Acid base to practice

A 44 year old moderately dehydrated man was admitted with a two day history of acute severe diarrhea.
Electrolyte results: Na+ 134, K+ 2.9, Cl- 108, HCO3- 16, BUN 31, Cr 1.5.
ABG: pH 7.31 pCO2 33 mmHg
HCO3 16 pO2 93 mmHg

What is the acid base disorder?

1. **History**: Based on the clinical scenario, likely acid base disorders in this patient are:

- Normal anion gap acidosis from diarrhea or
- Elevated anion gap acidosis secondary to lactic acidosis as a result of hypovolemia and poor perfusion.

2. Look at the **pH**.
The pH is low, (less than 7.35) therefore by definition, patient is **acidemic**.

3. What is the process? Look at the **PCO2, HCO3-** .
PCO2 and HCO3- are **abnormal in the same direction**, therefore less likely a mixed acid base disorder. Need to distinguish the initial change from the compensatory response. A low PCO2 represents alkalosis and is not consistent with the pH. A low HCO3- represents acidosis and is consistent with the pH, therefore it must be the initial change. The low PCO2 must be the compensatory response. Since the primary change involves HCO3-, this is a metabolic process, i.e. Metabolic Acidosis.

4. Calculate the **anion gap**
The anion gap is Na - (Cl + HCO3-) = 134 -(108 + 16) = 10
Since gap is less than 16, it is therefore normal.

5. Is **compensation adequate**? Calculate the estimated PCO2.
Using Winter's formula; PCO2 = 1.5 × [HCO3-]) + 8 ± 2 = 1.5 ×16 + 8 ± 2 = 30-34.

Since the actual PCO2 falls within the estimated range, we can deduce that the compensation is adequate and there is no seperate respiratory disorder present.

Assessment: Normal anion gap acidosis with adequate compensation most likely secondary to severe diarrhea.

Stepwise approach to interpreting the arterial blood gas.

1. **H&P.** The most clinical useful information comes from the clinical description of the patient by the history and physical examination. The H&P usually gives an idea of what acid base disorder might be present even before collecting the ABG sample

2. **Look at the pH**. Is there an acid base disorder present?
- If pH < 7.35, then acidemia
- if pH > 7.45, then alkalemia
- If pH within normal range, then acid base disorder not likely present.
- pH may be normal in the presence of a mixed acid base disorder, particularly if other parameters of the ABG are abnormal.

3. **Look at PCO2, HCO3-.** What is the acid base process (alkalosis vs acidosis) leading to the abnormal pH? Are both values normal or abnormal?

- In simple acid base disorders, both values are abnormal and direction of the abnormal change is the same for both parameters.
- One abnormal value will be the initial change and the other will be the compensatory response.

3a. **Distinguish the initial change from the compensatory response.**

- The initial change will be the abnormal value that correlates with the abnormal pH.
- If Alkalosis, then PCO2 low or HCO3- high
- If Acidosis, then PCO2 high or HCO3- low.

Once the initial change is identified, then the other abnormal parameter is the compensatory response if the direction of the change is the same. If not, suspect a mixed disorder.

3b. Once the initial chemical change and the compensatory response is distinguished, then **identify the specific disorder**. See table below.

- If PCO2 is the initial chemical change, then process is respiratory.
- if HCO3- is the initial chemical change, then process is metabolic.

Acid Base Disorder	**Initial Chemical Change**	**Compensatory Response**
Respiratory Acidosis	↑ PCO2	↑HCO3-
Respiratory Alkalosis	↓ PCO2	↓ HCO3-
Metabolic Acidosis	↓ HCO3-	↓ PCO2
Metabolic Alkalosis	↑ HCO3-	↑ PCO2

4. **If respiratory process, is it acute or chronic?**

- An acute respiratory process will produce a compensatory response that is due primarily to rapid intracellular buffering.
- A chronic respiratory process will produce a more significant compensatory response that is due primarily to renal adaptation, which takes a longer time to develop.
- To assess if acute or chronic, determine the **extent** of compensation.

