Acid-Base Homeostasis: Traditional Approach

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IFA Commentary (PN)

Acid-base disorders are a common occurrence in critically ill patients, and it is crucial to approach them systematically. There are different methods of interpreting acid-base disorders, including the traditional approach, Stewart's physiochemical approach, and Siggaard-Anderson's base excess approach, as shown in Fig. 6.1.

The traditional approach is the most commonly used method in clinical practice, based on the assumption that bicarbonate is a strong buffer and determinant of pH. It uses the Henderson-Hasselbalch equation, although it has various limitations. Despite this, it is widely used in clinical practice, and studies have not consistently shown the superiority of one approach over another.

After identifying the primary acid-base disorder, compensation formulae can be used to detect mixed disorders. It is important to note that compensation cannot normalize the pH, except in cases of chronic respiratory alkalosis. Calculating the delta anion gap (observed vs expected) is a useful tool for identifying mismatches between bicarbonate and anion gap and can help detect a third existing metabolic acid-base disorder.

It is essential to understand that the interpretation of arterial blood gas should not be done in isolation. It must be accompanied by a comprehensive patient history and physical assessment to provide a complete clinical picture.

Overall, the interpretation of acid-base disorders in critically ill patients requires a systematic approach, and understanding the various methods of interpretation is essential for clinicians. The use of compensation formulae and the calculation of the delta anion gap can help identify mixed disorders and existing third metabolic acid-base disorders. By utilizing these approaches and considering the patient's history and physical assessment, clinicians can make informed treatment decisions to optimize patient outcomes.

