Acid-Base status

Examining the ABG data for evidence of pH and PCO2 changes and appropriate compensations will help to identify multiple disorders. The HCO3 is calculated by the ABG machine based on the pH and PCO2. There are two approaches to understand the acid-base abnormalities

- The traditional Henderson-Hasselbalch approach
- The most contemporaneous, the Stewart approach

Either is appropriate, it is a matter of being familiarized with either one. My preference is the Stewart approach, to me it is more physiologically sounded.

The Stewart Approach

There are only three independent variables to determine the pH, any other variable including HCO3 depend on these independent variables (HCO3 does not alter pH):

- PCO2
- Total weak acids (Atot) (albumin and phosphate being the more relevant)
- Strong ion difference (SID)
    - Effective SID (eSID): difference between measured and unmeasured strong cations and strong anions
    - Apparent SID (aSID): difference between measured strong cations and strong anions
        - aSID: (Na + K + Ca + Mg) - (Cl + sulfate)
        - Abbreviated aSID: Na - Cl (normal value: 38-42 meq/L)

The key point is analyzing the pH

- If pH is decreased:
    - PCO2 elevated: respiratory acidosis
    - Atot elevated: hyperalbuminemia (rare) or hyperphosphatemia
    - SID decreased:
        - aSID decreased: Cl increase more than Na or Na decrease more than Cl
        - aSID normal: increased lactate, β-hydroxybutyrate/acetoacetate, renal failure, alcohol, others (GOLDMARK)
    - If no cause is identified determine the unmeasured strong anions calculating the strong ion gap (SIG)
        - SIG: (BD) + (SID - 38) + 2.5 (4.2 - albumin) - lactate
            - If SIG >2: presence of unmeasured strong anions
- If pH elevated: vice versa analysis

The Henderson-Hasselbalch Approach

- First is to determine if pH, $PaCO_2$, or HCO_3 is out of the normal range; if so, an acid-base disturbance is present.
- Next is to determine if compensation is appropriate for the acid-base disturbance (compensatory changes are always in the same direction). If compensation is not appropriate, it is likely that a complex acid-base disturbance is present.
    - The Winter formula defines the relationship between HCO_3 and $PaCO_2$ for each of the 6 primary acid-base disturbances. For instance, in acute metabolic acidosis:
        - $PaCO_2$ should be 1.5 x HCO3 + 8 ± 2
        - Measured PaCO2 = predicted PaCO2 → pure metabolic acidosis

        - Measured PaCO2 **>** predicted PaCO2 → metabolic acidosis and respiratory acidosis
        - Measured PaCO2 **<** predicted PaCO2 → metabolic acidosis and respiratory alkalosis
    - There is also a table (see below) that converts each of these equations into an easily recalled sequence of numbers for expected compensation that can be used to estimate the appropriate compensation for each of the six primary disorders.
- Next is to determine the anion gap (AG) to identify the etiology (AGMA or NAGMA)
- If an AG is present, determine the delta gap
    - Delta gap (delta AG – delta HCO3) = (AG -12)- (24 – HCO3)
        - <6, NAGMA is present
        - >6, an underlying metabolic alkalosis is present
        - Between -6 and 6, only AGMA is present (GOLDMARK)

Acid-Base Compensations Table

Primary Acid-Base Disorder	Change in P (mm Hg)	Change in HCO^- (mEq/L)
Acute respiratory acidosis	10*	1
Acute respiratory alkalosis	10*	2
Chronic respiratory acidosis	10*	3-4
Chronic respiratory alkalosis	10*	5
Metabolic acidosis	10	10*
Metabolic alkalosis	10	15*

**Primary change.*

Metabolic acidosis with normal aSID or elevated AG

The potential causes of metabolic acidosis with normal aSID or AGMA are often remembered with mnemonic MUDPILES or MULEPAK in the past and more recently GOLDMARK due to the recognition of 5-oxoproline as an additional cause.

- 5-Oxoproline is an intermediate substrate involved in the synthesis of glutathione
- It can accumulate in patients with chronic acetaminophen use and other risk factors for depleted glutathione stores
    - Malnutrition
    - Chronic alcoholism
    - Liver disease
    - Female sex

GOLDMARK
G: Glycols (ethylene and propylene)
O: Oxoproline
L: Lactate
D: D-lactate
M: Methanol
A: ASA
R: Renal failure
K: Ketoacidosis

Hyperchloremic metabolic acidosis - decreased aSID

Etiology

- GI losses of Na more than Cl (diarrhea, fistulas)
- RTAs
    - Distal RTA (type 1) – hypokalemia
        - Autoimmune disorders such as Sjögren syndrome, rheumatoid arthritis, and lupus
        - Toluene inhalation, or "huffing
    - Proximal RTA (type 2) - hypokalemia
        - Multiple myeloma and amyloidosis
    - Type 4 RTA – hyperkalemia due to decreased aldosterone secretion or resistance
        - CKD-DM nephropathy
        - Drugs - acetazolamide, ACE-I, cyclosporine, trimethoprim, or potassium-sparing diuretics (spironolactone)

The urine anion gap (Na + K - Cl, normal is 0 or slightly positive) can be used to differentiate between GI and renal causes

