28 0ctober 2022
No.

Understanding Acid-Base Disorders

Dr TT Curtis

Moderator: Dr K Govender

School of Clinical Medicine
Discipline of Anaesthesiology and Critical Care

Table of Contents

Introduction

The arterial blood gas (ABG) is a tool used to measure and analyse the amount of oxygen and carbon dioxide in the blood as well as the acidity (pH) of the blood[1]. It is a routine test used commonly in clinical practice and is an important "Point-of-Care" assessment tool. As anaesthetists, it is important to understand:

- The need for ABG sampling
- The electrochemistry behind the ABG
- The difference between what is measured and what is calculated

This will help us with requesting the correct information and interpreting the arterial blood gas correctly[2].

The blood gas does come with limitations:

- It guides you towards the patient's acid-base status but does not yield a specific diagnosis
- ABG analysis cannot be used as a screening tool for early disease (e.g. pulmonary disease)[3]

Procedure:

Blood is usually drawn from an artery, as arterial blood is the best indicator of gaseous exchange in the lungs[3]. ABG analysis produces a measurement of the concentration of the following substances found in arterial blood[4]:

- The partial pressure of oxygen (PaO_2)
- The partial pressure of carbon dioxide ($PaCO_2$)
- H+ ion concentration / Acidity (pH)
- Oxy-haemoglobin saturation (SaO_2)
- Bicarbonate (HCO_3^-) [4]

It is important that arterial blood gas (ABG) results are interpreted as one result, compared to other laboratory tests where it is important to interpret each test on the panel separately[4].

Three variables are measured by the blood gas analyser: pH, PaO_2 and $PaCO_2$[6]. Other variables are calculated: e.g. [HCO_3^-] – derived from the Henderson-Hasselbach equation and BE (base excess) from the Siggaard-Anderson normogram. Haemoglobin and oxygen saturation are measured with a co-oximeter[7]. Co-oximetry can also measure methaemoglobin and carboxyhaemoglobin.

Temperature changes affect PCO_2, PO_2 and pH. A drop in temperature, will lower the partial pressure of a gas in solution (total gas content does not change), due to gas solubility being inversely proportional to temperature (Henry's Law)[7].

Hypothermia:

- Decreases PCO_2 and PO_2
- Increases pH: temperature does not alter [HCO_3^-] and therefore dissociation of water decreases→ decreasing [H^+] and increasing pH.

Physiological effects of acidaemia:

- Direct myocardial and smooth muscle depression→ reduction in cardiac contractility and peripheral vascular resistance→ hypotension
- Tissue hypoxia (even though right shift of oxygen haemoglobin dissociation curve)
- Less response to endogenous and exogenous catecholamines in cardiac and vascular smooth muscle
- The ventricular threshold is decreased
- Hyperkalemia (movement of K^+ out of cells in exchange for raised extracellular H^+)
- CNS depression (respiratory acidosis→ CO_2 narcosis)

Physiological effect of alkalaemia:

- Left shift of the oxygen heamoglobin dissociation curve→ increased affinity of heamoglobin for oxygen
- Hypokalemia (H^+ moves out of the cell, in exchange for extracellular K^+ into the cell)
- Decrease in ionized plasma [Ca^{2+}]→circulatory depression and neuromuscular irritability
- Reduces cerebral blood flow (respiratory alkalosis)
- Bronchoconstriction and decreased pulmonary vascular resistance (respiratory alkalosis)

Indications for an Arterial blood gas:

- To identify and monitor problems with gas exchange → PaO2
- To monitor respiratory adequacy (ventilation) → PaCO2
- Identify and monitor acid base disturbances
- Monitoring of electrolytes (Na^+, K^+, Ca^{2+}) and metabolites (bilirubin, glucose, lactate)
- Diagnose and monitor treatment of methaemoglobinaemia and carbon monoxide poisoning through the use of co-oximetry

Standards required to perform ABG – in order to be interpreted correctly:

- Common site for the collection of arterial blood→ radial artery. It is accessible, easy to palpate and has a good collateral supply (must be checked with a Modified Allen test before specimen collection)[4].
- Aseptic technique
- Draw blood from an artery (radial, femoral), using a small needle (22-25G) and a syringe (heparinised to prevent clot formation). Blood can also be drawn from an indwelling catheter.

- Put a stopper on the syringe IMMEDIATELY (prevents arterial blood from interacting with oxygen in the air)*.
- Prompt analyses is required (within minutes)→ or put the sample on ice ASAP and transport to the Lab (can be delayed up to 1hr)
- Volume required by the ABG machine for measurement varies from 0.65 – 1.5ml. The lower the volume, the fewer the number of variables measured.

* Rapid analyses/ice ensures that there is no rapid decline in the PaO_2 due to the metabolism that continues to take place by the erythrocytes and white blood cells.

Important questions to consider:

1. Is the blood gas taken on room air or supplemental oxygen?
2. Is the blood gas an arterial or venous sample?

Hypoxaemia and Hypoxia:

Important to check if hypoxaemia or hypoxia is present?

Hypoxaemia is a PaO_2 < 8kPa (60mmHg) and hypoxia is a low oxygen content in the tissue

Normal PaO_2 depends on the sampling site:

- Mixed venous → pulmonary artery
- Central venous sample → internal jugular or subclavian veins

PaO_2 is low in a mixed venous sample → central venous sample → peripheral sample (lowest)

Normal values for PaO_2:

- Sea level:
    - PaO_2 100mmHg / 13,3kpa (room air)
    - 240mmHg/32kpa (40% FM)
    - PvO_2 40mmHg / 5.3kpa (room air)
- At altitude (Johannesburg-1700m):
    - PaO_2 77mmHg/10.2kpa
    - 187mmHg/25kpa (40% FM)
    - PvO_2 35mmHg/4.7kpa

Calculate the A-a gradient: $PAO_2 – PaO_2$

A – a gradient = $[FiO_2 (P_{atm} – P_{H2O}) – PACO_2 / R] – PaO_2$

A normal A-a gradient is normally less than 2kpa (15mmHg). It increases with age and is not affected by altitude. An increased A-a gradient suggests a V/Q mismatch, diffusion abnormality or right to left shunt.