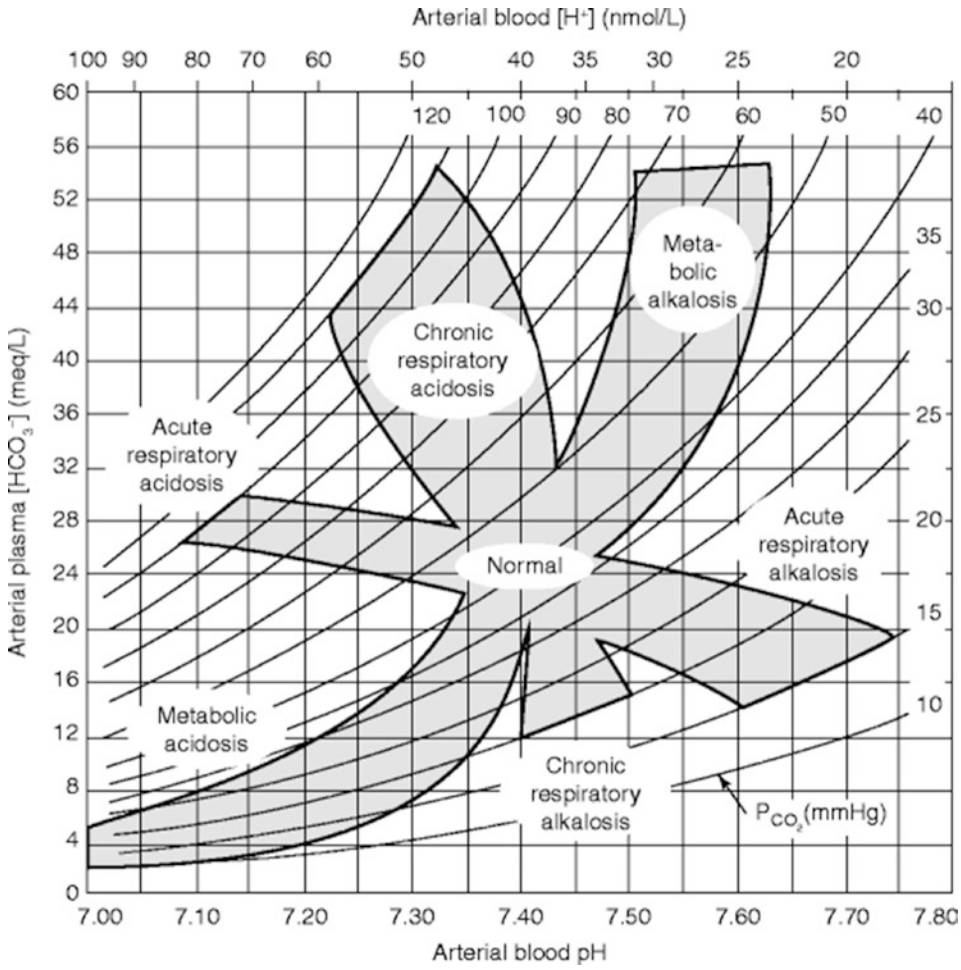

Fig. 6.1 Traditional Siggaard Anderson acid-base nomogram. Shown are the 95% confidence limits of the normal respiratory and metabolic compensations for primary acid–base disturbances (From Cogan MG (editor): Fluid and Electrolytes: Physiology and Pathophysiology. Appleton & Lange, 1991)

Learning Objectives

After reading this chapter, you will learn:

1. To understand the interpretation of acid-base disorders following the approach proposed by Henderson and Hasselbalch.
2. To interpret the presence of any primary acid-base disorder.
3. To understand and interpret the presence of any secondary disorder by applying compensatory response formulae.
4. To understand the concept of anion gap and its various application.
5. To interpret the presence of third acid-base disorder (if any) by applying the concept of delta gap.

Case Vignette
Mrs. A, a 50-year-old-woman with history of insulin-dependent diabetes mellitus (IDDM), was admitted to the ICU in semi-comatose state. She had been ill for several days. Her medications included subcutaneous insulin for managing IDDM, calcium supplement and indapamide for hypertension. On examination, she was barely rousable to verbal command, afebrile, dehydrated with a heart rate of 112/min, blood pressure of 94/60 mmHg and respiratory rate of 32/min. Systemic examination was otherwise unremarkable. Initial blood investigations showed Na-132 mmol/L, K-2.7 mmol/L, Cl-79 mmol/L, HCO_3-19 mmol/L, blood glucose-815 mg/dl, lactate 0.9 mmol/L and urine ketones 3+. Arterial blood gas analysis revealed pH 7.41, $PaCO_2$-32 mmHg, HCO_3-19 mmol/L and PaO_2-82 mmHg (in room air).

Question
Q1. How do we interpret her blood gases?

Introduction

Interpretation of acid-base disorders is critical for understanding the pathophysiology of underlying disease and making a correct diagnosis. It also helps in deciding appropriate treatment and following the progress of the patient. Acid-base disorders can be broadly classified into respiratory or metabolic disorders. There are three major approaches to the interpretation of acid-base physiology: traditional approach (or so-called physiological approach), Stewart's physicochemical approach and Siggaard-Anderson's base excess approach. All the three approaches, more or less, agree in their interpretation of respiratory disorder and differ only in their method of interpreting metabolic problems.

The traditional approach defines acid as hydrogen-ion donors and bases as hydrogen-ion acceptors (as proposed by Bronsted and Lowry) and uses the carbonic acid–bicarbonate buffer system for the interpretation of acid-base disorders. This approach suggests that a primary change in the partial pressure of carbon dioxide or $PaCO_2$ will cause secondary changes in bicarbonate and vice versa (also known as "adaptive" response). In this chapter, we shall review the traditional approach in detail. See also Chap. 7 to learn more about the Stewart's approach to acid-base.

Definitions

Following are some definitions relevant for understanding traditional approach.

- **pH:** pH is the negative logarithm of hydrogen ion concentration ($[H^+]$). Since the concentration of $[H^+]$ is normally very low (4.0×10^{-8} mol/L), the concept of pH is used in clinical medicine to describe acid-base issues. The lower the pH, the higher the $[H^+]$

concentration and vice versa. For example, a pH of 6.8 corresponds to 1.6×10^{-7} mol/L $[H^+]$ or pH 7.6 to 2.5×10^{-8} mol/L $[H^+]$. The normal range of pH in the whole blood is between 7.35 and 7.45. However, in this chapter, we will be taking a narrower range of normal pH as 7.40 ± 0.02 (for the purpose of calculation).

- **Acidemia:** If the pH is below the physiological limit, it is called acidemia.
- **Alkalemia:** If the pH is above the physiological limit, it is known as alkalemia.
- **Acidosis:** Acidosis is defined as the clinical processes that tend to lower the pH below the physiological limit.
- **Alkalosis:** Alkalosis is defined as the clinical processes that tend to raise the pH above the physiological limit.

