Society of Mechanical Ventilation

Acid-Base Balance
and
Arterial Blood Gases
Part I

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Objectives

Introduction

The Acid-Base balance in the human body is a critical aspect of maintaining homeostasis and ensuring the proper functioning of cells and organs. It refers to regulating hydrogen ion (H^+) concentration in body fluids, particularly in the blood. It ensures that blood pH stays within the narrow range of 7.35 to 7.45, with an average of 7.40, which is crucial for oxygen delivery, protein function, and overall cellular activity. Hemoglobin loses its affinity in an acidic medium and is not fully saturated in an alkaline medium. In addition, proteins must maintain a certain charge in order not to lose their configuration and function. To preserve this balance, the body relies on three main mechanisms: chemical buffers, the respiratory system, and the kidneys. These systems work together to neutralize excess acids or bases, respond to physiological changes, and restore equilibrium. When these regulatory processes fail or become overwhelmed, it can result in acid-base disorders such as metabolic or respiratory acidosis and alkalosis, each requiring prompt evaluation and management.

Normal Values:

- The level of H+ in the blood is normally maintained within a narrow range of 37 to 43 nanomoles per liter (nEq/L), which corresponds to a pH range of 7.37 - 7.43.
- pH is calculated as the negative logarithm of the hydrogen ion concentration ($pH = -log[H^+]$)
- If the pH drops below 7.35, the condition is called acidemia; if it rises above 7.45, it's referred to as alkalemia.

Sources of Acids and Bases

Acid sources

A- Most Acids:

- Carbon dioxide (CO_2): Produced in large quantities through carbohydrate and fat metabolism.

The breakdown of carbohydrates and fats during metabolism produces approximately 15,000 to 20,000 millimoles of carbon dioxide (CO_2) each day. While CO_2 itself isn't an acid, it becomes acidic when it reacts with water (H_2O) in the bloodstream—a process facilitated by carbonic anhydrase enzymes. This reaction forms carbonic acid (H_2CO_3), which quickly splits into hydrogen ions (H^+) and bicarbonate (HCO_3^-). The hydrogen ions temporarily bind to hemoglobin in red blood cells. When blood reaches the lungs, oxygenation causes the hydrogen ions to be released, and the reaction is reversed: carbonic acid is converted back into CO_2 and water. The CO_2 is then exhaled, and the water is eliminated by the kidneys.

B-Lesser amounts of organic acids:

- Organic acids from incomplete metabolism: lactic acid, ketoacids.
- Sulfuric acid from sulfur-containing amino acids (e.g., cysteine, methionine).
- Phosphoric acid from dietary phosphate
-Cationic amino acids (arginine, lysine)

Fixed (nonvolatile) acids: Must be neutralized by HCO_3^- in the extracellular fluid or excreted by the kidneys.

Under normal insulin levels, carbohydrates and fats are fully broken down into carbon dioxide (CO_2) and water (H_2O). However, when insulin is deficient, as in diabetes mellitus, the body shifts to an alternative metabolic pathway, leading to the formation of organic keto acids like β-hydroxybutyric acid.

Similarly, when oxygen levels are low (a condition known as hypoxia), cells switch to anaerobic metabolism, producing organic acids such as lactic acid instead of CO_2 and H_2O. This can happen even in healthy individuals during intense exercise. Additionally, poor blood flow—for instance, from low cardiac output—can reduce oxygen delivery to tissues, causing cells to rely on anaerobic metabolism, which also results in acid accumulation and a drop in body fluid pH, a state known as acidosis.

Base sources

- Anionic Amino acids like glutamate and aspartate.

- Oxidation of organic anions such as lactate and citrate, generating bicarbonate (HCO_3^-).

The body can develop four primary acid-base disorders: metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis. Because maintaining blood pH within a narrow, optimal range is vital for health, the body is equipped with compensatory mechanisms. When one of these imbalances occurs, the body attempts to restore balance by triggering a compensatory response in the opposite direction to minimize pH disruption.

Buffering Systems in the Body

The body uses buffer systems to prevent major pH changes:
- Bicarbonate buffer (main extracellular system)
- Hemoglobin buffer (binds CO_2 and H^+)
- Protein buffer (regulates intracellular pH)
- Phosphate buffer (mainly for urine)

Bone buffer in acid load by releasing sodium bicarbonate ($NaHCO_3$) and potassium bicarbonate ($KHCO_3$) in early stages and calcium-based compounds, such as calcium carbonate ($CaCO_3$) and calcium phosphate ($CaPO_4$) in later stages.

All of these contain bases that accept hydrogen ions which keep the pH from plummeting.
Carbon dioxide (CO_2), a byproduct of cellular respiration, plays an important role in maintaining the body's acid-base balance. In the presence of water (H_2O), CO_2 forms carbonic acid (H_2CO_3), which then dissociates into hydrogen ions (H^+) and bicarbonate ions (HCO_3^-). This reaction is reversible and remains in dynamic equilibrium under normal physiological conditions.

The enzyme carbonic anhydrase, found in renal tubules, red blood cells, the stomach lining, and pancreatic cells, speeds up this process. This reaction functions as a major buffer system, helping to stabilize blood pH within a tight and healthy range:

$$H_2O + CO_2 \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

According to Le Chatelier's Principle, if the equilibrium is disrupted—such as during metabolic acidosis, where the body struggles to remove excess H^+ ions, the reaction will shift to the left. This reduces the concentration of free H^+ by converting it into CO_2, which the lungs then expel by increasing ventilation, helping restore acid-base balance.

Compensation Mechanisms

A- Pulmonary Compensation: Rapid (minutes to hours), adjusts CO_2 levels via breathing.

B- Renal Compensation: Slower (days), regulates HCO_3^- and H^+ excretion.

C- Chemical Buffering: Immediate response to pH changes.