1. pH is the negative logarithm (base 10) of the H^+ ion concentration → $pH = -\log_{10}[H^+]$
   - expression of hydrogen ion concentration
   - normal arterial pH = -log (40×10^{-9}) = 7.40
2. Acid: chemical substance that acts as a proton (H^+) donor
3. Base: substance that acts as proton acceptor
4. Acidaemia: pH less than 7.35→ a state of acidic blood
5. Alkalaemia: pH greater than 7.45→ a state of alkaline blood
6. Acidosis: a disorder that tends to reduce the pH
7. Alkalosis: a disorder that tends to increase the pH
8. Henderson-Hasselbach equation:

- expresses the relationship between pH, pK_a and [acid] and [base][6]

$$pH = pK_a + \log {}^{base}/_{acid}$$

- for blood gas interpretation: the equation can be expressed as:

$$pH = pK_a + \log {}^{[HCO3]}/_{[H2CO3]}$$

or simply:

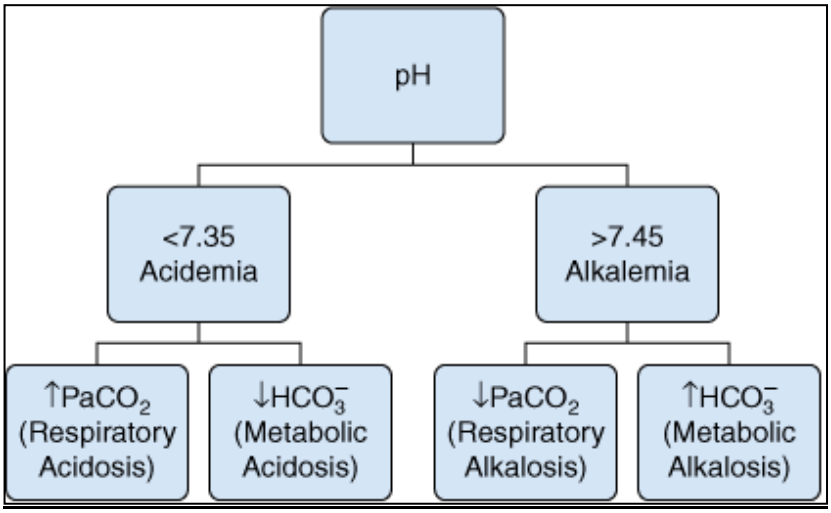
$$pH = 6.1 + \log [HCO_3^-] / 0.03\ PCO_2$$

NB: 0.03 is the solubility coefficient of CO_2 when expressed in mmHg (0.225 solubility coefficient in kPa). 6.1 is the pKa of the bicarbonate buffer system.

9. Standard Bicarbonate: the measurement of the bicarbonate concentration under standard conditions: PCO_2=40mmHg (5.3kPa), temperature of 37^0C, and haemoglobin fully saturated with oxygen. It corrects for any respiratory abnormality and is more accurate in describing a metabolic disturbance than calculated HCO_3^- [6].
10. Base excess: the amount of acid or base that must be added to a sample of blood to return the pH to 7.40 and $PaCO_2$ to return to 40mm Hg at full oxygen saturation and 37^oC. It is the representation of the metabolic component of an acid base disturbance and is therefore affected by the above factors of $PaCO_2$, Hb and temperature.
11. Standard Base excess: the quantity of ACID or ALKALI required to return the plasma in-vivo to a normal pH under standard conditions → represents the best measure of the metabolic disturbance. It the base excess value calculated for anaemic blood (Hb=5g/dl), based on the principle that this represents the whole human being[6].
12. Buffer: a solution that contains a weak acid and its conjugate base or a weak base and its conjugate acid (conjugate pairs). By readily accepting or giving up hydrogen ions, they minimise any change in [H^+]. E.g. the bicarbonate buffer system in plasma.

13. Strong ion difference (SID): the sum of all the strong cations (completely or almost completely) dissociated (Na+, K+, Ca^{2+}, Mg^{2+}) minus the strong anions (lactate-, Chloride)[7]
14. Strong acid: a substance that readily and almost irreversibly gives up an H^+ and increases [H^+]
15. Strong base: binds H^+ and decreases [H^+]
16. Weak acid: reversibly donates H^+
17. Weak base: reversibly bind H^+
18. Hypoxia: a condition where oxygen supply is inadequate to the body (general hypoxia) or to a specific region (tissue hypoxia).
19. Hypoxaemia: reduced oxygen in the blood
20. PaO_2: partial pressure of oxygen dissolved in arterial plasma
21. SpO_2: percentage saturation of haemoglobin with oxygen
22. PAO_2: the partial pressure of oxygen in the alveoli
23. Haldane effect: Deoxygenated blood can carry increased amounts of carbon dioxide, whereas oxygenated blood has a reduced carbon dioxide capacity.
24. Simple acid base disorder: one pathological process occurs by itself to explain the change in pH
25. Mixed acid-base disorder: the presence of two or more primary processes to explain the change in pH

Simple Acid-Base disorders:



STEP 1: Look at the pH (Normal pH: 7.35 – 7.45)

- Decreased → **acidaemia**
- Increased → **alkalaemia**
- pH < 7.35 is an acidaemia
- pH > 7.45 is an alkalaemia

STEP 2: Look at the $PaCO_2$: assesses the respiratory contribution to the pH

-Sea Level:

Normal $PaCO_2$(arterial): 40mmHg or 5.3 kPa

PvCO2(venous): 45mmHg or 6 kPa

-Altitude: Johannesburg(1700m)

$PaCO_2$: 35mmHg or 4.7 kPa

$PvCO_2$: 40mmHg or 5.3 kPa

If elevated: respiratory acidosis

If decreased: respiratory alkalosis

NB:

1. The greater the altitude, the lower the partial pressure
2. Altitude increases minute ventilation → lowers $PaCO_2$
3. Lower PaO_2 directly increases $PaCO_2$ (Haldane effect)
4. Venous or arterial blood is adequate at assessing $PaCO_2$

Does the change in $PaCO_2$ explain the change in arterial pH? If not, check if the change in $[HCO_3^-]$ indicates a metabolic component.

STEP 3: Look at $[HCO_3^-]$ and BE to assess the metabolic component

As mentioned earlier: Bicarbonate is a calculated variable. It is used to assess for a metabolic component if no respiratory abnormality is present. It can be affected by both respiratory and metabolic disturbances and is merely a product of calculation (pH and PCO_2). Standard bicarbonate corrects for any respiratory abnormality and is a better measurement of the metabolic component[6].

The Standard Base excess, if available represents the **best** measure of a metabolic disturbance.

Neither standard bicarbonate, or standard base excess, can fully explain the mechanism of any metabolic disturbance but is very useful in the identification of a metabolic disturbance.

Ask yourself: Does the change in $[HCO_3^-]$ indicate a metabolic component?

DISORDER	**PRIMARY CHANGE**	**COMPENSATION**
METABOLIC		
Acidosis	Decreased HCO_3^-	Decreased $Paco_2$
Alkalosis	Increased HCO_3^-	Increased $Paco_2$
RESPIRATORY		
Acidosis	Increased $Paco_2$	Increased HCO_3^-
Alkalosis	Decreased $Paco_2$	Decreased HCO_3^-

Let us put the above 3 steps into practice in the following 3 scenarios.

