Chapter 12
Acid-Base Disorders

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Key Points

- Acid-base disorders can either be metabolic (primary change in HCO_3) or respiratory (primary change in $PaCO_2$).
- Every primary acid-base disorder results in a compensatory response. Use rules of thumb to differentiate single from mixed disorders.
- Metabolic acidosis can be partitioned using the Fencl-Stewart equation into strong ion difference, albumin and unmeasured anions.
- A corrected anion gap is useful in determining the cause of metabolic acidosis.
- The underlying cause of the acid-base disorder needs to be identified and treated.

Introduction

> Life is a struggle....sin, not against money power, not against malicious animal magnetism, but against hydrogen... – H.L. Mencken

Disorders of acid-base balance are very common in acutely ill patients, and accurate diagnosis of the acid-base disorder and appropriate management may be life-saving. A systematic approach to the diagnosis and treatment of these disorders is therefore essential. An arterial blood gas (ABG) is required to identify the acid-base disorder and to document its severity. This is best performed by collecting the blood in an anticoagulant-lined syringe designed for this purpose and analysing

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immediately on an analyser placed at point of care. In the absence of a point-of-care device, the sample should be placed in ice and hand carried to the central laboratory as quickly as possible. Transport of ABG samples through pneumatic tube systems is not recommended as such transport can potentially alter blood gas values.

The 'Normal' Arterial Blood Gas [1] (Table 12.1)

The statistical 'normal' is derived from healthy populations. However, clinically relevant abnormal values are those beyond which there is a derangement of function and therapy is mandatory.

The Stepwise Approach to Interpreting Arterial Blood Gas [1]

Step 1: Assess Oxygenation

- First look at the absolute value of PaO_2.
  - Treat hypoxia if <60 mmHg – oxygen therapy.
  - Reduce FiO_2 if >100 mmHg.
- Then assess PaO_2/FiO_2 (P/F) ratio or A-a gradient.
  - For example, FiO_2 21 %, i.e. 0.21, PaO_2 84 mmHg, P/F ratio = 84/0.21 = 400
  - P/F ratio gives an indication of the degree of severity of lung pathology.
  - Normal P/F ratio 400–500. Acceptable >300.

Step 2: Identify the Primary Problem

The $PaCO_2$ and HCO_3 impact the pH and determine the acid-base status of the patient. The $PaCO_2$ is determined by the respiratory system, and the HCO_3 is regulated by the kidney, liver, gut and muscle, collectively referred to as the metabolic system. Therefore, broadly four acid-base disorders are possible (see Table 12.2).

Table 12.1 Normal and clinically acceptable arterial blood gas (ABG) values

	Normal range	Clinically acceptable
pH	7.35 to 7.45	7.30 to 7.50
PCO_2	35 to 45 mmHg	30 to 50 mmHg
PO_2	80 to 100 mmHg	>60 mmHg
HCO_3	24 to 28 mEq/L	24 to 28 mEq/L
Base excess	−2 to +2	−5 to +5

Table 12.2 Primary acid-base disorders

Primary disorder	Primary change
Respiratory acidosis	Increased $PaCO_2$
Respiratory alkalosis	Decreased $PaCO_2$
Metabolic acidosis	Decreased HCO_3
Metabolic alkalosis	Increased HCO_3

Table 12.3 Compensatory acid-base disorders

Primary disorder	Primary change	Compensation	Compensatory change
Respiratory acidosis	Increased $PaCO_2$	Metabolic alkalosis	Increased HCO_3
Respiratory alkalosis	Decreased $PaCO_2$	Metabolic acidosis	Decreased HCO_3
Metabolic acidosis	Decreased HCO_3	Respiratory alkalosis	Decreased $PaCO_2$
Metabolic alkalosis	Increased HCO_3	Respiratory acidosis	Increased $PaCO_2$

Look at pH, $PaCO_2$ and HCO_3 for values outside acceptable range.

If the pH is abnormal, the direction in which it has moved indicates the nature of the primary disorder. For example, if the pH is 7.10, the primary disorder is definitely an acidosis. We can then look at the $PaCO_2$ and the HCO_3 to see if the acidosis is respiratory or metabolic.

If the pH is normal with an abnormal $PaCO_2$, then two possibilities exist. Either it is a mixed state, where there are two primary opposing acid-base disorders, one respiratory and one metabolic, or there is a fully compensated respiratory acid-base disturbance.

