO_2 retention. **An elevated PaCO_2 is a feature of respiratory acidosis.**

One can see that by examining the pH, bicarbonate and PaCO_2 it is possible to deduce the nature of the primary acid-base disorder present and the compensatory response.

Question 4: What is the anion gap?

The final step in assessing an acid-base disorder is to calculate the anion gap. Bodily fluids are electrically neutral, meaning that the number of positive charges (cations) present equals the number of negative charges (anions). The most abundant anions are chloride and bicarbonate; numerous other anions are not routinely quantitated, for example proteins and sulphate ions. Sodium is by far the most abundant plasma cation; other cations present in much lower quantities include potassium, calcium and magnesium. If it were feasible to measure all charged substances in blood, it could be shown that the sum of the positively charged particles is exactly balanced by the number of those substances carrying negative charges. It is routine practice to measure only four charged particles: sodium, potassium, chloride and bicarbonate ions. As discussed earlier, total CO₂ on the electrolyte profile may be considered as a convenient surrogate measure of bicarbonate and can be used in the calculation of the anion gap. When the numbers of cations (sodium and potassium) are added, one will always find that they outnumber the anions (chloride and bicarbonate). This difference is what is meant by the term ‘anion gap’ and reflects the unmeasured anions in Equation 4 or Equation 5. An anion gap may be low, normal or high, and can be conveniently calculated using Equation 4:

$$\text{Anion Gap} = [\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] + [\text{HCO}_3^-], \text{ where all concentrations are in mmol/L.}$$

Equation 4

Since the extracellular fluid potassium concentration is very much lower than the sodium, chloride or bicarbonate concentrations and because it can only vary by a few mmol/L, it is often ignored making the anion gap calculation simpler as shown in Equation 5:

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

Equation 5

The reference interval (normal range) for anion gap varies from laboratory to laboratory, and is inherently imprecise because of the number of measurements required for its calculation. An anion gap greater than 20 mmol/L is always considered to be abnormally elevated and a gap of less than 10 mmol/L abnormally low. There is some debate in the literature about the significance of anion gaps in the range 10-20 mmol/L, but a pragmatic approach would be to actively seek out causes of a high anion gap in patients with gaps exceeding 14 mmol/L (or 18 mmol/L if potassium is included in the equation).

TABLE 2

Causes of metabolic acidosis (common causes are in bold)

Normal anion gap	High anion gap
Gastrointestinal losses of bicarbonate	Renal failure
Renal tubular acidosis	Ketoacidosis
Treatment with carbonic anhydrase inhibitors	Lactic acidosis
Urinary diversion procedures	Salicylate poisoning
Excessive administration of 0.9% saline	Glycol ingestion (ethylene glycol, propylene glycol)
	Methanol ingestion

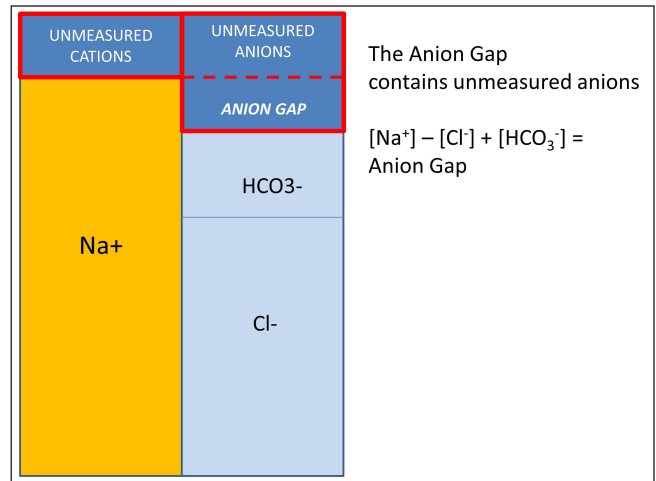
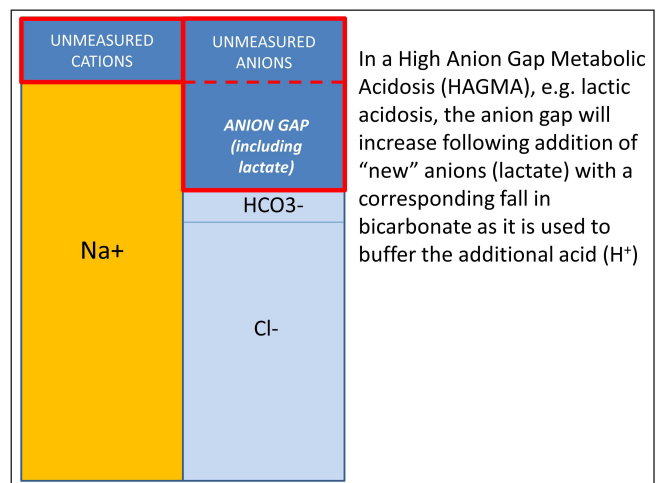


Fig 3

(a) Illustration of the “normal” anion gap



(b) High anion gap present in a metabolic acidosis

Consider the following normal electrolyte profile: Na⁺ 136 mmol/L, K⁺ 4.0 mmol/L, Cl⁻ 100 mmol/L, HCO₃⁻ (or total CO₂) 25 mmol/L. The anion gap is calculated as 140 – 100 – 25 = 11 mmol/L (or 15 mmol/L if potassium is included in the calculation). The Anion Gap is illustrated in Figure 3a.