Scenario 1

A 20-year-old male patient is brought into casualty after he was knocked off his motorcycle and sustained a closed head injury. His GCS on scene was 10/15 with equal and reactive pupils and no other focal neurological signs. His vitals are: HR 100, BP 130/80, SpO2 99% on RA, Resp Rate 8bpm, Temp 37, GM 7.0 mmol/L. Describe his acid-base abnormality below:

ABG:
pH 7.20
pCO2 50mmHg
pO2 95mmHg
HCO3 24
BE +1
SpO2 99%

Step 1: pH <7.35, therefore an acidaemia is present: 2 possible scenarios exist: a respiratory cause (if so, the PaCO2 will be elevated) or there may be a metabolic cause (if so, the HCO3- with be decreased)
Step 2: PaCO2 is elevated at 50mmHg. This confirms a respiratory cause of the acidosis
Step 3: HCO3- is within normal limits.

Assessment: Respiratory acidosis secondary to hypoventilation.

Scenario 2

A 25-year-old female patient is booked for an emergency laparotomy for a ruptured appendix. Her vitals are: HR 100, BP 110/70, SpO2 99% on RA, Resp Rate 15bpm, Temp 37, GM 7.0 mmol/L, Hb 8.0g%. Describe her acid-base abnormality below:

ABG:
pH 7.20
pCO2 38mmHg
pO2 100mmHg
HCO3 20
BE -4
Lac 3.0 mmol/L
SpO2 100%

Step 1: pH <7.35, therefore an acidaemia is present. 2 possible scenarios exist: a respiratory cause (if so, the PaCO2 will be elevated) or it may be a metabolic cause (if so, the HCO3- with be decreased)
Step 2: PaCO2 is within normal limits
Step 3: HCO3- is low (Metabolic acidosis)

Assessment: (Hyperlactataemic) metabolic acidosis secondary to compensated haemorrhagic shock (elevated lactate with a normal blood pressure).

Scenario 3

A 30-year-old male patient is brought to casualty following an MVA. He sustained a closed head injury and bilateral closed fractured femurs. His vitals are as follows: HR 120, BP 90/50, SpO2 98% on RA, Resp Rate 15bpm, Temp 37, GM 7.0 mmol/L, Hb 7.0g%. Describe his acid-base abnormality below:

ABG:
pH 7.36
pCO2 30mmHg
pO2 70mmHg
HCO3 18
BE -6
Lac 4.0 mmol/L
SpO2 97%

Step 1: pH is within normal range (7.35 – 7.45) – NB: it is important to complete all 3 initial steps of the ABG assessment.
Step 2: PaCO2 is low
Step 3: HCO3- is low

Assessment: Mixed metabolic and respiratory alkalosis.

NB: with 2 opposing acid-base disorders, the pH may be within normal limits. Therefore, further analysis is required.

***** NEW STEP *****

Step 4 in the ABG interpretation tries to determine if:

* Compensation is present, or
* a mixed acid-base abnormality co-exist.

Step 4: Check for appropriate compensation

The physiological response to changes in [H^+] occurs by 3 mechanisms[9,7]:

1. Neutralisation of acids via buffer systems (seconds to minutes)
2. Respiratory compensation (minutes to hours)
3. Clearance via the renal system (hours to days)

Buffer systems in the body include [9,7]:

Extracellular	Intracellular
Carbonic acid/bicarbonate buffer system (H_2CO_3/HCO_3)	Heamoglobin buffer (HbH/Hb^- and $OxyHb \cdot Hb/ OxyHb^-$)
Plasma proteins	Phosphate buffer ($H_2PO_4^-/HPO_4^{2-}$) Ammonia buffer (NH_3/NH_4^+) (Nb urinary buffers)
	Intracellular proteins (PrH/Pr^-)

1. Compare the change in $[HCO_3^-]$ with the change in $PaCO_2$
2. Does a compensatory response exist?

Arterial pH is related to the ratio of $PaCO_2/[HCO_3^-]$. Therefore, in respiratory and renal compensatory mechanisms, the $PaCO_2$ and $[HCO_3^-]$ change in the same direction. A change in opposite directions indicates a mixed acid-base disorder[7].

Boston Rules: Compensatory responses in primary acid-base disturbances:

DISTURBANCE	RESPONSE	EXPECTED CHANGE
Respiratory Disorders and Compensation		
Respiratory acidosis		
Acute	increased $[HCO_3^-]$	1mEq/L : 10mmHg increase in $PaCO_2$
Chronic	increased $[HCO_3^-]$	4mEq/L : 10mmHg increase in $PaCO_2$
Respiratory alkalosis		
Acute	decreased $[HCO_3]$	2mEq/L : 10mmHg decrease in $PaCO_2$
Chronic	decreased $[HCO_3]$	4mEq/L : 10mmHg decrease in $PaCO_2$
Metabolic Disorders and Compensation		
Metabolic acidosis	decreased $PaCO_2$	1.2 x the decrease in $[HCO_3^-]$ or 1.5 (actual HCO_3) + 8 (+/- 2)
Metabolic alkalosis	increased $PaCO_2$	0.7 x the increase in $[HCO_3^-]$ Or $0.7(HCO_3^-)$ +20 (+/-5)

Table adapted from Morgan and Mikhail (TABLE 50-7)[7,10]

A **mixed** acid-base disorder co-exists if the compensatory response is **more than** or **less than** the calculated expected value.

Scenario 4

7-year-old (22kg) male patient with Perthes disease is booked for elective orthopaedic surgery. He is intubated and ventilated: V_T 264ml; RR 15; PEEP 5. Two-hours into the procedure, the ABG is as follows:

ABG:

pH 7.48	**BE -2.3**
pCO_2 30mmHg	**Sats 98%**
pO_2 224mmHg	**Glu 5.9mmol/L**
HCO_3 22.3 mmol/L	**Lac 2.8 mmol/l**
Hb 11.9 g%	

Step 1: pH is elevated (Alkalosis)
Step 2: $PaCO_2$ is low (in keeping with a resp alkalosis)
Step 3: HCO_3^- is low-normal
Step 4: Apply the compensation rule for acute respiratory alkalosis as follows:

- **Decrease in [HCO_3^-] = 2mEq/L for every 10mmHg decrease in $PaCO_2$ (see table above)**
- The expected HCO3- should be: (40-30) = 10… therefore, the HCO3- should be approximately: (24mmol/L-2mmol/L)=22mmol/L (if there is appropriate compensation.)
- The Measured HCO3- is 22.3 mmol/L, therefore compensation is appropriate

Assessment: Respiratory alkalosis with appropriate metabolic compensation.