Acid-Base Homeostasis

Traditional approach is based on the Henderson–Hasselbalch equation, which states that: **$pH = pK + \log10 ([HCO_3^-]/[0.03 \times (PaCO_2)])$** (pK denotes the acid dissociation constant, $[HCO_3^-]$ is the bicarbonate ion concentration in plasma in mmol/L and $PaCO_2$ is the partial pressure of CO_2 in mmHg). Simplistically, according to the traditional approach, $[H^+]$ concentration is proportional to $[PaCO_2]/[HCO_3^-]$. An acid–base disorder is called "respiratory" when changes in $[H^+]$ ion concentration is primarily because of $[PaCO_2]$ and "metabolic" when changes in $[H^+]$ ion concentration is attributed to variation in $[HCO_3^-]$.

$[H^+]$ ion concentration (and pH) is tightly regulated within the physiological range as virtually all human enzymes and membranes work best within this range. With any deviation of pH, the body tries to adapt and compensate, in an attempt to maintain the pH. If the primary problem is metabolic, then the compensatory mechanism is respiratory by altering the respiratory drive. Respiratory compensation is quick and activated within minutes. In cases of primary respiratory disorders, kidneys adapt and change the $[HCO_3^-]$ concentration. This metabolic compensation is slow and the adaptation takes up to 5 days. Compensatory responses cannot fully normalize the pH, except in cases of chronic respiratory alkalosis. Compensatory changes in $PaCO_2$ and $[HCO_3^-]$ in response to primary metabolic and respiratory disorder follows a pattern and can be predicted using empirical formulae. Traditional approach to acid-base disorders is described in a step-wise manner in subsequent paragraphs.

Step 1: Observe the pH, $PaCO_2$ and HCO_3.

- The purpose of this step is to look for any acid-base abnormality and to recognize a primary disorder (if any). Remember that the so-called primary disorder is solely responsible for the purpose of calculating compensatory response and not to give undue importance of one disorder over another.
- For the analysis of acid-base abnormality using the physiological approach, we shall take normal values of pH as 7.40 ± 2, $[HCO_3^-]$ as 24 ± 2 mmol/L and $PaCO_2$ as 40 ± 2 mmHg.
- Algorithm depicted in Fig. 6.2 depicts a logical step to identify any primary disorder.

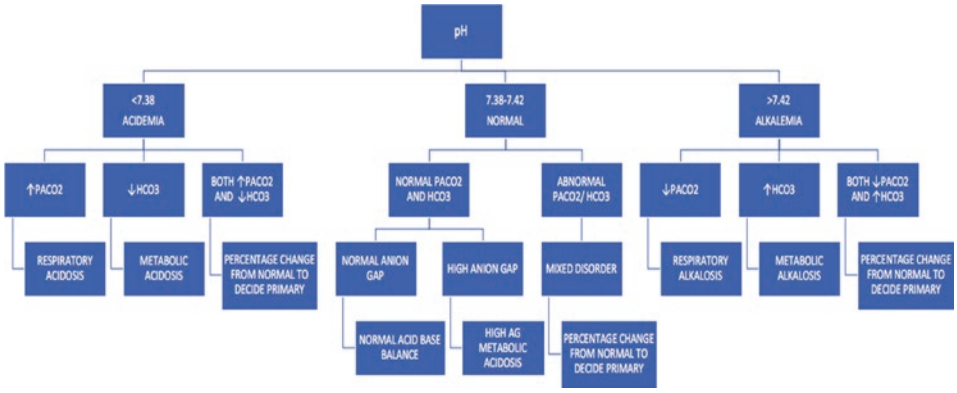

Fig. 6.2 Steps to identify primary disorder (if any)

Step 2: Look for compensatory response. Compensatory responses are calculated based on empirical formulae to identify any second disorder.