5. If metabolic acidosis, then look at the **Anion Gap**.

- If elevated (> than 16), then acidosis due to KULT. (Ketoacidosis, Uremia, Lactic acidosis, Toxins).
- If anion gap is normal, then acidosis likely due to diarrhea, RTA.

6. If metabolic process, is degree of **compensation adequate**?

- Calculate the estimated PCO2, this will help to determine if a seperate respiratory disorder is present.

Compensatory Responses: summary **and take home points**

1. Compensatory responses never return the ph to normal or overshoot.

2. The basis of compensatory responses is to maintain the PCO2/[HCO3-] ratio.

3. Therefore, the direction of the compensatory response is always the same as that of the initial change.

4. Compensatory response to respiratory disorders is two-fold; a fast response due to cell buffering and a significantly slower response due to renal adaptation.

5. Compensatory response to metabolic disorders involves only an alteration in alveolar ventilation.

6. Metabolic responses cannot be defined as acute or chronic in terms of respiratory compensation because the extent of compensation is the same in each case.

Below is table summarizing compensatory responses and their mechanisms.

Primary disorder	Initial chemical change	Compensatory response	Compensatory Mechanism	Expected level of compensation
Metabolic Acidosis	**↓HCO3-**	**↓PCO2**	**Hyperventilation**	**PCO2 = (1.5 × [HCO3-]) + 8 ± 2**
				↓PCO2 = 1.2 ×Δ [HCO3-]
				PCO2 = last 2 digits of pH
Metabolic Alkalosis	**↑HCO3-**	**↑PCO2**	**Hypoventilation**	**PCO2 = (0.9 × [HCO3-]) + 16 ± 2**
				↑PCO2 = 0.7 × Δ [HCO3-]
Respiratory Acidosis	**↑PCO2**	**↑HCO3-**		
Acute			**Intracellular Buffering (hemoglobin, intracellular proteins)**	**↑[HCO3-] = 1 mEq/L for every 10 mm Hg ΔPCO2**
Chronic			**Generation of new HCO3- due to the increased excretion of ammonium.**	**↑[HCO3-] = 3.5 mEq/L for every 10 mm Hg ΔPCO2**
Respiratory Alkalosis	**↓PCO2**	**↓HCO3-**		
Acute			**Intracellular Buffering**	**↓[HCO3-] = 2 mEq/L for every 10 mm Hg ΔPCO2**
Chronic			**Decreased reabsorption of HCO3-, decreased excretion of ammonium**	**↓[HCO3-] =4 mEq/L for every 10 mm Hg ΔPCO2**

Also: In acute respiratory acidosis, ↓pH = 0.008 × Δ PCO2
In chronic respiratory acidosis, ↓pH = 0.003 × Δ PCO2.

7. If anion gap is elevated, then calculate the **Delta-Ratio** (Δ/Δ) to assess for other simultaneous disorders.
- Δ/Δ compares the change in the anion gap to the change in bicarbonate.
- If ratio between 1 and 2, then pure elevated anion gap acidosis
- If < 1, then there is a simultaneous normal anion gap acidosis present.
- if > 2, then there is a simultaneous metabolic alkalosis present or a compensated chronic respiratory acidosis.

8. If normal anion gap and cause is unknown, then calculate the **Urine Anion Gap (UAG).** This will help to differentiate RTAs from other causes of non elevated anion gap acidosis.

- In RTA, UAG is positive.
- In diarrhea and other causes of metabolic acidosis, the UAG is negative. (ne**GUT**ive in diarrhea)

Physiologic Effects of Acidosis

Respiratory Effects
• Hyperventilation (**Kussmaul respirations**) • Shift of oxyhaemoglobin dissociation curve to the right • Decreases 2,3 DPG levels in red cells, which opposes the effect above. (shifts the ODC back to the left) This effect occurs after 6 hours of acidemia.
Cardiovascular Effects
• Depression of myocardial contractility (this effect predominates at pH < 7.2) • Sympathetic over-activity (tachycardia, vasoconstriction, decreased arrhythmia threshold) • Resistance to the effects of catecholamines (occur when acidemia very severe) • Peripheral arteriolar vasodilatation • Venoconstriction of peripheral veins • Vasoconstriction of pulmonary arteries • Effects of hyperkalemia on heart
Central Nervous System Effects
• Cerebral vasodilation leads to an increase in cerebral blood flow and intracranial pressure (occur in acute respiratory acidosis) • Very high pCo2 levels will cause central depression
Other Effects
• Increased bone resorption (chronic metabolic acidosis only) • Shift of K+ out of cells causing hyperkalemia (an effect seen particularly in metabolic acidosis and only when caused by non organic acids) • Increase in extracellular phosphate concentration