Defined as a primary decrease in $PaCO_2$. The cause is usually due to an inappropriate increase in alveolar ventilation compared to CO_2 production[7].
Compensation:
Acute respiratory alkalosis: plasma [HCO_3^-] decreases by 2mEq/L for every 10mmHg decrease in $PaCO_2$ below 40mmHg
Chronic respiratory alkalosis: plasma [HCO_3^-] decreases by 4mEq/L for every 10mmHg decrease in $PaCO_2$ below 40mmHg

Causes of Respiratory alkalosis:

Central stimulation:	**Peripheral stimulation:**
Pain	Hypoxemia
Anxiety	High Altitude
Ischemia	Pulmonary disease: Asthma/PE/CHF
Stroke	Severe Anaemia
Infection	
Fever	
Tumor	**Iatrogenic:**
Drug induced: • Salicylates • Progesterone(pregnancy)	Ventilator induced
Unknown mechanism: Sepsis Metabolic encephalopathies	

Treatment of Respiratory alkalosis[7]:

1. Treat the underlying cause
2. For severe alkalemia (pH > 7.60):
    a. IV Hydrochloric acid,
    b. Arginine chloride, or
    c. Ammonium chloride may be indicated.

Paramedics were called out for a 22-year-old female found unconscious in her bedroom. On arrival her vitals were: HR 100, BP 90/50, SpO2 88% on RA, GCS 9/15 with pinpoint pupils. Her ABG in casualty is as follows:

ABG:
pH 7.25
pCO_2 70mmHg
pO_2 65mmHg
HCO_3 26.8mmol/L
BE 1.0
Lac 1.8mmol/L

Step 1: pH is low (Acidosis)
Step 2: $PaCO_2$ is elevated (in keeping with a resp acidosis)
Step 3: HCO_3^- is elevated
Step 4: Apply the compensation rule for acute respiratory acidosis as follows:

- **Plasma HCO_3^- increases by 1mEq/L per 10mmHg increase in $PaCO_3$** (see table above)
- The expected HCO3- should be: (70-40) = 30… therefore, the HCO3- should be approximately: (24mmol/L + 3mmol/L)=27mmol/L (if there is appropriate compensation.)
- The Measured HCO3- is 26.8mmol/L, therefore compensation is appropriate

Assessment: Respiratory acidosis with appropriate metabolic compensation.

Scenario 6

A 50-year-old male patient is brought into the emergency room wheezing. He is known to have COPD. On arrival his vitals were: HR 110, BP 140/90, SpO2 92% on RA, GCS 15/15 with bilateral wheezes on auscultation. His ABG is as follows:

ABG:
pH 7.25
pCO_2 60mmHg
pO_2 75mmHg
HCO_3 31.2mmol/L
BE 1.0
Lac 1.2mmol/L

Hb 16 g%

Step 1: pH is low (Acidosis)
Step 2: $PaCO_2$ is elevated (in keeping with a resp acidosis)
Step 3: HCO_3^- is elevated
Step 4: Apply the compensation rule for chronic respiratory acidosis as follows:

- **Plasma HCO_3^- increases by 4mEq/L per 10mmHg increase in $PaCO_3$** (see table above)
- The expected HCO3- should be: (60-40) = 20… therefore, the HCO3- should be approximately: (24mmol/L + 8mmol/L)=32mmol/L (if there is appropriate compensation.)
- The Measured HCO3- is 31.2mmol/L, therefore compensation is appropriate

Assessment: Respiratory acidosis with appropriate metabolic compensation.

Respiratory Acidosis:

Known as a primary increase in $PaCO_2$. $PaCO_2$ represents the balance between carbon dioxide production and elimination.

$PaCO_2 = CO_2$ production / Alveolar ventilation

An increase in $PaCO_2$ leads to an increase in the $[H^+]$ and a decrease in arterial pH. $[HCO_3^-]$ is minimally affected.

$$H_2O + CO_2 <-> H_2CO_3 <-> H^+ + HCO_3^-$$

Causes of Respiratory Acidosis:

Alveolar hypoventilation:	**Increased CO_2 production:**
CNS depression • Drug induced • Sleep disorders • Cerebral ischemia/trauma • Obesity hypoventilation syndrome Neuromuscular disorders • Myopathies • Neuropathies Chest wall abnormalities • Flail chest • Kyphoscoliosis Pleural abnormalities • Pneumothorax • Pleural effusion Airway obstruction <u>Upper airway obstruction</u> • Foreign body • Tumor • Laryngospasm <u>Lower airway obstruction</u> • Severe asthma • COPD • Tumor Parenchymal lung disease • Pulmonary emboli • Pulmonary edema • Pneumonia • Aspiration • Interstitial lung dx Ventilator malfunction	Large caloric loads Malignant hyperthermia Intensive shivering Thyroid storm Burns Prolonged seizure activity

Table adapted from Morgan and Mikhail[7]

There is an acute and chronic compensatory response that occurs in response to a raised PaCO2.

Acute respiratory acidosis (compensation is limited and can occur within 6-12hrs):

(i) Acute Compensation:

1. Haemoglobin buffer
2. Exchange of extracellular H^+ for Na^+ and K^+ from bone and the intracellular compartment
3. Minimal renal response to retain HCO_3

Plasma [HCO_3^-] increases 1mEq/L for every 10mmHg increase in $PaCO_2$ above 40mmHg

Chronic respiratory acidosis:

(ii) Chronic Compensation:

1. Renal compensation seen after 12-24hrs and reaches its peak at 3-5days.

Plasma [HCO_3^-] increases 4mEq/L for each 10mmHg increase in $PaCO_2$ above 40mmHg

Alternative equations for respiratory compensation:[11]

Acute respiratory acidosis:

- Expected HCO_3^- = Baseline HCO_3^- + (0.1) [Actual $PaCO_2$ – Baseline $PaCO_2$]

Chronic respiratory acidosis:

- Expected HCO_3^- = Baseline HCO_3^- + (0.4) [Actual $PaCO_2$ – Baseline $PaCO_2$]

Treatment of Respiratory acidosis:

- Treat the cause→ increase the alveolar ventilation/reduce CO_2 production
- In severe acidosis (pH <7.20), CO_2 narcosis and respiratory muscle fatigue: mechanical ventilation may be required
- Hypoxemia is common with respiratory acidosis, so increase FIO_2
- $NaHCO_3$ is rarely indicated and can increase the $PaCO_2$ and worsen intracellular acidosis.

Scenario 7

70-year-old female patient with a history of weakness and areflexia lives in a care facility. She has had poor oral intake for 3 days. Her medications include: Thiazide diuretic and a sleeping tablet.