Remember, an abnormal $PaCO_2$ or HCO_3 indicates an acid-base disturbance even when the pH is near normal or normal.

Additionally an anion gap >20 usually points to a metabolic acidosis irrespective of the actual values of the $PaCO_2$ or HCO_3.

Step 3: Assess Adequacy of the Compensatory Response – Single (Simple) and Mixed Disorders

The body aims to keep the extracellular pH tightly regulated. Hence, every primary acid-base disorder initiates a compensatory response (see Table 12.3).

It can be observed that the compensatory change moves in the same direction as the primary change. For example, an *increase* in $PaCO_2$ leads to a compensatory *increase* in HCO_3, and a *decrease* in $PaCO_2$ leads to a compensatory *decrease* in HCO_3.

The diagnosis of a single acid-base disorder implies both the initial process and the appropriate compensatory mechanisms. Inappropriateness (excess or inadequate) of the expected compensatory response indicates a mixed disorder. This can be diagnosed for clinical purposes by using a few bedside rules:

1. *Metabolic disorders.*

   In a primary metabolic acidosis, the correct compensatory change is a drop in $PaCO_2$ due to hyperventilation. The numerical value of the reduced $PaCO_2$ should be within + or – 5 mmHg of the number formed by the two digits after the decimal point of the pH value down to 7.10. The $PaCO_2$ usually goes no lower than 10 mmHg even with a profound metabolic acidosis [2]. For example, in a primary metabolic acidosis with a pH of 7.20, the expected normally compensated $PaCO_2$ value will be 20 ±5 (i.e. 15–25 mmHg). If the $PaCO_2$ is within this range (e.g. 20 mmHg), the diagnosis is an appropriately compensated metabolic acidosis. On the other hand, if the $PaCO_2$ is higher than this expected range (e.g. 30 mmHg), then the diagnosis is mixed metabolic and respiratory acidosis, and if it is lower than this expected range (e.g. 10 mmHg), then the diagnosis is mixed metabolic acidosis and respiratory alkalosis. Similarly, in a primary metabolic alkalosis, the appropriate value of the elevated $PaCO_2$ is within ±5 mmHg of the number formed by the two digits after the decimal point of the pH value up to 7.60.

   However, these calculations of appropriate compensation as given above should be applied to spontaneously breathing patients and not to those who are mechanically ventilated because in such patients, ventilator settings determine the $PaCO_2$.

2. *Respiratory disorders.*

   In primary respiratory disorders, the initial change is in the $PaCO_2$ with a compensatory change in HCO_3. The degree of change in HCO_3 depends on both the $PaCO_2$ and also on whether the process is acute or chronic. The differentiation between acute and chronic respiratory disorders is based on the presence of an abnormal pH. If the change in $PaCO_2$ is associated with a pH <7.30 or >7.50, the disorder is *acute*, while in a *chronic* process, the compensatory process brings the pH to the lower limit of the clinically acceptable range (7.30–7.50). Table 12.4 shows the thumb rule of 1, 4; 2, 5 to calculate appropriate HCO_3 response in respiratory disorders.

   The rise in $PaCO_2$ is calculated from a normal value of 40 mmHg.

   As an example, in acute respiratory acidosis, if the CO_2 is 100 mmHg, the rise in CO_2 is (100 minus 40) = 60. Since the expected rise is 1 mEq/L of HCO_3 for every 10 mmHg rise in CO_2, in this situation, the expected HCO_3 rise is 6. The expected HCO_3 is thus 6 mEq/L above the normal range of 24–28. The new expected range for HCO_3 will therefore be 30–34. If the actual HCO_3 is out of

Table 12.4 Appropriate HCO_3 values in respiratory disorders

Condition	Acute	Chronic
Respiratory acidosis (for every 10 mmHg increase in CO_2)	1 mEq/L increase in HCO_3	4 mEq/L increase in HCO_3
Respiratory alkalosis (for every 10 mmHg decrease in CO_2)	2 mEq/L decrease in HCO_3	5 mEq/L decrease in HCO_3

this range, there is a second process affecting it. If the actual HCO_3 is higher than 34, there is an associated metabolic alkalosis and, if less than 30, an associated metabolic acidosis.