A- Pulmonary Compensation

The concentration of carbon dioxide (CO_2) in the blood is carefully controlled through adjustments in tidal volume (the amount of air moved per breath) and respiratory rate together referred to as minute ventilation. When blood pH drops (becomes more acidic), arterial chemoreceptors detect this change and trigger an increase in breathing rate or depth. This enhanced ventilation helps expel more CO_2, which in turn helps raise the pH back toward normal. However, this respiratory compensation is only partially effective, correcting about 50 to 75% of the imbalance and rarely restoring pH completely on its own.

B- Renal Compensation

The nephron, the kidney's functional unit, plays a critical role in maintaining acid-base balance. Blood flows through structures called glomeruli, which filter various substances into the renal tubules. Some of these substances, such as hydrogen ions (H^+) and bicarbonate (HCO_3^-), are either eliminated or reabsorbed back into the bloodstream.

All the bicarbonate in the blood is filtered through the glomerulus. Most of it is reabsorbed in the proximal tubule, with a smaller portion reabsorbed in the collecting tubule. In the distal tubule, water (H_2O) inside the cells splits into H^+ and hydroxide ions (OH^-). Under the action of carbonic anhydrase, OH^- combines with CO_2 to form new HCO_3^-, which is then returned to the bloodstream. Meanwhile, H^+ is secreted into the tubule, where it binds with filtered HCO_3^- to form CO_2 and H_2O, which can be reabsorbed again. This means the bicarbonate recovered distally is newly generated, not just reabsorbed from what was filtered.

Several factors affect bicarbonate handling:

- Low blood volume (as with diuretic use) increases HCO_3^- reabsorption.
- High PCO_2 levels also enhance HCO_3^- reabsorption.
- Parathyroid hormone, released during acidosis, reduces HCO_3^- reabsorption.
- Chloride deficiency increases sodium and bicarbonate reabsorption in the proximal tubule.

Acid (H^+) is actively secreted into both proximal and distal tubules, where it binds to urinary buffers such as phosphate (HPO_4^{2-}), creatinine, uric acid, and especially ammonia. The ammonia buffer system is vital because, unlike other fixed buffers, the kidney can increase ammonia production in response to greater acid loads.

The amount of acid secreted is mainly determined by arterial pH, but it is also influenced by:

- Potassium levels (K^+): When K^+ is low, H^+ secretion increases, which may result in metabolic alkalosis.
- Chloride levels (Cl^-) and the hormone aldosterone also play regulatory roles.

In summary:

- If the kidneys reabsorb more bicarbonate or excrete more acid, the blood becomes more alkaline (higher pH).
- If bicarbonate isn't reabsorbed or acid isn't excreted, the blood becomes more acidic (lower pH).

C- Chemical Compensation

Chemical buffers are systems that help stabilize pH by resisting sudden changes. Each buffer consists of a weak acid and its conjugate base. The conjugate base binds to excess hydrogen ions (H^+), while the weak acid can release H^+ when levels drop. This dynamic balance helps maintain a steady concentration of free hydrogen ions in a solution. Buffers are most effective when the pH is close to the pKa.

The relationship between the pH of a buffer system and the concentration of its components is described by the Henderson-Hasselbalch equation:

$$pH = pKa + log(\frac{[anion]}{[weak\ acid]})$$

where pKa is the dissociation constant of the weak acid

The relationship between pH, HCO_3^-, and CO_2 in the system as described by the Henderson-Hasselbalch equation is thus:

$$pH = 6.1 + log(\frac{[HCO_3^-]}{[0.03 \times P\mathrm{CO_2}]})$$

Or similarly, by the Kassirer-Bleich equation, derived from the Henderson-Hasselbalch equation:

$$H^{+} = 24 \times \frac{P\text{CO}_2}{HCO_3^-}$$

- Note: to convert arterial pH to [H+] use:

$$pH = -log[H^{+}]$$

$$[H^{+}] = 10^\wedge(-pH)$$

Both equations illustrate that acid-base balance depends on the ratio of carbon dioxide partial pressure (PCO_2) and HCO_3-, not on the absolute value of either one alone.

In a healthy person, acid-base balance is maintained through the combined action of several key processes. These include the amount of acid naturally produced in the body (net endogenous acid production, or NEAP), the buffering capacity of both intracellular and extracellular systems, and the kidneys' ability to reabsorb filtered bicarbonate and generate new bicarbonate. If any of these mechanisms are impaired, especially in conditions like chronic kidney disease (CKD), it can lead to metabolic acidosis

Types of Acid-Base Disorders

Metabolic Acidosis: Increased acid production or ingestion, decreased acid excretion, or HCO_3^- loss.

Metabolic Alkalosis: Loss of acid or excess HCO_3^-.

Respiratory Acidosis: $PaCO_2 > 40$ mmHg (Hypercapnia)

Respiratory Alkalosis ($PaCO_2 < 35$ mmHg) (Hypocapnia)

Simple: One primary disturbance.

Mixed: Two or more abnormalities.

Diagnosing Acid-Base Imbalances

Tests

- ABG: pH, $PaCO_2$, HCO_3^-, oxygenation

- Electrolyte Panel

- Anion Gap = $Na^+ - (Cl^- + HCO_3^-)$

-If metabolic acidosis is present, the Delta gap is calculated and Winters formula applied

-Search for compensatory changes

Arterial blood gas (ABG) testing provides direct measurements of arterial pH and partial pressure of carbon dioxide ($Paco_2$). However, in situations like circulatory collapse or cardiopulmonary resuscitation (CPR), venous blood samples may better reflect the metabolic state of the tissues. In these cases, venous readings can be more helpful for guiding decisions on bicarbonate therapy and assessing whether ventilation is sufficient.

HCO_3 level:

- Reported on the arterial blood gas panel
- Calculated using the Henderson-Hasselbalch equation.
- Measured serum chemistry panel. Directly measured HCO_3 levels are considered more accurate in cases of discrepancy.