ABG:
pH 7.58
pCO_2 50mmHg
pO_2 65mmHg
HCO_3^- 48.0mmol/L

Biochemistry:
Na^+ 145
K^+ 1.9
CL^- 86
AG 12.9
Urinary CL^- 74mmol/L (raised)

Step 1: pH is elevated (Alkalosis)
Step 2: PaCO2 is elevated (in keeping with a respiratory acidosis)
Step 3: HCO3- is elevated (in keeping with a metabolic alkalosis)
Since pH is above 7.40, the "alkalotic condition" must have occurred first, i.e. Metabolic alkalosis.

Step 4: Apply the compensation rule for chronic metabolic alkalosis as follows:

- **Expected $pCO_2 = 0.7(HCO_3^-) + 20$** (measured PaCO2 range +/- 5mmHg)
- The expected PaCO2 should be: 0.7(48) + 20 = 53.6mmHg (if there is appropriate compensation the PaCO2 will be between 48.6 and 58.6mmHg)
- The Measured $PaCO_2$ is 50.0mmol/L, therefore compensation is appropriate

Assessment: Chloride-resistant Metabolic Alkalosis with appropriate respiratory compensation.

In **metabolic disorders**, the metabolic component can usually be further described. For a metabolic alkalosis, the source of the HCO3- loss can be further evaluated with the measurement of the urinary Chloride (see below: Metabolic Alkalosis).

***** NEW STEP *****

Step 5: Can the metabolic disorder be further defined?

Defined as a primary increase in [HCO_3^-]. It can be classified into chloride sensitive metabolic alkalosis and chloride resistant metabolic alkalosis (**based on the urinary chloride measurement**).

Chloride sensitive metabolic alkalosis is associated with NaCl deficiency and extracellular fluid volume depletion. Common causes in the GIT that deplete the ECF volume, are vomiting and loss of gastric fluid via gastric drainage (nasogastric tube suctioning). The use of diuretics can also lead to a metabolic alkalosis with increased Na^+, K^+, and CL^- excretion. This leads to a metabolic alkalosis with electrolyte abnormalities (eg, hypokalemia).

Chloride resistant metabolic alkalosis is seen in patients with increased mineralocorticoid activity. It does not cause depletion of the extracellular fluid volume. An inappropriate increase of mineralocorticoid activity can cause sodium retention and expansion of the extracellular fluid volume.

In both chloride resistant and sensitive metabolic alkalosis, it is important to measure the urinary chloride concentration.

Chloride sensitive metabolic acidosis has a urinary chloride concentration < 10mEq/L

- Vomiting / previous diuretic therapy
- Volume depletion
- Responds to saline infusion

Chloride resistant metabolic alkalosis has a urinary chloride concentration > 20mEq/L

- Excessive aldosterone / current diuretic therapy
- Associated with volume expansion
- Associated with hypokalemia
- Resistant to saline therapy

Important to note: the most common causes of metabolic alkalosis include: (i) diuretic therapy, (ii) NG tube suctioning and (iii) vomiting.

Causes of Metabolic Alkalosis

Chloride sensitive (Ur Cl <10)	Chloride resistant (Ur Cl >20)
Gastrointestinal • Vomiting • Gastric drainage • Chloride diarrhea Renal • Diuretics • Low chloride intake Sweat • Cystic Fibrosis **<u>Miscellaneous</u>** Massive blood transfusion Hypercalcemia • Bone metastases Acetate-containing colloid solutions Glucose feeding after starvation Alkaline administration with renal insufficiency	Increased Mineralocorticoid activity • Primary hyperaldosteronism • Cushing syndrome • Secondary hyperaldosteronism (oedematous disorders) • Severe hypokalemia • Liquorice

Table adapted from Morgan and Mikhail[7].

Treatment of Metabolic Alkalosis:

1. Correct the underlying disorder
2. Any respiratory disorder contributing to the alkalemia should be corrected by normalising the $PaCO_2$.
3. Treat chloride sensitive metabolic alkalosis with normal saline and potassium.
4. Primary increases in mineralocorticoid activity responds to spironolactone (aldosterone antagonist)
5. pH > 7.60 can be treated with IV hydrochloric acid (0.1 mol/L), ammonium chloride (0.1mol/L), arginine hydrochloride or dialyses.

As mentioned earlier, metabolic acidosis is a primary decrease in [HCO_3^-]. It can be initiated by one of the following three mechanisms:

1. Consumption of HCO_3^- by a strong non-volatile acid.
2. Renal or gastrointestinal wasting of bicarbonate
3. Rapid dilution of the extracellular fluid compartment with a bicarbonate-free fluid

A fall in plasma [HCO_3^-] without an appropriate reduction in $PaCO_2$, decreases the arterial pH. The pulmonary compensatory response will reduce the $PaCO_2$, but never to a level that will normalize the pH.

Important to calculate the Anion Gap (AG):
AG is defined as the difference between the major measured cations and the major measured anions.

Anion gap = Major measured cations – Major measured anions
Anion gap = [Na^+] – ([CL^-] + [HCO_3^-]) (K^+ can be included in the equation)
Anion gap = 140 – (104 + 24) = 12 mEq/L (normal range = 7-14 mEq/L)

Electroneutrality must be maintained in the body: sum of all the anions must equal the sum of all the cations.

Therefore:

Anion gap = Unmeasured Cations – Unmeasured Anions

Plasma Albumin accounts for a large amount of the anion gap. As a guide, the anion gap decreases by 2.5mEq/L for every 1g/dL decrease in plasma albumin concentration[7].

Causes of Metabolic acidosis:

Increased AG:

Increased production of endogenous non-volatile acids:

- Renal failure
- Ketoacidosis → Diabetic, Starvation
- Lactic acidosis
- Mixed → Nonketotic hyperosmolar coma, Alcoholic
- Inborn errors of metabolism

Ingestion of toxin

- Salicylate
- Methanol
- Sulphur
- Ethylene glycol

Normal AG (hyperchloremic):

Increased gastrointestinal losses of HCO_3^-

- Diarrhoea
- Fistulas (pancreatic, biliary or small bowel)
- Ingestion of $CaCl_2$, $MgCl_2$

Increased renal losses of HCO_3^-

- Renal tubular acidosis
- Hypoaldosteronism
- Carbonic anhydrase inhibitors

Dilutional

- Large amounts of bicarbonate-free fluids (eg, 0.9% NaCl

TPN (total parenteral nutrition)

Increased intake of chloride-containing acids

Normal Anion gap metabolic acidosis is associated with hyperchloremia. As HCO_3^- ions are lost, they are replaced by Cl^- ions in the plasma. The most common causes of hyperchloremic metabolic acidosis are from abnormal gastrointestinal or renal losses of HCO_3^-, or from excessive intravenous administration of 0.9% NaCl solution[7].