TABLE 3

Mnemonics for high anion gap metabolic acidosis

Mnemonic	Causes of a high anion gap metabolic acidosis
GOLD MARK	Glycols, Oxoprolin, L-lactate, D-lactate, Methanol, Aspirin, Renal failure, and Ketoacidosis
KARMEL	Ketoacidosis, Aspirin, Renal Failure, Methanol, Ethylene Glycol, and Lactic Acidosis
MUDDPILES	Methanol, Uraemia, Diabetes, Paraldehyde, Iron/Isoniazid, Lactate, Ethylene glycol and Salicylate
KUSMALE	Ketoacidosis, Uraemia, Salicylate, Methanol, Aldehyde, Lactate and Ethylene glycol

Calculation of the anion gap is particularly useful in cases of metabolic acidosis since it can help in formulating a differential diagnosis¹⁰. There are two main categories of metabolic acidosis: high anion gap metabolic acidosis (HAGMA) and normal anion gap metabolic acidosis (NAGMA). A HAGMA is illustrated in Figure 3b. Common causes of HAGMA and NAGMA are detailed in Table 2.



Several mnemonics for common causes of HAGMA have been developed¹¹, and some of the more useful examples are included in Table 3.

From a clinical perspective, if a HAGMA is identified then the simplest approach to establishing a cause is to consider if the patient has one (or more) of the three common aetiologies (lactic acidosis, ketoacidosis or kidney failure)¹².

If these conditions are not present then the HAGMA may be linked to ingestion of a toxin e.g. methanol or ethylene glycol, or be due to the build-up of another acid such as 5-oxoproline (also known as pyroglutamic acid) which may accumulate with chronic paracetamol use in susceptible individuals¹³.

As the laboratory tests for toxic alcohols are not rapidly available it can be useful in a patient with an unexplained HAGMA to assess the “osmolal gap”¹⁴. This “gap” is the difference between the calculated serum osmolality and the laboratory measurement of serum osmolality (from a U&E sample). The calculated osmolality can be simply derived by using Equation 6. A high osmolal gap suggests the presence of toxic alcohols such as methanol or ethylene glycol.

$$\text{Calculated osmolality (mmol/L)} = 2 \times [\text{Na}^+] + [\text{glucose}] + [\text{urea}]$$

Equation 6

Rarely, patients with short bowel syndrome or following bariatric surgery can develop severe D-lactic acidosis and an associated encephalopathy¹⁵. Unabsorbed carbohydrates act as a substrate for colonic bacteria to produce D-lactate. This will result in a high anion gap metabolic acidosis but the standard laboratory measured lactate (L-lactate) will be normal¹⁵.

Calculated anion gaps that are low (below the reference interval) are uncommon. Causes include laboratory error or hypoalbuminaemia but rarely may be found in association with a paraproteinaemia or intoxication with lithium, bromide, or iodide¹⁰.

ILLUSTRATIVE CASES

Case 1

An elderly man is admitted with septic shock. Shortly after admission, blood tests reveal the following:

pH 7.18, PO₂ 34.2 kPa, PaCO₂ 2.1 kPa, HCO₃⁻ 7 mmol/L

Na⁺ 138 mmol/L, K⁺ 3.9 mmol/L, Cl⁻ 95 mmol/L, Total CO₂ 8 mmol/L, Urea 8.2 mmol/L, Creatinine 102 µmol/L, eGFR >60 mL/min/1.73m²

Question 1: What is the pH? The pH is low indicating an acidosis.

Question 2: What is the bicarbonate? Bicarbonate is low, indicating that the acidosis is metabolic in nature.

Question 3: What is the PaCO₂? The PaCO₂ is low, reflecting a respiratory alkalosis. The low level seen here is a reflection

of the body's compensation in an attempt to correct the pH, i.e. a compensatory respiratory alkalosis is present.

Question 4: What is the anion gap? The anion gap is high, indicating HAGMA.

The most likely cause for this acid-base disorder is lactic acidosis due to poor tissue perfusion as a result of septic shock.

Case 2

A woman is being treated for congestive cardiac failure on the coronary care unit. After several days of treatment, the following results are returned:

pH 7.49, PO₂ 11.6 kPa, PaCO₂ 5.8 kPa, HCO₃⁻ 42 mmol/L

Na⁺ 142 mmol/L, K⁺ 3.0 mmol/L, Cl⁻ 85 mmol/L, Total CO₂ 44 mmol/L, Urea 9.3 mmol/L, Creatinine 84 µmol/L, eGFR >60 mL/min/1.73m²

Question 1: What is the pH? The pH is high indicating an alkalosis.