- **Metabolic Acidosis**: If the primary disorder is metabolic acidosis, then expected compensatory response is a fall in $PaCO_2$.
  - Expected $PaCO_2 = (1.5 \times [HCO_3] + 8) \pm 2$ mmHg (Winter's formula).
  - If measured $PaCO_2 >$ expected $PaCO_2$ = additional respiratory acidosis.
  - If measured $PaCO_2 <$ expected $PaCO_2$ = additional respiratory alkalosis.
- **Metabolic Alkalosis**: If the primary disorder is metabolic alkalosis, then expected response is an increase in $PaCO_2$.
  - Expected $PaCO_2 = (0.7 \times [HCO_3^-]) + 20 \pm 2$ mmHg.
  - If measured $PaCO_2 >$ expected $PaCO_2$ = additional respiratory acidosis.
  - If measured $PaCO_2 <$ expected $PaCO_2$ = additional respiratory alkalosis.
- **Respiratory Acidosis**: Expected compensatory response for primary respiratory acidosis is an increase in HCO_3. The compensation may take 2–5 days, based on that respiratory disorders may be classified as acute (without complete compensation) or chronic (with complete compensatory response).
  - For every 10 mmHg $PaCO_2$ increase above 40 mmHg, if $[HCO_3^-]$ increase by 1 mmol/L = acute respiratory acidosis.
  - For every 10 mmHg $PaCO_2$ increase above 40 mmHg, if $[HCO_3^-]$ increase by 4–5 mmol/L = chronic respiratory acidosis.
  - For every 10 mmHg $PaCO_2$ increase above 40 mmHg, if $[HCO_3^-]$ increase by <1 mmol/L = additional metabolic acidosis.
  - For every 10 mmHg $PaCO_2$ increase above 40 mmHg, if $[HCO_3^-]$ increase by >5 mmol/L = additional metabolic alkalosis.
- **Respiratory Alkalosis:** The expected compensatory response in primary respiratory alkalosis is a fall in $[HCO_3^-]$. Complete compensation takes 2–5 days.

- For every 10 mmHg $PaCO_2$ decrease below 40 mmHg, if $[HCO_3^-]$ decrease by 2 mmol/L = acute respiratory alkalosis.
- For every 10 mmHg $PaCO_2$ decrease below 40 mmHg, if $[HCO_3^-]$ decrease by 4–5 mmol/L = chronic respiratory alkalosis.
- For every 10 mmHg $PaCO_2$ decrease below 40 mmHg, if $[HCO_3^-]$ decrease by <2 mmol/L = additional metabolic alkalosis.
- For every 10 mmHg $PaCO_2$ decrease below 40 mmHg, if $[HCO_3^-]$ decrease by >5 mmol/L = additional metabolic acidosis.

Step 3: Look for anion gap.

- According to the principle of electroneutrality, the sum of cations in any body fluid (including plasma) must be equal to the sum of anions in the fluid. This can be seen from the Gamblegram (originally created by acid-base pioneer James L. Gamble to graphically represent concentrations of plasma cations (e.g., Na^+ and K^+) and plasma anions (e.g., Cl^- and HCO_3^-) (Fig. 6.3).
- That means: **$[Na^+] + [K^+]$ + Unmeasured cations = $[Cl^-] + [HCO_3^-]$ + Unmeasured anions**. To state the equation differently: **Unmeasured anions − Unmeasured cations = $[Na^+] + [K^+] - [Cl^-] - [HCO_3^-]$**.
- This difference in the concentration between plasma unmeasured anions and cations is also known as **anion gap (AG)**. Since the extracellular concentration of K^+ is low and the body needs to maintain its concentration within a narrow range, $[K^+]$ can be omitted from this equation. Thus, the anion gap can be calculated simply as **= $[Na^+] - ([Cl^-] + [HCO_3^-])$**.
- Normally, the gap between unmeasured anions and cations (or anion gap) is filled up mostly by albumin (as can be seen from the Gamblegram above) and to a lesser extent by phosphate or lactate. The albumin level is often low in critically ill patients and the calculated AG must be corrected for low albumin level.
  - Correction for albumin: For every 1 g/dl albumin decrease (normal value 4 gm/dl), increase calculated anion gap by 2.5 mmol/l.