NB to calculate the urine AG:

Urine Anion Gap = $([Na^+] + [K^+]) – [CL^-]$

Normal Urine AG = positive or close to zero (+10 to +100mEq/L)[11]

Used in normal AG metabolic acidosis to determine where the bicarbonate loss is taking place: GIT/Kidney[10]:

A negative urinary AG = GIT loss of bicarbonate

A positive urinary AG = impaired distal renal acidification

Treatment of metabolic acidosis:

1. Treat the underlying cause
2. Correct any respiratory component → control respiration - a $PaCO_2$ in the low 30's can partially return the pH to normal.
3. If pH remains below 7.20, and depending on the underlying cause, $NaHCO_3^-$ can be given.

   Dosing of $NaHCO_3^-$:

   As a fixed dose: 1 mEq/Kg

   Or

   $NaHCO_3$ = Base Deficit x 30% x body weight in kg[7]

Delta Ratio (Also known as: Delta ratio or Gap-Gap ratio or Delta-Delta)**:**

If the patient has an AG metabolic acidosis, the delta ratio can be calculated. The Delta ratio can help to determine if the AG is a pure AG acidosis, a non-AG acidosis or a metabolic alkalosis.

It compares the size of the anion gap increase to the decrease in serum HCO_3^-.

Delta-Delta equation = (Calculated AG) – (Expected AG) / (Expected Serum HCO_3^-) – (Actual Serum HCO_3^-)

Or

Delta ratio = Increased Anion ions / Decreased HCO_3^- ions

Important to use the serum HCO_3^- as a surrogate for the serum CO_2
If the HCO_3^- is different from 24mEq/L, use the patients baseline serum HCO_3^-[11]

Interpretation of the delta-delta equation[11]:

Delta Ratio value	**Condition Present**
< 0.4	Pure NAGMA
0.4 – 0.9	HAGMA and NAGMA present
1.0 – 2.0	Pure HAGMA
>2.0	HAGMA with a Metabolic Alkalosis

Scenario 8

30-year-old female patient presents with a 3-day history of watery diarrhoea. She is known to have HIV with a CD4 count of 300. She has been taking ARVs for the last 3-months.

ABG:
pH 7.27
pCO_2 33mmHg
pO_2 80mmHg
HCO_3^- 16mmol/L
Lac 1.5 mmol/L

Biochemistry:
Na^+ 136
K^+ 2.9
CL^- 113
AG 10

Step 1: pH is low (Acidosis)
Step 2: PaCO2 is reduced (in keeping with a respiratory alkalosis or compensation)
Step 3: HCO3- is reduced (in keeping with a metabolic acidosis or compensation)
Since pH is below 7.40, the "acidotic condition" must have occurred first, i.e. Metabolic acidosis.

Step 4: Apply the compensation rule for acute metabolic acidosis as follows:

- **Expected PaCO2 = 1.5(HCO3)+8** (measured PaCO2 range +/- 2mmHg)
- The expected PaCO2 should be: 1.5(16) + 8 = 32mmHg (if there is appropriate compensation the PaCO2 will be between 30 and 34mmHg)
- The Measured PaCO2 is 33mmHg, therefore compensation is appropriate

Step 5: Can the metabolic component be described further?
For a metabolic acidosis, 2 further calculations can be made (see above):

- Anion Gap = (136+2.9)-(113+16) = 10 (NAGMA)
- Delta Gap: (12-10) / (24-16) = 2 / 6 = 0.3 (Delta gap <0.4 = pure NAGMA)

Assessment: Normal AG Metabolic Acidosis with appropriate respiratory compensation.

Scenario 9

40-year-old male patient presents with an altered level of consciousness. History from the family is that the patient was drinking homemade alcohol. He is also known to have a pancreatic fistula. His ABG is as follows:

ABG:
pH 7.15
pCO_2 30mmHg
pO_2 80mmHg
HCO_3^- 14mmol/L
s-Methanol 15mmol/L (toxic >6.25mmol/L)

Biochemistry:
Na^+ 132
K^+ 2.0
Cl^- 100
AG 20

Step 1: pH is low (Acidosis)
Step 2: PaCO2 is reduced (in keeping with a respiratory alkalosis or compensation)
Step 3: HCO3- is reduced (in keeping with a metabolic acidosis or compensation)
Since pH is below 7.40, the "acidotic condition" must have occurred first, i.e. Metabolic acidosis.

Step 4: Apply the compensation rule for acute metabolic acidosis as follows:

- **Expected PaCO2 = 1.5(HCO3)+8** (measured PaCO2 range +/- 2mmHg)
- The expected PaCO2 should be: 1.5(14) + 8 = 29mmHg (if there is appropriate compensation the PaCO2 will be between 27 and 31mmHg)
- The Measured PaCO2 is 30mmHg, therefore compensation is appropriate

Step 5: Can the metabolic component be described further?
For a metabolic acidosis, 2 further calculations can be made (see above):

- Anion Gap = (132+2)-(100+14) = 20 (High Anion Gap)
- Delta Gap: (20-12) / (24-14) = 0.8
  (Delta gap between 0.4 – 0.8 = Combined HAGMA and NAGMA)

Assessment: Mixed HAGMA and NAGMA with appropriate respiratory compensation.

HAGMA – caused by the toxic alcohol ingestion (methanol)
NAGMA – caused by the pancreatic fistula

Scenario 10

70-year-old male patient developed a cardiac arrest in the surgical high care ward. CPR was started within seconds of the arrest. He is intubated and ventilated every 6-seconds with uninterrupted chest compressions. His ABG is as follows:

ABG:
pH 6.85
pCO_2 80mmHg
pO_2 220mmHg
HCO_3^- 14mmol/L
Lac 12mmol/L

Biochemistry
Na 133.5
K^+ 4.5
Cl^- 100
AG 24

Step 1: pH is low (Acidosis)
Step 2: PaCO2 is elevated (in keeping with a respiratory acidosis)
Step 3: HCO3- is reduced (in keeping with a metabolic acidosis)

Step 4: Is there appropriate compensation?
Assuming the metabolic acidosis occurred first, the expected PaCO2 should be 29mmHg, however the PaCO2 is much higher than predicted (80mmHg), therefore a Respiratory Acidosis co-exists.