Winters Formula: Expected $PaCO_2 = 1.5 \times HCO_3^- + 8 \pm 2$

Delta Gap ($\Delta AG / \Delta HCO_3$): Identifies mixed disorders when anion gap is high.

Arterial Blood Gases (ABGs): Overview and Procedure

Purpose:

ABG analysis is a diagnostic technique used to evaluate a patient's acid-base balance, oxygenation, and ventilation status. It involves drawing a blood sample from an artery, usually the radial artery, and is especially useful in adjusting ventilation settings.

Clinical Indications:

- Assessing acid-base balance
- Measuring electrolytes
- Detecting levels of carboxyhemoglobin and methemoglobin
- Used in patients with difficult venous access, such as obese individuals or IV drug users, where the radial artery remains palpable

Contraindications:

Absolute contraindications:

- Trauma, infection, or burns at the puncture site
- Inadequate collateral circulation through the palmar arch
- History of vascular issues involving the radial or ulnar arteries

Perform an Allen test to ensure sufficient collateral blood flow before the procedure.

Relative contraindications (Use with Caution):

- Patients on anticoagulants or thrombolytic therapy, due to increased risk of bleeding, hematoma, or compartment syndrome

Required Equipment:

- Antiseptic pads (alcohol, chlorhexidine, or iodine)
- 2–3 mL heparinized syringe with a 23- to 25-gauge needle
- Syringe cap
- Gloves and protective equipment
- Gauze or dressing

Suggested Tools:

- 1–2% lidocaine for local anesthesia
- Ultrasound or Doppler if artery is hard to locate

- Rolled towel or kidney basin to stabilize and extend the wrist
- Ice if the sample will not be analyzed within 10 minutes

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Procedure:

1. Perform the Allen Test:
    - Ask the patient to clench their fist for 30 seconds.
    - Simultaneously compress both the radial and ulnar arteries.
    - Release the ulnar artery and observe for color return to assess blood flow.
    - Choose the wrist with better collateral circulation.

2. Prepare the Site:
    - Locate the radial artery (between the styloid process of the radius and the flexor carpi radialis tendon).
    - Place the forearm on a support and tape it in an extended position.
    - Clean the site thoroughly and apply local anesthetic.
    - Wait 1–2 minutes or gently massage to ensure anesthesia is effective.

3. Draw the Sample:
    - Insert the needle at a 30–45° angle toward the arterial pulse.
    - If blood doesn't flow, adjust the angle or depth carefully.
    - In critically ill patients, pulsatile flow may be reduced.

4. After Collection:
    - Remove the needle and expel any air from the syringe.
    - Seal with the syringe cap.
    - Apply firm pressure to the site to prevent hematoma.
    - Label the sample with date, time, and oxygen concentration.

- o Analyze immediately or refrigerate (up to 30 minutes if needed).

Possible Complications:

- Infection
- Bleeding
- Arterial injury or laceration
- Formation of pseudoaneurysm
- Arteriovenous malformation
- Nerve damage

Normal ranges

Breathing room air: PaO_2 >12 kPa (>10 in normal elderly) 80-100 mmHg, $PaCO_2$ 4.6– 5.9 kPa (35-45 mmHg)

-pH: pH less than 7.35 is denoted as acidotic, and pH above 7.45 is denoted as alkalotic

-PaO_2: reflects oxygenation adequacy

-$PaCO_2$ reflects ventilation, respiratory acid-base status, and its contribution in maintaining hemostasis.

-HCO_3^- reflects the metabolic or renal contribution

ABG Interpretation Summary

Changes in $PaCO_2$ reflect the respiratory component and changes in HCO_3^- reflect the metabolic component.

↓ pH + ↑ $PaCO_2$ = Respiratory Acidosis

- If the HCO_3^- ↑ = metabolic compensatory mechanism in response to the respiratory acidosis. HCO3− should compensate by increasing 3 to 4 mEq/L (3 to 4 mmol/L) for each 10 mmHg rise in $PaCO_2$ sustained for 4 to 12 hours (there may be no increase or only an increase of 1 to 2 mEq/L [1 to 2 mmol/L], which slowly increases to 3 to 4 mEq/L [3 to 4 mmol/L] over days). A greater increase in HCO_3^- implies primary metabolic alkalosis; a lesser increase suggests no time for compensation or coexisting primary metabolic acidosis.

↓ pH + ↓ HCO_3^- = Metabolic Acidosis

- $PaCO_2$ should decrease relative to the drop in HCO_3^- according to Winter's formula
  $PaCO_2 = (1.5 \times HCO_3^-) + 8 \pm 2$
  If $PaCO_2$ is higher then concomitant respiratory acidosis and if lower, then concomitant respiratory alkalosis

↑ pH + ↓ $PaCO_2$ = Respiratory Alkalosis

- The HCO_3^- should compensate over 4 to 12 hours by decreasing 4 to 5 mEq/L (4 to 5 mmol/L) for every 10 mmHg decrease in $PaCO_2$. A lesser decrease means there has been no time for compensation, or a primary metabolic alkalosis coexists. Greater decrease implies a primary metabolic acidosis.

↑ pH + ↑ HCO_3^- = Metabolic Alkalosis

- The $PaCO_2$ should compensate by increasing about 0.6 to 0.75 mm Hg for each 1 mEq/L (1 mmol/L) increase in HCO_3^- (up to about 55 mmHg) or $PaCO_2 = 0.7\ [HCO3-] + 20$ mmHg ± 5. .Greater increase implies concomitant respiratory acidosis; lesser increase, respiratory alkalosis.

- If pH is normal but $PaCO_2$ and HCO_3^- are abnormal → mixed disorder.
- Compensatory mechanisms begin to correct the pH whenever an acid-base disorder is present. Compensation cannot return pH completely to normal

When evaluating acid-base disorders, it is important to determine whether changes in $PaCO_2$ and HCO_3^- show the expected compensation. If not, then a second primary process should be suspected of causing abnormal compensation.