Physiologic Effects of Alkalosis

Respiratory Effects
• Shift of oxyhaemoglobin dissociation curve to the left (impaired unloading of oxygen • The above effect is however balanced by an increase in 2,3 DPG levels in RBCs. • Inhibition of respiratory drive via the central & peripheral chemoreceptors
Cardiovascular Effects
• Depression of myocardial contractility • Arrhythmias
Central Nervous System Effects

- Cerebral vasoconstriction leads to a decrease in cerebral blood flow (result in confusion, muoclonus, asterixis, loss of consciousness and seizures) Only seen in acute respiratory alkalosis. Effect last only about 6 hours.
- Increased neuromuscular excitability (resulting in paraesthesias such as circumoral tingling & numbness; carpopedal spasm) Seen particularly in acute respiratory alkalosis.

Other Effects

- Causes shift of hydrogen ions into cells, leading to hypokalemia.

Anion Gap

When acid is added to the body, the [H+] increases and the [HCO3-] decreases. In addition, the concentration of the anion, which is associated with the acid, increases. This change in the anion concentration provides a convenient way to analyze and help determine the cause of a metabolic acidosis by calculating what is termed the **anion gap**.

The anion gap is estimated by subtracting the sum of Cl- and HCO3- concentrations from the plasma Na concentration.

Na + Unmeasured cations = **Cl- + HCO3-** + Unmeasured anions

Anion gap = [Na] – ([Cl-] + [HCO3-])

The major unmeasured cations are calcium, magnesium, gamma globulins and potassium. The major unmeasured anions are negatively charged plasma proteins (albumin), sulphate, phosphates, lactate and other organic anions. The anion gap is defined as the quantity of anions not balanced by cations. This is usually equal to 12 ± 4 meq/L and is usually due to the **negatively charged plasma proteins** as the charges of the other unmeasured cations and anions tend to balance out.

If the anion of the acid added to plasma is Cl- , the anion gap will be normal (i.e., the decrease in [HCO3-] is matched by an increase in [Cl-]). For example:

HCl + NaHCO3 → NaCl + H2CO3 → CO2 + H2O

In this setting, there is a meq. for meq. replacement of extracellular HCO3- by Cl- ; thus, there is no change in the anion gap, since the sum of Cl-] + [HCO3-] remains constant. This disorder is called a hyperchloremic acidosis, because of the associated increase in the Cl- concentration. GI or renal loss of HCO3- produces the same effect as adding HCl as the kidney in its effort to preserve the ECV will retain NaCl leading to a net exchange of lost HCO3- for Cl-.

In contrast, if the anion of the acid is not Cl- (e.g. lactate, β-hydroxybutyrate), the anion gap will increase (i.e. the decrease in [HCO3-] is not matched by an increase in the [Cl-] but rather by an increase in the [unmeasured anion]:

HA + NaHCO3 → NaA + H2CO3 → CO2 + H2O, where A- is the unmeasured anion.

Causes of elevated Anion gap acidosis is best remembered by the mnemonic **KULT** or the popular **MUDPILES**

M = Methanol
U = Uremia
D = DKA (also AKA and starvation)
P = Paraldehyde
I = INH
L = Lactic acidosis
E = Ethylene Glycol
S = Salycilate

K = Ketoacidosis (DKA,alcoholic ketoacidosis, starvation)
U = Uremia (Renal Failure)
L =Lactic acidosis
T = Toxins (Ethylene glycol, methanol, paraldehyde, salicylate)

Because, negatively charged plasma proteins account for the normal anion gap, the normal values should be adjusted downward for patients with hypoalbuminemia.