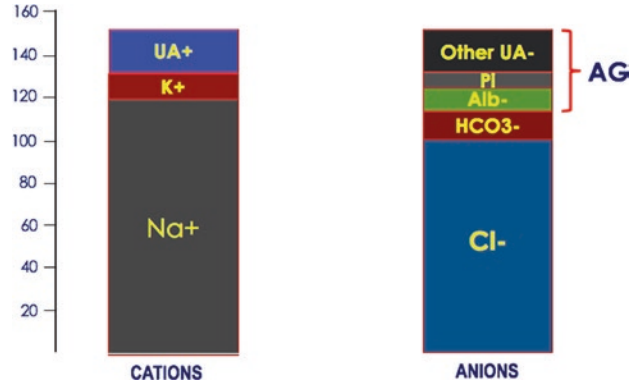

Fig. 6.3 Gamblegram depicting the principle of electroneutrality

  - For example: calculated AG = 5, albumin= 2 g/dl and corrected AG: 5+ [(4 − 2) × 2.5] = 10.
  - For the purpose of further calculation, we shall take a normal value of AG as 12 ± 2 mmol/L.
- Calculation of AG helps in the following aspects:
  - It helps in elucidating causes of metabolic acidosis—high AG or normal AG metabolic acidosis.
  - Presence of high AG may be the sole pointer towards the presence of hidden metabolic acidosis, with multiple opposing acid-base abnormalities normalizing pH, $PaCO_2$ and $[HCO_3^-]$.
  - Serial measurement of AG helps in following effectiveness of treatment, especially in diabetic ketoacidosis.
  - Elevated AG may be the only clue to certain clinical disorder. For example, D-lactate is not routinely measured in clinical laboratories. The presence of high AG in a patient presenting with neurological issues and past history of short bowel syndrome may be the only pointer towards D-lactic acidosis.
  - A low AG or negative AG may be a pointer towards unsuspected hypercalcemia or hypermagnesemia or other heavy metal toxicity. Other causes of negative AG include erroneous measurement of serum chloride in clinical laboratories (in the presence of bromide or iodide).

High AG Metabolic Acidosis

- Further analysis of high AG metabolic acidosis is based on history/physical examination, biochemical test results (including blood glucose, kidney function tests, electrolytes, serum osmolality, toxin levels, etc.). A proposed approach to high AG metabolic acidosis is given in Fig. 6.4.

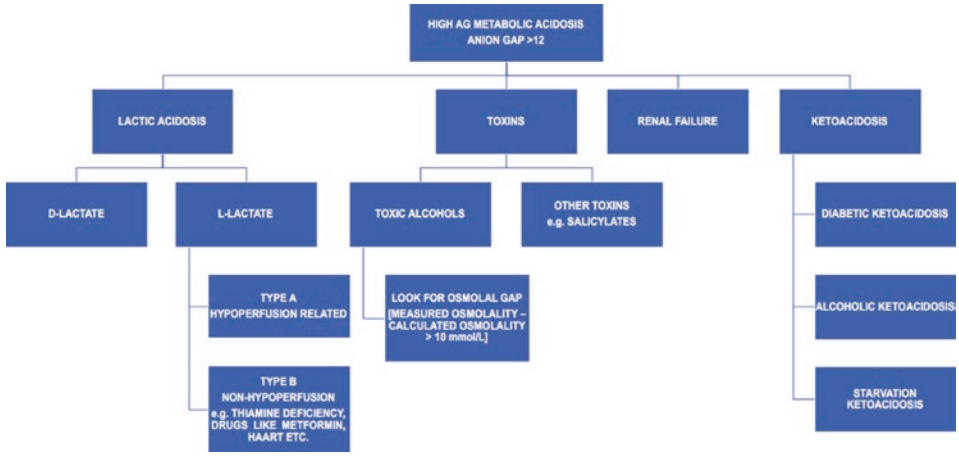

Fig. 6.4 Approach to high anion gap metabolic acidosis. Adapted from [1]. *HAART* highly active antiretroviral therapy, *AG* anion gap

Normal AG Metabolic Acidosis

- Further analysis of normal AG metabolic acidosis requires history/physical examination, serum and urinary electrolytes and urine pH. An approach to normal AG metabolic acidosis is shown in Fig. 6.5.