Nomograms, also known as acid-base maps, provide an alternative method for evaluating mixed acid-base disorders. These graphical tools allow clinicians to plot pH, bicarbonate (HCO_3^-), and carbon dioxide ($PaCO_2$) levels at the same time. The diagnostic nomogram uses logarithmic scales for both $PaCO_2$ and HCO_3^-, and it outlines distinct regions that represent different types of compensated acid-base imbalances. By plotting a patient's data, clinicians can more easily identify whether a single or mixed acid-base disorder is present. These graphs are increasingly used in digital formats for quick bedside analysis.

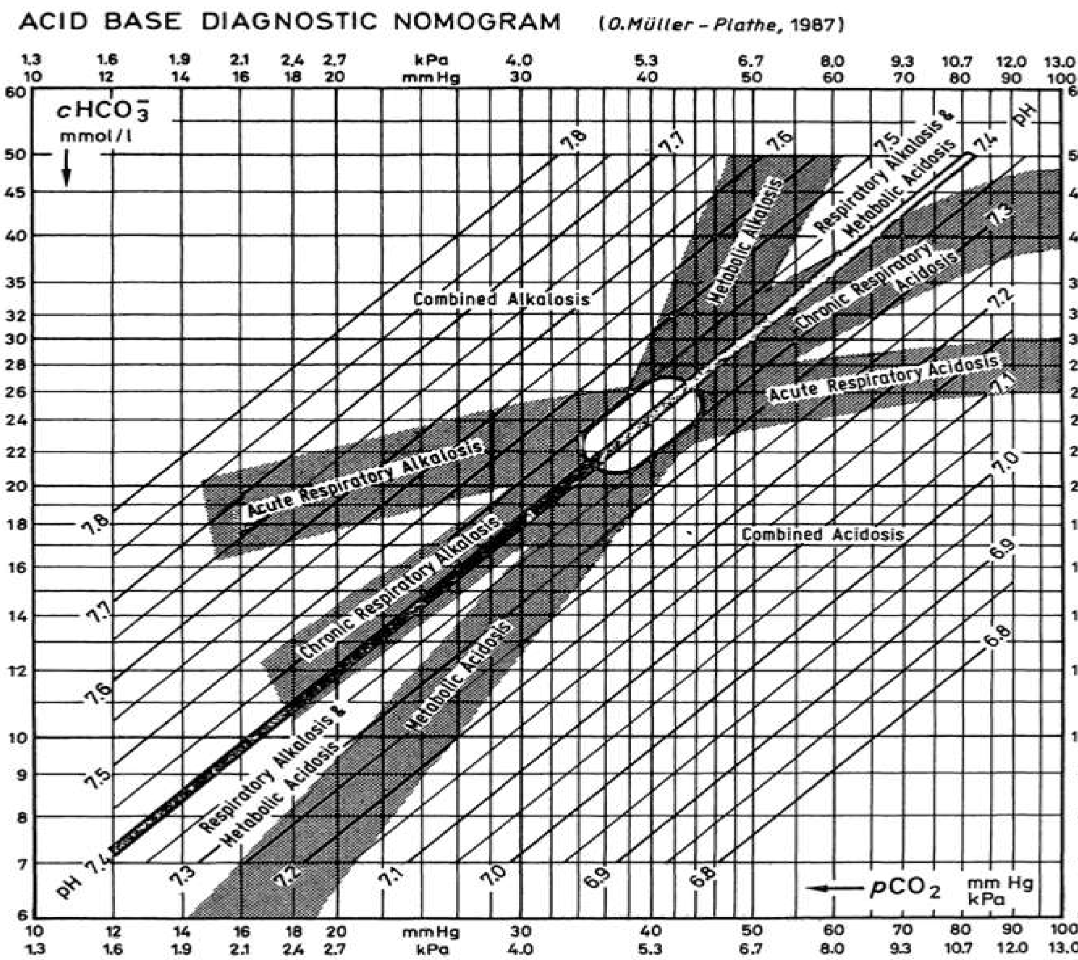

Figure 1: Nomogram showing the interaction between $PaCO_2$ and HCO_3 and the resultant Acid-Base imbalance. From reference 9 with permission

Understanding the Anion Gap and its clinical relevance

Unmeasured Ions and the Anion Gap

While the body is electrically neutral (-ve charge anions equal the +ve charge cations), not all ions are routinely measured in lab panels. The anion gap is a calculated value that helps reveal the presence of unmeasured ions.

- Unmeasured Anions (UA) include:
  - Phosphate (PO_4^{3-})
  - Sulfate (SO_4^{2-})
  - Negatively charged proteins
  - Organic acids

  These contribute approximately 20–24 mEq/L.

- Unmeasured cations (UC) include:
  - Potassium (K^+)
  - Calcium (Ca^{2+})
  - Magnesium (Mg^{2+})

  These total about 11 mEq/L.

  So, the typical anion gap = 23 − 11 = ~12 mEq/L

Why the Anion Gap Matters

The anion gap, which is used to detect hidden metabolic imbalances, normally ranges from 8 to 12 mEq/L

A significant portion of the anion gap comes from albumin, a negatively charged protein that isn't included in the standard anion gap formula. Since albumin has a strong influence on the gap, an abnormal albumin level can lead to misinterpretation of the anion gap unless adjusted mathematically.
Here's a useful rule of thumb:

- The normal anion gap (≈12) correlates with a normal albumin level of 4 g/dL.
- For every 1 g/dL decrease in albumin, subtract about 2.5 to 3 mEq/L from the expected normal anion gap.

Example: If a patient has:

- An anion gap of 24
- An albumin level of 3 g/dL

The expected gap should be adjusted from 12 to about 9 (since albumin is lower). Therefore, the actual excess gap is 15, not 12 indicating a more significant accumulation of unmeasured anions.