The approximate correction is a reduction in the normal anion gap of 2.5 meq/l for every 1g/dl decline in the plasma albumin concentration (normal value = 4 g/dl).

The Delta Ratio (Δ/Δ)

The delta ratio is sometimes used in the assessment of elevated anion gap metabolic acidosis to determine if a mixed acid base disorder is present.

Delta ratio = Δ Anion gap/Δ [HCO3-] or **↑anion gap/ ↓ [HCO3-]**

Delta Delta = Measured anion gap – Normal anion gap
Delta del Normal [HCO3-] – Measured [HCO3-]

Delta Delta = **(AG – 12)**
Delta delaaa(24 - [HCO3-])

In order to understand this, let us re-examine the concept of the anion gap.

If one molecule of metabolic acid (HA) is added to the ECF and dissociates, the one H+ released will react with one molecule of HCO3- to produce CO2 and H2O. This is the process of buffering. **The net effect will be an increase in unmeasured anions by the one acid anion A- (ie anion gap increases by one) and a decrease in the bicarbonate by one meq.**

Now, if all the acid dissociated in the ECF and all the buffering was by bicarbonate, then the increase in the AG should be equal to the decrease in bicarbonate so the ratio between these two changes (which we call the delta

ratio) should be equal to one.

As described previously, more than 50% of excess acid is buffered intracellularly and by bone, not by HCO_3^- . In contrast, most of the excess anions remain in the ECF, because anions cannot easily cross the lipid bilayer of the cell membrane. **As a result, the elevation in the anion gap usually exceeds the fall in the plasma $[HCO_3^-]$. In lactic acidosis, for example, the Δ/Δ ratio averages 1.6:1**.

On the other hand, although the same principle applies to ketoacidosis, the ratio is usually close to 1:1 in this disorder because the loss of ketoacids anions (ketones) lowers the anion gap and tends to balance the effect of intracellular buffering. Anion loss in the urine is much less prominent in lactic acidosis because the associated state of marked tissue hypoperfusion usually results in little or no urine output.

A delta-delta value below 1:1 indicates a greater fall in $[HCO_3^-]$ than one would expect given the increase in the anion gap. This can be explained by a mixed metabolic acidosis, i.e a combined elevated anion gap acidosis and a normal anion gap acidosis, as might occur when lactic acidosis is superimposed on severe diarrhea. In this situation, the additional fall in HCO_3^- is due to further buffering of an acid that does not contribute to the anion gap. (i.e addition of HCl to the body as a result of diarrhea)

A value above 2:1 indicates a lesser fall in $[HCO_3^-]$ than one would expect given the change in the anion gap. This can be explained by another process that increases the $[HCO_3^-]$,i.e. a concurrent metabolic alkalosis. Another situation to consider is a pre-existing high HCO_3^- level as would be seen in chronic respiratory acidosis.

Delta ratio	**Assessment Guidelines**
< 0.4	Hyperchloremic normal anion gap acidosis
< 1	High AG & normal AG acidosis
1 to 2	Pure Anion Gap Acidosis Lactic acidosis: average value 1.6 DKA more likely to have a ratio closer to 1 due to urine ketone loss
> 2	High AG acidosis and a concurrent metabolic alkalosis or a pre-existing compensated respiratory acidosis

Mixed Acid Base Disorders

Mixed acid base disorders occur when there is more than one primary acid base disturbance present simultaneously. They are frequently seen in hospitalized patients, particularly in the critically ill.

When to suspect a mixed acid base disorder:

1. The expected compensatory response does not occur
2. Compensatory response occurs, but level of compensation is inadequate or too extreme
3. Whenever the PCO2 and [HCO3-] becomes abnormal in the opposite direction. (i.e. one is elevated while the other is reduced). In simple acid base disorders, the direction of the compensatory response is always the same as the direction of the initial abnormal change.
4. pH is normal but PCO2 or HCO3- is abnormal
5. In anion gap metabolic acidosis, if the change in bicarbonate level is not proportional to the change of the anion gap. More specifically, if the delta ratio is greater than 2 or less than 1.
6. In simple acid base disorders, the compensatory response should never return the pH to normal. If that happens, suspect a mixed disorder.