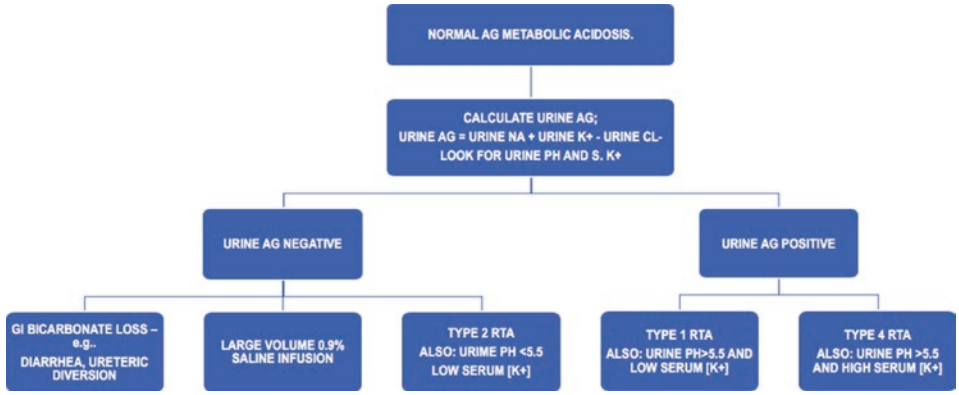

Fig. 6.5 An approach to normal anion gap metabolic acidosis. Adapted from [1]. *NA^+* sodium, *K^+* potassium, *Cl^-* chloride, *AG* anion gap

Metabolic Alkalosis

- Metabolic alkalosis is either because of gain of alkali or excess renal retention of HCO_3^-. If the effective circulating volume is reduced, the renin–angiotensin–aldosterone system is activated and kidneys try to restore volume by re-absorption of filtered sodium, bicarbonate, and chloride. In these patients, spot urine chloride concentration is usually <25 mmol/L and the pH may be restored by the administration of 0.9% saline (chloride responsive).
- Metabolic alkalosis is also seen in conditions with mineralocorticoid excess (either true or functional) and in patients with K^+ deficiency. In these patients, excretion of sodium and chloride in urine is inappropriately high (urine chloride level >40 mmol/L) and pH is not restored by the administration of normal saline (chloride unresponsive).
- A suggested approach to metabolic alkalosis is shown in Fig. 6.6.

Step 4: Exploring the delta anion gap—look for the third disorder.

- The magnitude of increase in anion gap from upper limit of normal (12 mmol/L) (henceforth Δ AG) is closely related to the decrease in $[HCO_3^-]$ Δ AG. The relationship is 1:1 in case of ketoacidosis (i.e., $[HCO_3^-]$ value will decrease by Δ AG (the normal delta AG is zero)) but 1:0.6 in cases of lactic acidosis (i.e., $[HCO_3^-]$ value will decrease by 60% of Δ AG).
- This relationship can be explored further to calculate expected $[HCO_3^-]$ from Δ AG:
  - For ketoacidosis or any other high AG acidosis: expected $[HCO_3^-] = [24 - \Delta \text{ anion gap}] \pm 5$
  - For lactic acidosis: expected $[HCO_3^-] = [24 - (0.6 \times \Delta \text{ anion gap})] \pm 5$
  - Actual $[HCO_3^-]$ < expected $[HCO_3^-]$ = additional normal AG metabolic acidosis
  - Actual $[HCO_3^-]$ > expected $[HCO_3^-]$ = additional metabolic alkalosis

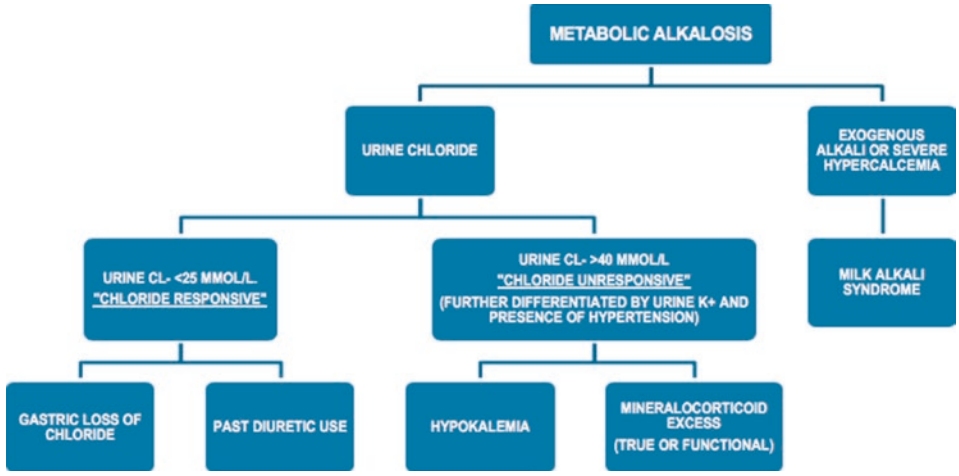

Fig. 6.6 An approach to metabolic alkalosis. Adapted from [1]. *Cl*$^{-}$ chloride

Case Vignette

Case 1: Looking into the case vignette (**1**) provided in the beginning of this chapter, we can interpret the acid-base disorders by following the steps mentioned.