This is due to unaccounted ions in standard panels. The relationship can be expressed as:

Na^+ + unmeasured cations (UC) = Cl^- + HCO_3^- + unmeasured anions (UA)

So, the anion gap equation becomes:

Anion Gap = $Na^+ - (Cl^- + HCO_3^-)$

= UA - UC

The anion gap is a valuable tool for detecting metabolic acidosis. It should always be calculated during acid-base analysis.

Metabolic acidosis occurs when there is an excess of hydrogen ions (H^+) in the blood, lowering the pH. It is classified into two main types:

- A high anion gap: The anion gap increases when bicarbonate is consumed as it buffers excess hydrogen ions. When bicarbonate (HCO_3^-) binds to a hydrogen ion (H^+), it forms carbonic acid (H_2CO_3). The source of the hydrogen ion is often an organic or inorganic acid, whose conjugate base is typically an unmeasured anion—any negatively charged ion other than bicarbonate or chloride.
- A normal anion gap with low HCO_3^- and elevated Cl^- suggests hyperchloremic (non-anion gap) metabolic acidosis. This type happens when bicarbonate is lost (such as in severe diarrhea or renal tubular acidosis), and chloride ions (Cl^-) increase to maintain electrical neutrality, thus the anion gap remains normal. In this case, there's a rise in serum chloride. Clinicians use the urine anion gap (UAG) to further diagnose the cause.

Causes of Increased Anion Gap (Table 1)

Usually due to excess negatively charged acids that consume bicarbonate:

- Ketones (e.g., in diabetic, alcoholic, starvation ketoacidosis)
- Lactic acid (e.g., types A, B, D) (Table 2)
- Toxins (e.g., methanol, ethylene glycol, salicylates)
- Uremia
- Hyperalbuminemia

Table 1: Causes of metabolic acidosis

Category	Examples	Mechanism
Increased Anion Gap	Lactic acidosis (e.g., sepsis, shock, hypoperfusion)	Accumulation of lactic acid
	Ketoacidosis (diabetic, alcoholic, starvation)	Accumulation of ketone bodies
	Renal failure (uremia)	Retention of organic acids due to decreased excretion
	Toxins (methanol, ethylene glycol, salicylates)	Metabolism of toxins generates acidic metabolites
Normal Anion Gap (Hyperchloremic)	Diarrhea	Bicarbonate loss exceeds chloride loss
	Renal tubular acidosis (Types 1, 2, 4)	Defective renal acid excretion or bicarbonate reabsorption
	Ureteral diversion (e.g., ileal conduit)	Reabsorption of urinary ammonium
	Early renal failure	Decreased acid excretion before anion gap increases
	Medications (e.g., acetazolamide)	Inhibition of renal bicarbonate handling
Dilutional	Saline overload	Dilution of bicarbonate and hyperchloremia

Table 2: Causes of high Anion Gap Acidosis with the mnemonic MUDPILES.

Mnemonic	Cause	Mechanism
M	Methanol	Metabolized to formic acid, which inhibits mitochondrial respiration.
U	Uremia	Kidney failure leads to accumulation of sulfuric, phosphoric, and other organic acids.
D	Diabetic Ketoacidosis (DKA)	Excess ketones (β-hydroxybutyrate, acetoacetate) from insulin deficiency.
P	Paraldehyde	(Now rare) Metabolizes to acetic and chloroacetic acids.
I	Iron tablets / Isoniazid / INH	Iron causes lactic acidosis via mitochondrial toxicity; INH inhibits lactate metabolism.
L	Lactic Acidosis	Type A (hypoxia, shock) or Type B (metabolic, toxins, liver disease).
E	Ethylene Glycol	Metabolized to oxalic acid, glycolic acid, causing renal toxicity.
S	Salicylates (Aspirin)	Uncouples oxidative phosphorylation, leading to lactic & ketotic acidosis.

Table 3: Types and causes of lactic acidosis

Type	Mechanism	Common Causes	Notes
Type A	Tissue hypoxia anaerobic metabolism)	- Shock (septic, cardiogenic, hypovolemic) - Severe hypoxemia - Cardiac arrest - Severe anemia - Respiratory failure - Regional ischemia (e.g., bowel infarction, limb ischemia)	Most common type; due to impaired oxygen delivery/utilization
Type B1 ***(Systemic disease)***	Impaired lactate metabolism without hypoxia	- Liver failure - Renal failure - Diabetes mellitus - Malignancy (especially leukemia/lymphoma)	Often multifactorial; liver is critical in lactate clearance
Type B2 ***(Drugs/toxins)***	Mitochondrial dysfunction or impaired oxidative metabolism	- Metformin (especially in renal impairment) - Antiretrovirals (e.g., NRTIs) - Linezolid	Common in ICU; often reversible if drug discontinued

		- Salicylates - Ethanol - Propofol (Propofol infusion syndrome) - Cyanide, carbon monoxide	
Type B3 ***(Inborn errors of metabolism)***	Congenital enzyme deficiencies affecting metabolism	- Pyruvate dehydrogenase deficiency - Mitochondrial myopathies - Glycogen storage diseases	Rare; often presents in childhood
Type D	D-lactate accumulation from bacterial fermentation	- Short bowel syndrome - Jejunoileal bypass - Carbohydrate malabsorption with bacterial overgrowth	D-lactic acidosis is not detected by standard L-lactate assays

Table 4: Types of Renal Tubular Acidosis (RTA)

Type	Primary Defect	Site of Defect	Serum Potassium	Urine pH	Common Causes
Type 1 (Distal RTA)	Impaired H+ secretion	Distal tubule	Low	>5.5	Autoimmune diseases (e.g., Sjögren's, SLE), amphotericin B, hereditary (e.g., mutations in H+-ATPase)
Type 2 (Proximal RTA)	Impaired HCO_3^- reabsorption	Proximal tubule	Low or normal	<5.5 after bicarbonate loss	Fanconi syndrome, multiple myeloma, carbonic anhydrase inhibitors
Type 4 RTA	Hypoaldosteronism or aldosterone resistance	Distal tubule	High	<5.5	Diabetes, ACE inhibitors, NSAIDs, heparin, adrenal insufficiency

Causes of Decreased Anion Gap

(Not typically linked to acidosis)

- Hypoalbuminemia (low anion concentration)
- Excess cations, such as:
  - Hypercalcemia
  - Hypermagnesemia
  - Lithium toxicity
- Hypergammaglobulinemia (e.g., multiple myeloma)
- Halide intoxication (e.g., bromide, iodide)
- Hyperviscosity syndromes
- Severe hypernatremia or hyperlipidemia (rare lab artifacts)

Adjust the normal anion gap downward by ~2.5 mEq/L for each 1 g/dL drop in albumin.