<u>Mixed metabolic disorders</u>

a. **Anion Gap and Normal Anion Gap Acidosis**.
   This mixed acid base disorder is identified in patients with a **delta ratio less than 1** which signifies that the reduction in bicarbonate is greater than it should be, relative to the change in the anion gap. Thus, implicating that there must be another process present requiring buffering by HCO3-, i.e a concurrent normal anion gap acidosis.
   Example:
   - Lactic acidosis superimposed on severe diarrhea. (note: the delta ratio is not particularly helpful here since the diarrhea will be clinically obvious)
   - Progressive Renal Failure
   - DKA during treatment
   - Type IV RTA and DKA

b. **Anion Gap Acidosis and Metabolic Alkalosis**
   This mixed acid base disorder is identified in patients with a delta **ratio greater than 1,** which signifies a reduction in bicarbonate less than it should be, relative to the change in the anion gap. This suggests the presence of another process functioning to increase the bicarbonate level without affecting the anion gap, i.e. metabolic alkalosis.
   Examples:
   - Lactic acidosis, uremia, or DKA in a patient who is actively vomiting or who requires nasogastric suction.
   - Patient with lactic acidosis or DKA given sodium bicarbonate therapy.

c. **Normal Anion Gap Acidosis and Metabolic Alkalosis**
   This diagnosis can be quite difficult, because the low HCO3- and low PCO2 both move back toward normal when metabolic alkalosis develops. Also, unlike elevated anion gap acidosis, the anion gap will not indicate the presence of the acidosis.
   Example:

- In patients who are vomiting and with diarrhea (note: all acid base parameters may fall within the normal range)

Mixed respiratory and respiratory–metabolic disorders

Having a good knowledge of compensatory mechanisms and extent of compensation will aid in identifying these disorders. Remember; compensation for simple acid-base disturbances always drives the compensating parameter (*ie*, the PCO2, or [HCO3-]) in the same direction as the primary abnormal parameter (*ie*, the [HCO3-] or PCO2). **Whenever the PCO2 and [HCO3] are abnormal in *opposite* directions, *ie*, one above normal while the other is reduced, a mixed respiratory and metabolic acid-base disorder exists.**

Rule of thumb:

- When the PCO2 is elevated and the [HCO3-] reduced, respiratory acidosis and metabolic acidosis coexist.
- When the PCO2 is reduced and the [HCO3-] elevated, respiratory alkalosis and metabolic alkalosis coexist

The above examples both produce very extreme acidemia or alkalemia and are relatively easy to diagnose. However more often, the disorder is quite subtle. For example, in cases of metabolic acidosis, the HCO3- is low and PCO2 low. If the PCO2 is normal or not aqequately reduced, this may indicate a subtle coexisting respiratory acidosis.

Mixed acid base disorders usually produce arterial blood gas results that could potentially be explained by other mixed disorders. Oftentimes, the clinical picture will help to distinguish. It is important to distinguish mixed acid base disorders because work up and management will depend on accurate diagnosis.

a. **Chronic Respiratory Acidosis with superimposed Acute Respiratory Acidosis**
   Example:
   - Acute exacerbation of COPD secondary to acute pneumonia
   - COPD patient with worsening hypoventilation secondary to oxygen therapy or sedative administration

b. **Chronic Respiratory Acidosis and Anion Gap Metabolic Acidosis**
   Example:
   - COPD patient who develops shock and lactic acidosis

c. **Chronic Respiratory Acidosis and Metabolic Alkalosis**
   Example:
   - Pulmonary insufficiency and diuretic therapy
   - or COPD patient treated with steroids or ventilation (important to recognize as alkalemia will reduce acidemic stimulus to breathe)

d. **Respiratory Alkalosis and Metabolic Acidosis**
   Example:
   - Salicylate intoxication
   - Gram negative sepsis
   - Acute cardiopulmonary arrest
   - Severe pulmonary edema

Metabolic Acidosis

A primary metabolic acidosis is characterized by low arterial pH (< 7.35), reduced plasma HCO3- concentration, and compensatory alveolar hyperventilation resulting in decreased PCO2.