Step 5: Can the metabolic component be described further?
For a metabolic acidosis, 2 further calculations can be made (see above):

- Anion Gap = (133.5+4.5)-(100+14) = 24 (High Anion Gap)
- Delta Gap: (24-12) / (24-14) = 12/10 = 1.2

(Delta gap between 1 – 2 = Pure HAGMA)

Assessment: HAGMA with a concomitant Respiratory Acidosis

Scenario 11

An 80-year-old female is brought to casualty in a semi-comatosed state. She lives in an assisted care facility and is known to have dementia and chronic left ventricular failure. Her chronic medication includes: Digoxin, Enalapril and Hydrochlorothiazide. Her ABG is as follows:

ABG:
pH 7.36
pCO_2 32mmHg
pO_2 85mmHg
HCO_3^- 19mmol/L
Lac 2.0 mmol/L

Biochemistry:
Na^+ 148.5
K^+ 4.5
Cl^- 100
AG 34

Step 1: pH is normal (Look for other abnormalities)
Step 2: PaCO2 is reduced (possible respiratory alkalosis or compensation)
Step 3: HCO3- is reduced (possible metabolic acidosis or compensation)

Step 4: Is there appropriate compensation?
Assuming the metabolic acidosis occurred first (as the pH is <7.40), the expected PaCO2 should be 36.5mmHg, however the PaCO2 is lower than predicted (32mmHg), therefore a Respiratory Alkalosis co-exists.

Step 5: Can the metabolic component be described further?
For a metabolic acidosis, 2 further calculations can be made (see above):

- Anion Gap = 34 (High Anion Gap)
- Delta Gap: (34-12) / (24-19) = 22/5 = 4.4

(Delta gap >2 = HAGMA with a pre-existing metabolic alkalosis)

Assessment: Mixed Respiratory Alkalosis and HAGMA (with a pre-existing metabolic alkalosis)

Calculating the pre-existing HCO3-:

- The anions increased by 22mmol/L (i.e. 34 – 12)
- The HCO3- should decrease by a similar amount
- If the HCO3 is now 19mmol/L, it must have been 41mmol/L (19+22) before the rise in anions.

Scenario 12

A 65-year-old male patient is admitted with congestive cardiac failure and respiratory distress. He has been unwell for 4-weeks and has been vomiting for the last 5 days. His chronic medication includes: Enalapril, Amlodipine, paracetamol and ibuprofen (for osteoarthritis). He was placed on a 40% oxygen facemask. His ABG is as follows:

ABG:
pH 7.58
pCO_2 15mmHg
pO_2 110mmHg
HCO_3^- 18mmol/L
Lac 4.0 mmol/L

Biochemistry:
Na^+ 136.8
K^+ 5.2
CL^- 100
AG 24

Step 1: pH is elevated (alkalosis)
Step 2: PaCO2 is reduced (possible respiratory alkalosis or compensation)
Step 3: HCO3- is reduced (possible metabolic acidosis or compensation)

Step 4: Is there appropriate compensation?
Assuming the respiratory alkalosis occurred first (as the pH is >7.40), apply the rule for chronic respiratory alkalosis. The expected HCO3- should be (24-10) = 14mmHg, however the HCO3- is higher than predicted (18mmHg), therefore a Metabolic Alkalosis co-exists.

Step 5: Can the metabolic component be described further?
For a metabolic acidosis, 2 further calculations can be made (see above):

- Anion Gap = 24 (High Anion Gap metabolic acidosis)
- Delta Gap: (24-12) / (24-18) = 12/6 = 2
  (Delta gap of 2 = pure HAGMA)

Assessment: Triple disorder: Respiratory Alkalosis + Metabolic Alkalosis + HAGMA

It is important to have a systematic approach to analysing an arterial blood gas. In a mixed acid-base disorder, two or more in-dependent acid-base disorders are occurring at the same time[12].

A 3-step approach to acid base disorders can help tackle and un-mask mixed acid-base disorders.

First: Look at the pH, pCO_2, $[HCO_3^-]$, this will help to identify the most obvious disorder. If you can spot more than one disorder, just pick one!

Second: Apply the formulae for the expected compensation for the disorder that you have identified. This will help identify a second disorder. Asking yourself the question: Is the compensation for this disorder appropriate?[12]

- In metabolic disorders, $[HCO_3^-]$ is abnormal. We are therefore checking for a co-existing respiratory disorder. Keeping the question in mind: What should the $PaCO_2$ be after compensation? If there is a great difference from that predicted, then a co-existing respiratory disorder is present.

- In a respiratory disorder, the $PaCO_2$ is abnormal, and we want to check for a metabolic disorder. Remember to ask: What should the $[HCO_3^-]$ be after compensation? If the $[HCO_3^-]$ differs greatly from the calculated formulae then a co-existing metabolic disorder exist.

Third: Calculate the anion gap. The normal value of the anion gap can vary from 9-16mEq/L, but some sources use a stricter range of 10-14mEq/L. The presence of a high anion gap is a strong indicator of a metabolic acidosis. If the calculated AG is normal, then you are done with your analyses or interpretation of the ABG[12].

- AG > 20mEq/L = high AG acidosis is probably present
- AG > 30mEq/L = high AG acidosis is most certainly present
- Lactic acidosis ratio of increase AG / decrease $[HCO_3^-]$ = 1.5
- Ketoacidosis ratio of increase AG / decrease $[HCO_3^-]$ = 1

Steward's theory of pH changes are governed by the application of the following basic physical principles:

- Law of mass action
- Law of conservation of mass
- Law of conservation of charge

Central to the understanding of the Steward's theory are some unique properties of water. Water has a high molar concentration, water can be ionised, solutes added to water alter the ionisation of water. The extent to which water ionises determines the H+ ion concentration and therefore the pH.

$$\text{Water dissociation: } K_w = \frac{[H^+][OH^-]}{H_2O}$$

The Steward approach describes the acid-base change in terms of **3 independent elements**:

1. **PaCO2**
   This is no different to the Henderson-Hasselbalch approach. The PaCO2 is measured on the arterial blood gas sample and directly influences the pH as described earlier.

2. **Strong Ion difference (SID)**
   The SID is the difference between the sum of all strong cations and all strong anions.

   SID = [Na+] + [K+] + [Ca2+] + [Mg2+] – [Cl-] + [Other strong anions]

   The normal SID is approximately 40mmol/L
   Any change from this value is approximately equal to the standard Base Excess, i.e. assuming a normal protein level, if the SID were 35mEq/L, then the standard base excess should be -5mEq/L. If the SID was 48mEq/L, then the standard base excess will be +8mEq/L.
   The mechanism by which the SID affects the pH is via the addition or removal of these strong ions. This causes a shift in the equilibrium of water resulting in more or less H+ ions in solution. E.g. if excess chloride was added to the system, this would decrease the SID. A decrease in the SID will shift the dissociation of water to produce more H+ ions in solution. This will result in an acidosis, i.e. hyperchloraemic metabolic acidosis.