The Delta Gap: Detecting Mixed Disorders

The delta gap is the difference between the patient's actual anion gap and the normal anion gap (typically 12).

- This difference reflects how much bicarbonate has been buffered by accumulating acids.
- By adding the delta gap to the patient's measured HCO_3^-, you can check if another metabolic disorder is present:
  - If the result is higher than normal (1-2 or +6), it suggests a coexisting metabolic alkalosis.
  - If it's lower (< 0.8 or -6), it may indicate an additional non-anion gap metabolic acidosis.

Compensation Mechanisms

The kidneys help compensate for metabolic acidosis by excreting ammonium (NH_4^+) in the urine. The Urine AG can provide insight into the cause of the acidosis.

$$[U[Na] + U[K]] - U[Cl]$$

- UAG between 20–90 mEq/L: Indicates low or normal ammonium secretion (abnormal renal response e.g. RTA).
- UAG between -20 and -50 mEq/L: Suggests normal renal response (e.g., diarrhea).

Winters Formula

Use the Winters formula to determine whether respiratory compensation is appropriate for metabolic acidosis:

$$\text{Expected } PaCO_2 = (1.5 \times HCO_3) + 8 \pm 2$$

If the actual $PaCO_2$ is within this expected range, it indicates only metabolic acidosis with respiratory compensation. Deviations suggest a mixed acid-base disorder.

If the actual PCO_2 is lower than expected, it suggests a respiratory alkalosis; if it's higher, it suggests a respiratory acidosis.

- A quick shortcut to estimate the expected $PaCO_2$ (using Winter's formula) is:

The last two digits of the pH ± 2 roughly equal the expected $PaCO_2$.

Base deficit

Base deficit is a clinical measurement that reflects the metabolic component of metabolic derangements. It is the amount of base (in mmol/L) required to titrate one liter of fully oxygenated blood to a normal pH (7.40) at a standard temperature and $PaCO_2$ (40 mmHg). It is used to assess the severity of shock, guide fluid resuscitation, and administer bicarbonate therapy in critically ill patients.

Interpretation Base Deficit:

Value	Interpretation
0 ± 2 mmol/L	Normal
> +2 mmol/L	Metabolic alkalosis (excess base)
< –2 mmol/L	Metabolic acidosis (base deficit)

Strong Ion Difference (SID)

Strong Ion Difference (SID) is the difference between the concentrations of strong cations and strong anions. The SID is considered an independent determinant of pH, according to the Stewart approach to acid-base balance. Changes in SID can lead to metabolic acid-base disturbances; for instance, a decrease in SID can cause metabolic acidosis, while an increase can lead to metabolic alkalosis. Clinically, SID helps in understanding the mechanisms behind acid-base disorders, particularly in cases where traditional bicarbonate-based analysis might be misleading, such as in hyperchloremic acidosis.

- SID = [strong cations] – [strong anions]
- Apparent SID = SIDa = $(Na^+ + K^+ + Ca^{2+} + Mg^{2+}) - (Cl^- + \text{L-lactate} + \text{urate})$
- Abbreviated SID = $(Na^+) - (Cl^-)$

Interpretation of SID:

Value	Interpretation
38-42 mmol/L	Normal
> 42 mmol/L	Metabolic alkalosis (excess cations)
< 36 mmol/L	Metabolic acidosis (excess anions)

Clinical Effects of pH Imbalances

Acidosis

❤️ Cardiovascular Effects

- Decreased cardiac output (CO)
- Arterial dilation → leads to low blood pressure (hypotension)
- Venous constriction
- Increased risk of arrhythmias, especially reentrant types
- Lower threshold for ventricular fibrillation (VF)
- Reduced effectiveness of catecholamines and vasopressors

🫁 Respiratory Effects

- Respiratory muscle fatigue
- Shortness of breath (dyspnea)

🔄 Metabolic Effects

- Increased metabolic demand
- Impaired anaerobic glycolysis
- Reduced ATP production
- Increased potassium levels (K^+)
- Insulin resistance

🧠 Neurological Effects

- Impaired regulation of brain cell volume
- Increased Cerebral blood flow and Intracranial pressure
- Can lead to coma

Alkalosis

❤️ Cardiovascular Effects

- Vasoconstriction of small arteries (especially in respiratory alkalosis)
- Can trigger:
  - Angina (chest pain)
  - Supraventricular tachycardia (SVT)
  - Ventricular tachycardia/fibrillation (VT/VF)

🫁 Respiratory Effects

- Slower breathing (↓ ventilation) can lead to low oxygen levels (hypoxemia)
- Loss of hypoxic pulmonary vasoconstriction worsens ventilation-perfusion (V/Q) mismatch

🔄 Metabolic Effects

- Shift toward anaerobic metabolism
- Increases lactate and ketones → raises the anion gap
- electrolyte imbalances:
  - ↓ Potassium (K^+)
  - ↓ Ionized calcium (iCa^{2+})
  - ↓ Magnesium (Mg^{2+})
  - ↓ Phosphate (PO_4^{3-})

🧠 Neurological Effects

- Reduced cerebral blood flow due to brain vessel constriction
- Can cause:
  - Tetany (muscle cramps/spasms)
  - Seizures
  - Lethargy
  - Delirium
  - Stupor

Treatment Overview

- Treat underlying cause
- Bicarbonate therapy for severe acidosis
- THAM for respiratory failure
- Hemodialysis for rapid correction
- Fluids/Chloride/Potassium for alkalosis
- Adjust ventilation for respiratory causes

Sodium Bicarbonate ($NaHCO_3$)

Can be used to correct acidosis but must be given slowly to avoid complications like overshoot alkalosis.