3. *Compensatory changes tend to return the pH to near normal.*

   Compensatory mechanisms do not necessarily correct the pH to the middle of the acceptable range as the drive for correction reduces as the acceptable levels are reached. These mechanisms often only bring it to the lower limit of the acceptable range. Compensatory mechanisms *never* overcorrect. Hence, in a chronic respiratory acidosis, for example, the HCO_3 will compensatorily rise and move the pH to between 7.30 and 7.35. It will not move it to 7.40 and will definitely not create an alkalosis by pushing it to 7.50, unless there is a superimposed secondary or mixed acid-base disorder.

Step 4: In a Metabolic Process, Use Story's Modification of the Fencl-Stewart Equation to Identify the Contributing Factors

The previous steps help to diagnose most forms of metabolic acid-base disorders but may miss derangements caused by abnormal chloride or albumin levels. The Fencl-Stewart approach which was suggested to overcome this issue [1, 3] is able to identify other contributors to the metabolic acid-base balance.

The Fencl-Stewart approach to acid-base disorders uses five equations of varying complexity to estimate the base excess effects of the important components: the strong ion difference (sodium and chloride), the total weak acid concentration (albumin) and unmeasured ions. Although this approach is straightforward, most people would need a calculator to use the equations.

D.A. Story simplified these equations into one, making it usable at the bedside [4].

In this approach, the base excess (which represents the metabolic component of the acid-base dysfunction) is partitioned into three domains:

(a) Acidosis/alkalosis caused by the difference between serum Na and chloride (the strong ion difference or SID).
(b) Acidosis/alkalosis caused by the changes in levels of albumin.
(c) Acidosis/alkalosis caused by the unmeasured anions (UMA) such as keto acids, phosphate etc. Lactate used to be considered in this category but is now measured by most ABG machines.

$$\text{BASE EXCESS} = \left[\left(\text{Na} - \text{Cl}\right) - 38\right] + \left[2.5\left(4.2 - \text{serum albumin}\right)\right] + \left[2 - \text{lactate}\right] + \left[\text{minus UMA}\right]$$

The normal SID (Na – Cl) is 38.

Table 12.5 Physiological effects of acidaemia and alkalaemia

Effects of acidaemia	Effects of alkalaemia
Decreased myocardial contractility	Cerebral vasospasm
Arterial vasodilation and venoconstriction	Seizures
Tachyarrhythmias and bradyarrhythmias	Confusion and drowsiness
Reduced renal blood flow and urine output	Tetany and muscle cramps
Confusion and drowsiness	Decreased myocardial contractility
Hyperkalaemia	Supraventricular and ventricular tachyarrhythmias
Hyperglycaemia	Hypokalaemia, hypocalcaemia, hypomagnesaemia

The albumin in this equation is measured as gm/dl.

The UMA represents unmeasured anions. Examples are keto acids and fixed acids in renal failure and sepsis. The algebraic signs must be correctly entered for the above equation to be mathematically correct.

A low Na – Cl difference results in an acidosis and vice versa.

A low albumin level results in a metabolic alkalosis and vice versa.

If the base excess value is not fully explained by its components, there is an unmeasured anion contributing to the process.

This process of teasing out the contributing components of the metabolic acidosis is very useful in the management of critically ill patients who often have many processes affecting the metabolic acid-base balance. For example, a patient with severe metabolic acidosis will often have a bit of SID acidosis, lactic acidosis, hypoalbuminaemic alkalosis and acidosis due to unmeasured anions. Therefore, if the predominant contributor is SID, the best treatment is an infusion of sodium bicarbonate, but if it is UMA, then haemodialysis may probably be the best option.

Causes and Treatment of Acid-Base Disorders

Now that a diagnosis has been made, the cause of the acid-base disorder must be pinpointed and appropriate therapy started as soon as possible since both acidaemia and alkalaemia have adverse physiological effects as listed in Table 12.5.

Respiratory Acidosis

This results from a reduction in minute ventilation.

Causes This could be central (affectations of the respiratory centre) or peripheral (chest wall and muscles or lung parenchyma).