Step 1: Here, two opposing disorders (low $PaCO_2$ and low HCO_3) are leading to the normalization of pH. The percentage of change of HCO_3 from the normal value (normal value 24 mmol/L) is marginally more than the percentage of change of $PaCO_2$ (normal value 40 mmHg). For the purpose of compensatory response calculation, we shall take "Metabolic Acidosis" as the primary disorder.

Step 2: Applying Winter's formula, expected $PaCO_2$ is 36.5 mmHg (range—34.5–38.5) [$1.5 \times 19 + 8 = 36.5$]. Since measured $PaCO_2$ < expected $PaCO_2$, there is an associated "Respiratory Alkalosis".

Step 3: Calculated AG is 34 [$132 - (79 + 19)$] classifying the condition as "High Anion Gap Metabolic Acidosis", possibly due to diabetic ketoacidosis (from the history and presence of ketonuria).

Step 4: On further analysis, Δ anion gap is 22 ($34 - 12 = 22$) and expected HCO_3 is ($24 - 22$) ± 5, i.e., 0–7 mmol/L. Actual HCO_3 is > expected HCO_3, confirming associated "Metabolic Alkalosis".

Final Diagnosis: High anion gap metabolic acidosis (possibly diabetic ketoacidosis) with metabolic alkalosis.

Some More Illustrative Cases

Case 2: Police brought a 22-year-old-man to the ED in an unconscious state. ABG: pH 7.27, $PaCO_2^-$ 26 mmHg, and HCO_3^- 11 mmol/L. The serum chemistry result showed Na^- 130 mmol/L, K^- 4 mmol/L, Cl^- 94 mmol/L, BUN 56 mg/dl, serum creatinine 2 mg/dl, and glucose 72 mg/dl. His measured serum osmolality is 320 mosmol/L. Serum lactate, ketones, and ethanol levels are all within normal range.

Step 1: With low pH and [HCO_3^-], primary disorder is "Metabolic Acidosis".

Step 2: On calculating compensatory response, expected $PaCO_2$ is 24.5 mmHg (1.5 × 11 + 8 = 24.5 mmHg) which is close to the measured $PaCO_2$, ruling out additional respiratory disorder.

Step 3: Anion gap is 25 [130 − (94 + 11)] classifying the condition as "High Anion Gap Metabolic Acidosis". On further analysis, the calculated serum osmolality is 284 mosmol/L [2 × 130 + (72/18) + (56/2.8)] with an osmolal gap of 36 (320 − 284) raising high likelihood of toxic alcohol ingestion as the cause of high AG metabolic acidosis.

Step 4: Δ Anion gap is 13 (25 − 12). With this, expected [HCO_3^-] is between 4 to 14 mmol/L. Actual [HCO_3^-] is within this range, ruling out other metabolic abnormalities.

Final diagnosis: High anion gap metabolic acidosis possibly due to toxic alcohol ingestion.

Case 3: A 28-year-old-woman with a history of Sjogren's syndrome reports 3–4 episodes of watery diarrhea lasting for a day, 4-days before her visit to the Rheumatology clinic. ABG done in the clinic is revealed, pH 7.15, $PaCO_2$ 17 mmHg, and HCO_3^- 5 mmol/L. Serum chemistry results are Na^- 135 mmol/L, K 2.5 mmol/L and Cl^- 120 mmol/L/L.

Step 1: Low pH and [HCO_3^-] suggests metabolic acidosis as the primary disorder.

Step 2: Expected $PaCO_2$ applying Winter's formula is 15.5 mmHg, that is closure to measured $PaCO_2$, ruling out additional respiratory disorder.

Step 3: An anion gap of 10 suggests normal AG metabolic acidosis.