➢ When to Consider Sodium Bicarbonate ($NaHCO_3$) Therapy

Initiate when:

- pH ≤ 7.10, or
- pH ≤ 7.20 with cardiovascular compromise
- Stop when:
- Serum HCO_3^- reaches 8–10 mmol/L

📏 Dosage Calculation

- HCO_3^- distribution volume ≈ 50% of body weight
- Example: 70-kg patient
- Goal: raise HCO_3^- from 4 to 8 mmol/L
- $\Delta HCO_3^- = 4$ mmol/L
- Dose = $0.5 \times \text{weight} \times \Delta HCO_3^-$

  👉 $0.5 \times 70 \times 4 = 140$ mmol $NaHCO_3$ needed
- Base deficit = desired serum [HCO3−] – actual serum [HCO3−]

💧 Infusion Method

- Preferred: Slow infusion in isotonic solution
- E.g., 3 amps $NaHCO_3$ in D5W (≈150 mmol/L)
- Infusion rate: from minutes to hours
- Note: Bolus is not recommended in ACLS (Advanced Cardiac Life Support) anymore unless critically indicated

- Each ampule of 50 mEq of $NaHCO_3$ can increase $PaCO_2$ by about 5 mmHg or 25%, which can cause worsening respiratory acidosis if minute ventilation is not increased

✓ **Hemodialysis** is an effective way to rapidly correct acid-base disturbances.

✓ **Calcium (Ca^{2+})** should be administered after bicarbonate therapy to prevent hypocalcemia

Complications in Acidemia Treatment

1. Overshoot Alkalosis
   - What happens: If the underlying condition (e.g., diabetic ketoacidosis) resolves and bicarbonate is still being given, the patient may shift from acidemia to alkalemia.
   - Why it's a problem: Alkalosis can impair oxygen delivery, reduce potassium levels, and cause neuromuscular excitability.
2. 🫁 Paradoxical Acidosis
   - Mechanism:
     - HCO_3^- buffers H^+ → forms CO_2.
     - CO_2 diffuses into cells much faster than HCO_3^-.
     - If lungs can't exhale excess CO_2 (e.g., in CPR or poor pulmonary reserve), intracellular or extracellular acidosis may worsen.
   - Result: Despite increasing HCO_3^-, acidosis persists or worsens in tissues due to CO_2 retention.

🚨 Key Takeaways

- Always monitor pH, $PaCO_2$, and clinical context during therapy.
- Use bicarbonate cautiously - titrate slowly and reassess frequently.
- Ensure adequate ventilation to eliminate extra $PaCO_2$.

Metabolic Alkalosis

Causes, Diagnosis, and Treatment

Metabolic alkalosis is characterized by an increase in serum bicarbonate (HCO_3^-) in the blood, raising the pH. It can be divided into two types:

- Chloride Responsive Alkalosis
  Caused by conditions like vomiting, hypovolemia, or diuretic use. The urine chloride level is typically less than 20 mEq/L.
- Chloride Resistant (Unresponsive) Alkalosis
  Typically seen in cases of mineralocorticoid excess (e.g., hyperaldosteronism), where the urine chloride is greater than 20 mEq/L.

Causes of Metabolic Alkalosis

Type	Causes
Chloride Responsive (saline-responsive)	• Vomiting or Nasogastric suction • Diuretic therapy (e.g., thiazides, loop diuretics) • Volume depletion • Post-hypercapnia
Chloride Resistant (saline-unresponsive)	• Primary hyperaldosteronism • Cushing's syndrome • Severe hypokalemia • Bartter syndrome • Gitelman syndrome • Excess alkali intake

Treatment of Metabolic Alkalosis

✅ 1. Treat the Underlying Cause

- Vomiting/Nausea (N/V): Use antiemetics
- NG suction: Use H_2 blockers if necessary
- Diuretic-related alkalosis:
  - Reduce loop/thiazide diuretics
  - Consider adding a K^+-sparing diuretic or acetazolamide
- Volume depletion: Rehydrate with IV fluids like normal saline (NS) + KCl

📉 2. When to Correct

- Aim to treat until:
  - Bicarbonate (HCO_3^-) < 40 mmol/L
  - OR pH < 7.55

💡 3. Most Cases Are Chloride-Responsive

- Replacing sodium (Na^+), chloride (Cl^-), and potassium (K^+) can restore balance and lead to bicarbonate excretion (bicarbonaturia)

🚨 4. For Severe or Rapid Correction

- IV Hydrochloric Acid (HCl):
  - Use 100–200 mmol of 0.1–0.2 N HCl/L in D5W
  - Infuse via central line
  - Max rate: 0.2 mmol/kg/hour
- Alternatives (less common, higher risk):
  - Arginine HCl
  - Ammonium chloride (NH_4Cl)

    ⚠️ May cause hyperkalemia and encephalopathy
- Hemodialysis (HD): Can rapidly correct alkalemia in critical cases

🚫 5. Special Case: Saline-Resistant Alkalosis

- Usually due to mineralocorticoid excess
- Treat the cause and aggressive KCl repletion

⚠️ 6. Watch for Fluid Overload

- Especially important in patients with heart failure or renal impairment
- Monitor fluids closely during alkalosis correction

Respiratory and Renal Compensation in Fetal and Neonatal Acid-Base Balance

Fetal Acid-Base Regulation

The fetus relies heavily on the placental circulation for CO_2 elimination and acid-base balance. However, respiratory and renal compensation mechanisms are limited, and the developing fetus relies more on the maternal systems for compensation.