Table 12.6 Peripheral causes of respiratory acidosis

Chest wall and muscles	Lung parenchyma
Phrenic nerve injury	Upper airway obstruction
Myasthenia gravis	Chronic obstructive lung disease
Guillain-Barré syndrome	Severe pulmonary oedema
Organophosphate poisoning	Severe ARDS
Neurotoxic snakebite	Pneumothorax
Flail chest	Large pleural effusions
Severe kyphoscoliosis	

Table 12.7 Causes of respiratory alkalosis

Central	Lung parenchyma
Brainstem stroke	Hypoxia
CNS infection	Asthma
Traumatic brain injury	Acute lung injury
Salicylate poisoning	Pneumonia
Sepsis	Pulmonary embolism
Liver failure	Hyperventilation during mechanical ventilation
Pregnancy	Interstitial lung disease
Pain and anxiety	

Central

- Sedative and narcotic drugs
- CNS injury or infection
- Brainstem infarctions

Peripheral (see Table 12.6)

Treatment Treat the underlying cause. Mechanical ventilation – invasive or non-invasive may be required.

Respiratory Alkalosis

This results from an increase in minute ventilation.

Causes This could be central (affectations of the respiratory centre) or peripheral (lung parenchyma) (Table 12.7).

Treatment Treat the underlying cause.

Metabolic Acidosis

In addition to using the Fencl-Stewart equation, an anion gap is useful in trying to identify the cause of metabolic acidosis.

The anion gap exists because not all electrolytes are measured. The quantity of unmeasured cations is much less than unmeasured anions. The difference between these two is called the anion gap. In practice, it is calculated as:

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

The normal value is 16 ± 4 mEq/L. If potassium is not included while calculating anion gap, then the normal value is 12 ± 4 mEq/L. Since the normal value of the anion gap decreases with hypoalbuminaemia, it is useful to correct the anion gap for the albumin level.

The corrected anion gap = calculated anion gap + 2.5 (4.0 – albumin). The albumin in this equation is measured as gm/dl.

Once the anion gap is calculated, it is easy to consider causes of metabolic acidosis as those causing an increased anion gap and those presenting with a normal anion gap.

Causes of High Anion Gap Metabolic Acidosis

High anion gap metabolic acidosis is usually caused by conditions where there is an accumulation of acids with a strong anion, and these can be remembered with the mnemonic 'MUDPILES'.

M methanol; *U* uraemia; *D* diabetic ketoacidosis; *P* propylene glycol; *I* infection, sepsis; *L* lactic acidosis; *E* ethylene glycol, ethanol; *S* salicylates

Lactic Acidosis

Lactic acidosis is very common in acutely ill patients. It can result from an overproduction of lactate or a reduction in excretion. Common reasons for this are:

1. *Impaired oxygen delivery to tissues*: This can happen during shock, when abnormal global haemodynamics cause inadequate perfusion of all tissues, leading to anaerobic metabolism and production of lactic acid. It can also happen when tissue microcirculation is abnormal in the presence of normal global haemodynamics or when there is impaired blood flow to any one region or organ as can be seen in limb or bowel gangrene.
2. *Mitochondrial dysfunction*: This can be seen in sepsis and also as a result of use of drugs such as metformin and nucleoside reverse transcriptase inhibitors.
3. *Pyruvate dehydrogenase deficiency*: This is seen in severe sepsis and thiamine deficiency.

Table 12.8 Causes of normal anion gap acidosis

Mechanism	Dilution	High urinary SID	Loss of high SID enteric fluids	High chloride intake
Causes	Saline infusion Psychogenic polydipsia TURP syndrome	Renal tubular acidosis Amphotericin Lithium Aminoglycosides Valproate ACE inhibitors Spironolactone Adrenal insufficiency	Small intestinal diarrhoea	Total parenteral nutrition Ammonium chloride

Causes of Normal Anion Gap Metabolic Acidosis

Normal anion gap metabolic acidosis results from conditions which reduce the strong ion difference in the extracellular fluid (Table 12.8).

Dilutional acidosis: Large volumes of intravenous fluids produce a metabolic acidosis when the SID of the infused fluids is less than the SID of extracellular fluid. This is typically seen with saline infusions as the SID of saline is 0 (Na 154 mEq/L, Cl 154 mEq/L). This tends to lower the extracellular SID and cause an acidosis.

High urinary SID: In various forms of congenital and drug-induced renal tubular acidosis, urinary SID is high even though extracellular SID is low. This happens because of defects in the proximal or distal renal tubule which impair chloride excretion resulting in hyperchloraemia and a low SID acidosis.

Loss of high SID enteric fluids: Small intestinal, pancreatic and biliary secretions have low chloride content and a high SID. Conditions such as certain diarrheal illnesses result in increased losses of such fluids resulting in a narrowing of extracellular SID.