3. **Total amount of weak non-volatile acid (Atot)**
   The non-volatile acids are made up of albumin, inorganic phosphate and other plasma proteins. The greatest influence of the Atot is the albumin which acts as a weak acid. As the albumin concentration in plasma decreases, the Atot will decrease and an alkalosis will develop. A decrease in phosphate level is unlikely to have a major impact on Atot as the levels are already normally low in comparison to other anions. However, in hyperphosphataemic states e.g. renal failure, high phosphate levels can contribute towards an elevated Atot and therefore an acidaemia.

Independent variable	Variation	Acid-base effect
PCO_2 [mm Hg]	↑	Respiratory acidosis
	↓	Respiratory alkalosis
SID [mEq L^{-1}]	↑	Metabolic alkalosis
	↓	Metabolic acidosis
A_{TOT} [mmol L^{-1}]	↑	Metabolic acidosis
	↓	Metabolic alkalosis

PCO_2 — carbon dioxide partial pressure; SID — strong ion difference; Atot — total non-volatile weak acids

Acute acidaemia is frequently observed during critical illness and in ICU, and persistent severe acidaemia is linked to poor outcomes. Sodium bicarbonate infusion to treat severe metabolic acidosis is a possible treatment option but remains controversial as no randomised controlled trials have yet evaluated its effect on patient outcomes.

This trial tried to answer whether an infusion of sodium bicarbonate in critically ill patients with severe metabolic acidaemia (defined as a pH ≤7·20) decreases the composite outcome of mortality by day 28 or the presence of at least one organ failure at day 7. Na Bicarbonate was used to maintain a pH of 7.30.

This trial was a multicentre (26 French ICUs), open labelled, randomised controlled trial between May 2015 and May 2017.

Population:

- Inclusion: adult patients (aged ≥18 years) who were admitted within 48 h to the ICU with severe acidaemia: pH ≤7·20, PaCO2 ≤45 mm Hg, and sodium bicarbonate concentration ≤20 mmol/L
- And, with a SOFA score of 4 or more or an arterial lactate concentration of >2 mmol/L
- Exclusion: respiratory acidosis, proven digestive or urinary tract loss of sodium bicarbonate (volume loss ≥1500 mL per day), stage IV chronic kidney disease, ketoacidosis, and sodium bicarbonate infusion (including renal replacement therapy) within 24 h before screening
- **389** patients were included

Intervention

- 4.2% sodium bicarbonate intravenously infused

Comparator:

- No infusion of intravenous 4.2% sodium bicarbonate or placebo

Outcome:

Primary outcome: No statistical difference in the following outcomes:
(1) composite of death from any cause by 28 days after randomisation and the presence of at least one organ failure at 7 days after randomisation - absolute difference estimate –5·5%, 95% CI –15·2 to 4·2; p=0·24.
(2) Day 28 mortality: 54% in the control group vs 45% in the bicarbonate group; p=0.07
(3) One or more organ failure at day 7: 69% in the control group vs 62% in the bicarbonate group; p=0.15.

In patients with Acute Kidney Injury (AKIN) score of 2-3 (n=182), there was a statistically significant difference in:
(1) primary composite outcome: 74/90 (82%) in the control group vs 64/92 (70%) in the bicarbonate group; p=0·0462, day 28 mortality: 57/90 (63%) in the control group vs 42/92 (46%) in the bicarbonate group; p=0·0166, and
(2) one or more organ failure at day 7: 74/90 (82%)in the control group vs 61/92 (66%) in the bicarbonate group; p=0·0142

Adverse events: Metabolic alkalosis, hypernatraemia, and hypocalcaemia were observed more frequently in the bicarbonate group than in the control group, with no life threatening complications reported.

Conclusion

In patients with severe metabolic acidaemia, sodium bicarbonate had no effect on the primary outcomes. However, sodium bicarbonate decreased the primary composite outcome and day 28 mortality in the a subgroup of patients with acute kidney injury.

Conclusion:

It is very common to come across acid base disturbances(disorders) in patients in theatre and the ICU. The arterial blood gas is a tool and if used correctly, can help in the prevention and treatment of morbidity and mortality. Therefore, a good understanding of the arterial blood gas interpretation is essential.

References:

1. https://medical-dictionary.thefreedictionary.com/blood+gas+analysis
2. Nolte D. Principles of measurement: Arterial blood gas and electrodes. UCT Part 1 Anaesthesia Refresher Course. 2018.
3. Singh V, Khatana S, Gupta P. Blood gas analysis for bedside diagnosis. Natl J Maxillofac Surg 2013; 4:136-41.
4. Hermann DA. Arterial blood gas interpretation demystified. Physician Assist Clin 4 (2019) 551–560. https://doi.org/10.1016/j.cpha.2019.02.008.
5. Eager M, Nicoll A, Tipping R. Mechanisms of hypoxemia and the interpretation of the arterial blood gas. Surgery (Oxford). Volume 39, Issue 10, October 2021, Pages 641-647.
6. Joubert I. Siggard Anderson vs Stewart. UCT Part 1 Anaesthesia Refresher Course. 2018.
7. Butterworth JF, Mackey DC, Wasnick JD. Morgan and Mikhail's Clinical Anesthesiology. 2018; 6: 1985-2025.
8. Nejthardt M. An Approach to Blood Gas Interpretation. UCT Part 1 Anaesthesia Refresher Course. 2018.
9. Shaw, I. et al. Acid-base balance: a review of normal physiology. BJA Education, Volume 22, Issue 10, 396-401. DOI: https://doi.org/10.1016/j.bjae.2022.06.003.
10. Oosthuizen E. Acid-Base interpretation. University of Pretoria Part 1 Anaesthesia Refresher course. 2008.
11. Healy, Z. Critical Concept Mastery Series: Acid-Base Disturbance Cases. McGraw Hill/Medical; 1st Edition: 1-720.
12. Preston, RM. Acid-base, fluids and electrolytes made ridiculously simple. Pg: 97-153.
13. Seifter JL. Integration of acid–base and electrolyte disorders. New England Journal of Medicine. 2014 Nov 6;371(19):1821-31.
14. Kamel KS, Halperin ML. Acid–base problems in diabetic ketoacidosis. New England Journal of Medicine. 2015 Feb 5;372(6):546-54.
15. Jaber S, Paugam C, Futier E, Lefrant JY, Lasocki S, Lescot T, Pottecher J, Demoule A, Ferrandiere M, Asehnoune K, Dellamonica J. Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial. The Lancet. 2018 Jul 7;392(10141):31-40.
16. Mittal K. OH's intensive care manual. Journal of Pediatric Critical Care. 2019 Mar 1;6(2):80.