It can be induced by either increased endogenous acid production, increased exogenous acid administration, loss of HCO3-, or by decreased ability to excrete the normal dietary H+ load.

Differential Diagnosis

The differential diagnosis of metabolic acidosis is vast and is best approached if one breaks down the causes of metabolic acidosis into normal vs elevated **anion gap** metabolic acidosis. See below.

Elevated Anion Gap (>16 meq)	Normal Anion Gap (8-16 meq)
Increased Endogenous production: Ketoacidosis (Alcohol, Starvation, DKA)	Loss of Bicarbonate: Diarrhea Carbonic anhydrase inhibitors Type 2 RTA (proximal) Pancreatic ileostomy Pancreatic, biliary, intestinal fistula
Lactic Acidosis	Exogenous Administration: ammonium chloride or HCL
Uremia	Decreased Renal Acid Excretion: Type 1(distal) ,4 RTA Renal Failure
Intoxications: Methanol, Ethylene Glycol, Paraldehyde, Salicylates, INH	Miscellaneous: Hyperkalemia Recovery from DKA

Metabolic Alkalosis

Primary metabolic alkalosis is characterized by an elevation in the arterial pH, an increase in the plasma HCO3- concentration, and a compensatory hypoventilation, resulting in a rise in the pCO2. It is often accompanied by **hypochloremia** and **hypokalemia**.

Pathogenesis

Metabolic Alkalosis can be induced by **a loss of hydrogen ions, transcellular H+ shift, exogenous alkali administration or by contraction alkalosis**. These factors are known as **initiator factors** because they are said to initiate the alkalosis. Under normal circumstances, alkalosis should never develop because the kidney is excellent at excreting excess bicarbonate. However in conditions where kidney function might be impaired, excretion of bicarbonate may become compromised. Metabolic alkalosis is always associated with an initiating factor and and an impairment in kidney function referred to as the **maintenance factor,** that is thought to maintain the alkalosis . See table below.

The most common maintenance factor is a **reduction in ECV** that leads to a reduction in GFR and an increase in Na and HCO3- reabsorption. Another factor that maintains alkalosis is **Hypokalemia**. Alkalosis can be both a cause and a result of hypokalemia, as will be discussed. **Mineralocorticoid excess** is another factor that initiates metabolic alkalosis. In those cases, the alkalosis is maintained by the development of hypokalemia as will be discussed.

Metabolic alkalosis that is associated with a reduction in volume responds very well to treatment with normal saline and is said to be **saline responsive**. Mineralocorticoid or hypokalemia induced alkalosis does not respond to volume administration and is said to be **saline unresponsive.** This will be discussed.

Initiating Factors	**Maintenance Factors**	
1. Loss of hydrogen ions from GI 2. Exogenous addition of alkali 3. Transcellular H+ shift 4. Contraction alkalosis	1. Reduced ECV – decreased GFR and increased absorption of **HCO3-** 2. Hypokalemia	Saline Responsive
1. Mineralocorticoid excess 2. Severe Hypokalemia	Hypokalemia	Saline Unresponsive

Causes of metabolic Alkalosis

1) Loss of hydrogen

A. Gastrointestinal loss
1. Removal of gastric secretions: Vomiting or nasogastric suction
2. Chloride-losing diarrhea
3. Gastrocolic fistula
4. Villous adenoma
5. Antacid therapy, particularly if combined with cation exchange resin

B. Renal loss
1. loop or thiazide diuretics
2. Mineralocorticoid excess (Primary Aldo, Cushings, steroids, licorice)
3. Post chronic hypercapnia
4. Hypercalcemia, including the milk of alkali syndrome

C. H+ movement into cells
1. Hypokalemia

2) Exogenous Alkali

A. Administration of NaHCO3, sodium citrate, gluconate, acetate, antacids

B. Massive blood transfusion
C. Antacids - Milk alkali syndrome

3) Contraction alkalosis

A. Loop or thiazide-type diuretics
B. Sweat losses in cystic fibrosis
C. Gastric losses in achlorhydria

4) Miscellaneous

A. Bartter's syndrome
B. Gitelman's syndrome