Neonatal Acid-Base Regulation

After birth, neonates must adapt to maintaining their own acid-base balance. Initially, their renal function is immature, and their ability to handle acid-base disturbances is limited. The kidneys begin to function more effectively over the first few days of life. However, premature neonates may face additional challenges with acid-base regulation due to underdeveloped renal systems.

Key Considerations in Neonatal Acid-Base Management:

- Renal Compensation: Neonates depend on renal adjustments (excreting H^+ and reabsorbing bicarbonate) to maintain pH. This process matures over the first 2-3 days.
- Drug Interactions: Certain medications (e.g., dopamine) can impair renal bicarbonate reabsorption in neonates, further complicating acid-base management.

Inherited Disorders Affecting Acid-Base Balance

Some rare inherited conditions affect how the kidneys handle acid-base balance. Examples include:

- Proximal Renal Tubular Acidosis (RTA): Caused by mutations in transporters like the Na^+/HCO_3^- cotransporter, leading to bicarbonate wasting.
- Distal Renal Tubular Acidosis (RTA): Results from defects in proton excretion due to mutations in genes like ATP6V1 or FOXI1, leading to an impaired ability to acidify urine.
- Carbonic Anhydrase II Deficiency: Affects multiple nephron segments and results in both proximal and distal renal tubular dysfunction.

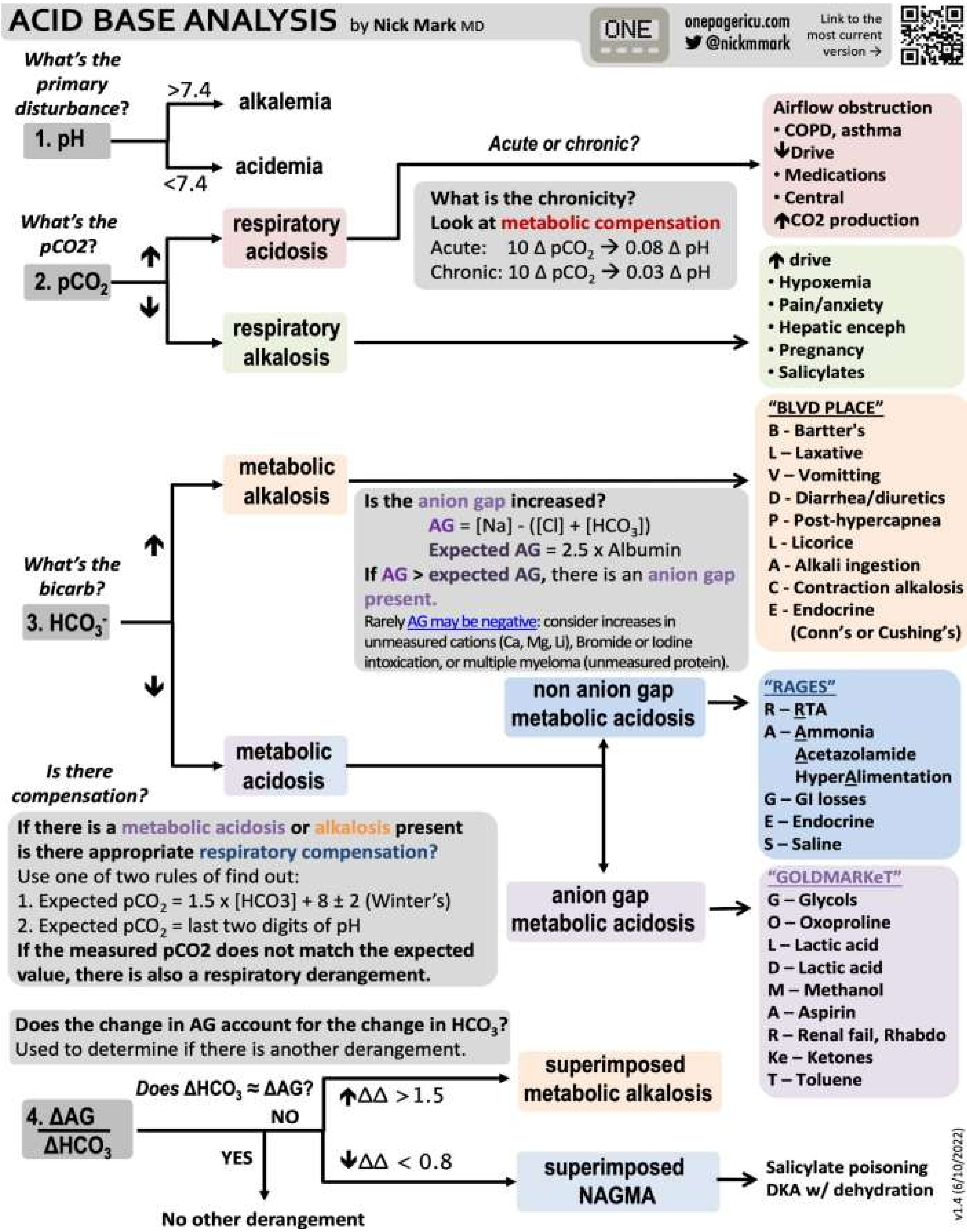

Figure 2: Overview of causes and diagnosis of Acid-Base disturbances. From ICU one pager with permission.

Conclusion

Acid-Base disturbances are common in critically ill patients, and understanding their mechanisms is essential for appropriate treatment. Whether the imbalance is metabolic or respiratory, the body compensates through a variety of mechanisms. Treatment focuses on correcting the underlying cause and supporting physiological compensation.

In severe cases, interventions like dialysis, ventilatory support, or medication adjustments are necessary for managing life-threatening acid-base imbalances.

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