Step 4: With normal AG, this step is not applicable in this case.

On further investigations (following approach provided in Fig. 6.5), to elucidate the underlying cause of normal AG acidosis: Urine K^- 31 mmol/L, urine Na 100 mmol/L, urine Cl^- 105 mmol/L and urine pH: 6. Calculated urine anion gap is +26 [(100 + 31) − 105]. Positive urine AG, urine pH >5.5 and low serum K^+ suggests Type 1 renal tubular acidosis as the underlying cause of normal AG acidosis.

Final diagnosis: Normal anion gap metabolic acidosis possibly due to Type 1 RTA.

Case 4: A 62-year-old woman was admitted with history of recurrent vomiting and was diagnosed as small bowel obstruction. She is on nasogastric suction. Arterial blood gases: pH 7.40, pCO_2 40 mmHg, HCO_3 25 mmol/L. Lab results showed Na 135 mEq/L, K 3.5 mEq/L, Cl 85 mEq/l, HCO_3 25 mEq/l, blood glucose 90 mg/dl, blood urea nitrogen 110 mg/dl and serum creatinine 4.5 mg/dl.

Step 1 and 2: Normal pH, HCO_3^- and PCO_2 makes compensatory response calculation is invalid.

Step 3: High anion gap of 25 mmol/L 135 − (85+25) is the only clue to underlying high anion gap metabolic acidosis.

Step 4: On further analysis, Δ anion gap is 13 (25 − 12) and expected [HCO_3^-] is between 6 and 16 mmol/L. Actual [HCO_3^-] is higher than this range, suggesting associated metabolic alkalosis.

Final diagnosis: High anion gap metabolic acidosis with metabolic alkalosis.

Case 5: A 65-year-old man collapsed in the general ward. He was admitted on the same day for acute exacerbation of COPD. The ward nurse noticed him to be apneic with an easily palpable carotid pulse. He was intubated by the rapid response team and was transferred to the ICU. ABG done while on bag ventilation and 15 L O_2/min: pH—7.10, PaO_2—147 mmHg, $PaCO_2$—135 mmHg and HCO_3^-—36 mmol/L.

Step 1: Low pH with high PCO_2 suggests respiratory acidosis as the primary abnormality.

Step 2: For 95 mmHg increase in $PaCO_2$ above normal 40 mmHg, HCO_3^- has changed by 12 mmol/L from normal; that is just 3 mmol/L for every 10 mmHg change in $PaCO_2$, suggesting some "Chronic respiratory acidosis".

Step 3 and 4: In the absence of any metabolic abnormality, these steps are not required.

Final diagnosis: Acute respiratory acidosis possibly related to respiratory arrest.

Conclusion

The biggest strength of the traditional approach is its simplicity, easy understanding, availability of variables used, wide acceptability and its ability to identify a vast majority of acid-base abnormalities in clinical medicine. But there are several limitations to this approach. Traditional approach describes $PaCO_2$ and [HCO_3^-] as independent determinants of respiratory and metabolic components, respectively. But the fact is [HCO_3^-] is not an independent variable and it varies with changing $PaCO_2$ as can be seen in the Henderson–Hasselbalch equation. Moreover, various formulae describing compensatory responses are empirical and based on animal experiments performed more than half a century ago.

Take Home Messages

- Traditional approach considers $PaCO_2$ and HCO_3^- concentration in plasma as independent variables to determine acid-base disorders. Any change in $PaCO_2$ or HCO_3^- beyond normal value produces respiratory or metabolic acid-base disorders.
- Change in $PaCO_2$ or HCO_3^- concentration leads to compensatory response through kidneys or lungs, respectively, in an effort to normalize pH.
- Various empirical formulae can quantify expected compensatory changes and provide an approach to interpret presence of any second base disorder.
- Traditional approach provides the concept of anion gap to further elucidate causes of metabolic acid-base disorders. The concept of anion gap is also useful in various other ways.
- The concept of delta anion gap provided in the traditional approach can be used to find out any third metabolic acid-base disorder.

Reference

1. Berend K, de Vries APJ, Gans ROB. Physiological approach to assessment of acid–base disturbances. N Engl J Med. 2014;371:1434–45. https://doi.org/10.1056/NEJMra1003327.