High chloride intake: Total parenteral nutrition and ammonium chloride administration can sometimes result in this.

Delta Anion Gap/Delta Bicarbonate

The anion gap allows differentiation of high and normal gap acidosis. However, it is possible for a high anion gap acidosis to coexist with a normal anion gap acidosis. The delta/delta concept allows the diagnosis of this situation.

The concept behind delta/delta is based on the assumption that for every increase in anion gap of 1 mmol/L above normal (12 mmol), serum HCO_3- will drop by an equal amount, that is, the change in anion gap should be equal to change in HCO_3. Therefore, in a pure high anion gap acidosis, delta anion gap = delta HCO_3.

When the delta HCO_3 > delta anion gap, it is because a normal anion gap acidosis is present along with the high anion gap acidosis, leading to an additional drop in bicarbonate.

Treatment

In a high anion gap acidosis, there is an accumulation of a strong acid, and treatment is directed first at stopping the production of more acid, e.g. insulin therapy in keto-acidosis, haemodynamic optimisation in shock, and secondly at hastening the removal of the acid, e.g. dialysis. The underlying cause of the acid accumulation needs to be treated.

If the problem is due to a high chloride with a normal sodium (low extracellular SID), the therapy is to use chloride-free IV fluids and to give sodium without the chloride ion, e.g. in the form of sodium acetate or sodium bicarbonate or sodium lactate.

Administration of Buffers

Except for normal anion gap acidosis, the use of $NaHCO_3$ is not recommended for pH > 7.15. In diabetic ketoacidosis, this threshold is lowered to a pH of <7.0.

The aim of administering the $NaHCO_3$ is to increase the SID. Therefore, the active ingredient is Na, not HCO_3. In fact the bicarbonate ion combines with hydrogen ion and is converted to carbon dioxide and water. This potential to increase $PaCO_2$ levels is the reason why it should not be administered as boluses but as a continuous infusion.

$NaHCO_3$ can also adversely result in paradoxical intracellular acidosis, hypernatraemia, hyperosmolarity, hypocalcaemia and decreased oxygen delivery.

Metabolic Alkalosis

Metabolic alkalosis is less common than acidosis.

Causes

Metabolic alkalosis occurs by four main mechanisms (Table 12.9):

Low urinary SID: Loop and thiazide diuretics among other causes result in a tubular loss of chloride resulting in a low urinary SID and therefore a high extracellular SID leading to alkalosis.

Enteric losses of low SID fluid: Gastric secretions have no sodium, only chloride. Loss of this low SID fluid by vomiting or nasogastric aspiration results in a high SID metabolic alkalosis.

Gain of high SID fluid: Administration of large quantities of $NaHCO_3$ or sodium citrate (in transfusions) will also raise the SID and create an alkalosis.

Volume depletion: This has the opposite effect on extracellular SID as dilution. While dilution narrows SID, dehydration widens it.

For another diagnostic approach, see [4].

Table 12.9 Causes of metabolic alkalosis

Mechanism	High urinary SID	Enteric losses of low SID fluid	Gain of high SID fluid	Volume depletion
Causes	Furosemide Thiazides Corticosteroids Mineralocorticoids Cushing's syndrome Post hypercapnia Bartter's syndrome Gitelman's syndrome	Vomiting Nasogastric suction Gastric outlet obstruction Laxative abuse	$NaHCO_3$ administration Massive transfusion Dialysis	Pure water dehydration

Treatment

The underlying cause needs to be treated while also attempting to reduce the extracellular SID. This may include:

1. *Repletion of ECF volume*: Saline or similar low SID fluids need to be administered. Almost all metabolic alkalosis responds to this if enough saline can be given. In hypoalbuminaemic patients, albumin administration accelerates normalisation of the pH as it repletes volume and additionally removes the alkalosis due to low albumin levels (see the Fencl-Stewart equation above).
2. *Replacement of potassium as chloride salt*: While alkalosis produces hypokalaemia that may need replacement therapy, the more important reason to do this is to replace chloride.
3. *Acetazolamide therapy*: Acetazolamide increases proximal tubular chloride reabsorption and increases urinary SID, decreasing extracellular SID.
4. *Administration of chloride-containing solutions*: Ammonium chloride or lysine or arginine hydrochloride has occasionally been used.

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Further Reading

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