Question 2: What is the bicarbonate? Bicarbonate is high, in keeping with a metabolic alkalosis

Question 3: What is the PaCO₂? The result towards the higher end of the reference range reflects a degree of respiratory compensation for the metabolic alkalosis.

Question 4: What is the anion gap? The anion gap is 13 mmol/L which is normal.

The most likely cause for this acid-base abnormality is extracellular fluid volume loss and hypokalaemia due to treatment with diuretics.

Case 3

An elderly woman with chronic obstructive pulmonary disease (COPD) is admitted with increasing confusion. Shortly after admission, blood tests reveal the following:

pH 7.21, PO₂ 8.2 kPa, PaCO₂ 11.1 kPa, HCO₃⁻ 35 mmol/L

Na⁺ 140 mmol/L, K⁺ 4.7 mmol/L, Cl⁻ 94 mmol/L, Total CO₂ 34 mmol/L, Urea 8.2 mmol/L, Creatinine 66 µmol/L, eGFR >60 mL/min/1.73m²

Question 1: What is the pH? The pH is low indicating an acidosis.

Question 2: What is the bicarbonate? Bicarbonate is high, indicating that a metabolic alkalosis is present. The pH is low so the primary problem is an acidosis and is likely to be respiratory in nature.

Question 3: What is the PaCO₂? The PaCO₂ is very high and indicates a respiratory acidosis is present. The very high PaCO₂ level seen here is typical of a person with respiratory disease that results in retention of CO₂ i.e. the primary clinical problem is respiratory failure due to COPD.



Question 4: What is the anion gap? The calculated anion gap is 12 mmol/L i.e. normal.

The most likely cause for this acid-base abnormality is an acute exacerbation of COPD.

Case 4

An elderly man developed profuse diarrhoea following antibiotic treatment of a chest infection. He is thirsty and light headed. Shortly after admission, blood tests reveal the following:

pH 7.25, PO₂ 13.2 kPa, PaCO₂ 4.2 kPa, HCO₃⁻ 17 mmol/L

Na⁺ 134 mmol/L, K⁺ 3.4 mmol/L, Cl⁻ 104 mmol/L, Total CO₂ 18 mmol/L, Urea 9.3 mmol/L, Creatinine 102 µmol/L, eGFR >60 mL/min/1.73m²

Question 1: What is the pH? The pH is low indicating an acidosis.

Question 2: What is the bicarbonate? Bicarbonate is low, indicating that a metabolic acidosis is present.

Question 3: What is the PaCO₂? The PaCO₂ level is just below the lower end of the normal range indicating a respiratory alkalosis is present. The pH is low so the primary problem is an acidosis (metabolic acidosis). The respiratory alkalosis therefore represents partial compensation of the metabolic acidosis.

Question 4: What is the anion gap? The anion gap is 12 mmol/L, indicating that this is a normal anion gap metabolic acidosis.

The most likely cause for this acid-base disorder is bicarbonate loss from the gastrointestinal tract due to diarrhoea.

Returning to our initial case...

Applying the four question approach to this case, it should now be apparent that the patient has a high anion gap metabolic acidosis with respiratory compensation. The common causes for this presentation can be quickly eliminated since his renal function is normal, and lactate and ketone levels are not elevated. A more unusual explanation for the presentation should be sought (see Table 2). In this case, the patient was subsequently found to have ingested 500 mL of screenwash containing ethylene glycol (antifreeze) in an attempt to end his life.

Prompt recognition of the likely cause of this patient's high anion gap metabolic acidosis helps inform further investigation and management. This would include quantitation of ethanol and toxic alcohol concentrations to confirm the type of ingested poison. Ethylene glycol and methanol are metabolised by alcohol dehydrogenase to very toxic metabolites. If this diagnosis seems likely it is important to urgently seek senior help. Fomepizole is an alcohol dehydrogenase inhibitor which is easy to administer and prevents metabolism of these alcohols to their toxic

metabolites. Haemodialysis will rapidly clear ethylene glycol, methanol and their metabolites and should be started if the patient is severely acidaemic or has evidence of end organ damage e.g. renal failure or visual loss.

CONCLUSION

Acid-base disorders are commonly encountered in clinical practice and a structured approach to assessment includes taking a history, performing a physical examination and careful interpretation of routine biochemical tests and arterial blood gas analysis. Additional investigations such as lactate, glucose, ketones or toxicology testing may be needed to more fully characterise a metabolic acidosis.

Answering four questions will help determine the problems present in the clinical scenario: What is the pH? What is the bicarbonate? What is the PaCO₂? What is the anion gap? Using this approach will help guide further investigations and management of the patient.

There are no conflicts of interest.

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