- Normal functioning kidneys excrete Cl and make the urine anion gap negative anion gap
    - GI losses – the urine gap is negative
    - RTAs – positive urine gap

Hypochloremic metabolic alkalosis – increase aSID

Most common acid-base abnormality in the ICU

- Frequently due to diuresis, vomiting, nasogastric suctioning (losses of chloride, potassium, and free water)
- Treatment
    - NaCl is the preferred agent for reversing metabolic alkalosis when both chloride and volume are depleted
    - Acetazolamide helpful in severe metabolic alkalosis but does not correct the chloride deficiency
    - Adjust diuretics
    - Enteral administration of potassium chloride + free water

Alcohol osmolar gap

- Ethanol and isopropanol
    - Unlike methanol and ethylene glycol produce an osmolar gap but does not cause an anion gap metabolic acidosis unless hypotension leads to lactic acidosis
    - Significant intoxication does increase the osmolar gap and often stimulates ketogenesis
    - Isopropanol is a skin disinfectant, antifreeze, and solvent
        - Accidental or intentional ingestion resembles ethanol intoxication and can cause deep sedation and coma
- Ethylene glycol and methanol are similar
    - Methanol - retinal edema is more common
    - Ethylene glycol - calcium oxalate crystals
    - Treatment

        - Fomepizole
        - Ethanol is sometimes used as a competitive inhibitor of ADH, but it is not as effective as fomepizole
    - RRT if fomepizole fails to rapidly clear the acidosis

The BICAR-ICU trial (moderate-sized N = 389)

$NaHCO_3$ (4.2%; roughly 1 ampoule of 150 mL of sterile water)

- Pts with AKI and acidemia (pH ≤7.20 with $PaCO_2$ ≤45 mm Hg, and serum bicarbonate ≤20 mEq/L
- Led to lower rates of renal replacement therapy

THAM) - treatment for acidemia

Tris-Hydroxymethyl Aminomethane (**THAM)** is an amino alcohol that acts as a buffer base. This has the effect of increased base excess

- From the Henderson-Hasselbach approach perspective THAM generates bicarb (HCO_3^-)
    - THAM + CO_2 + water ⟹ Protonated THAM + bicarb
    - R-NH_2 + CO_2 + H_2O ⟹ R-NH_3 + HCO_3^-
- From the Stewart approach perspective THAM binds to H^- ion forming a weak base
    - THAM + H^+ ⟹ Protonated THAM
    - R-NH_2 + H^+ ⟹ R-NH_3
        - Adds new independent variable (weak base - B_{TOT}) to the previous independent variables:
            - PCO_2
            - A_{TOT} (weak acids)
            - Strong ion difference

Alternatively, **$NaHCO_3$** generates CO2 and Na

- $NaHCO_3^+ + H^- \leftrightarrow H_2CO_3 + Na \leftrightarrow H_2O + CO_2 + Na$

THAM clinical effects

Acts as a buffer base increasing base excess

- Osmolar effect in plasma and ECF
    - THAM causes elevated plasma and ECF osmolality (crosses the intact blood-brain barrier) resulting in: Osmotic diuresis
    - Decrease intracranial pressure (ICP)

THAM adverse Effects - reported as very rare

- Hypoglycemia probably from increased insulin release
- Hyperkalemia- unknown mechanism

THAM pharmacokinetics

It is primarily eliminated from plasma by renal filtration of its protonated form.

- It can accumulate in patients with renal insufficiency and produce an 'osmolar gap' with pseudohyponatremia just like glucose
- Excreted in urine. if the patient is acidotic, it takes a Cl with it

Clinical Use

Severe acidemia with pH < 7.20

- Unlike NaBicarb, THAM does not increase Na or release CO_2, on the contrary, lowers $PaCO_2$ for which is particularly useful when the acidemia is associated with the following conditions in which NaHCO3 usefulness is limited:
    - ARDS with permissive hypercapnia and concomitant metabolic acidosis
    - Hypernatremia
    - Severe hyponatremia ($NaHCO_3$ can produce rapid sodium shifts)
    - Intracranial hypertension ($NaHCO_3$ generated CO_2 with resulting acidosis and vasodilatation and therefore increased intracranial hypertension)

Dosing
Available as THAM Acetate (0.3 mol/L i.e. 300 mmol/l) in 500 mL bottles (36 grams of THAM per liter)

Initial loading dose can be estimated as:

- Lean bodyweight (kg) × base deficit (mmol/L) x 1.1
    - The maximum daily dose is 15 mmol/kg for an adult (3.5L of a 0.3 mol/L solution in a 70kg patient)
    - A loading dose of 25 to 50% of the calculated dose is given intravenously over 5 to 10 minutes, and the balance is administered over 1 hour
    - To prevent rapid changes in plasma glucose or potassium levels, the rate of administration should not exceed 2 mmol/kg in 30 minutes or 5 mmol/kg in 1 hour
    - The 24-hour dosage should be limited to 15 mmol/kg.
- Pragmatic dose:
    - THAM 500 mL over 60 min and re-check venous or arterial blood gases after each bottle
        - The first 250 mL is given as a bolus over 10 min, then slow down the infusion in an attempt to run the remaining 250 mL over 30 minutes