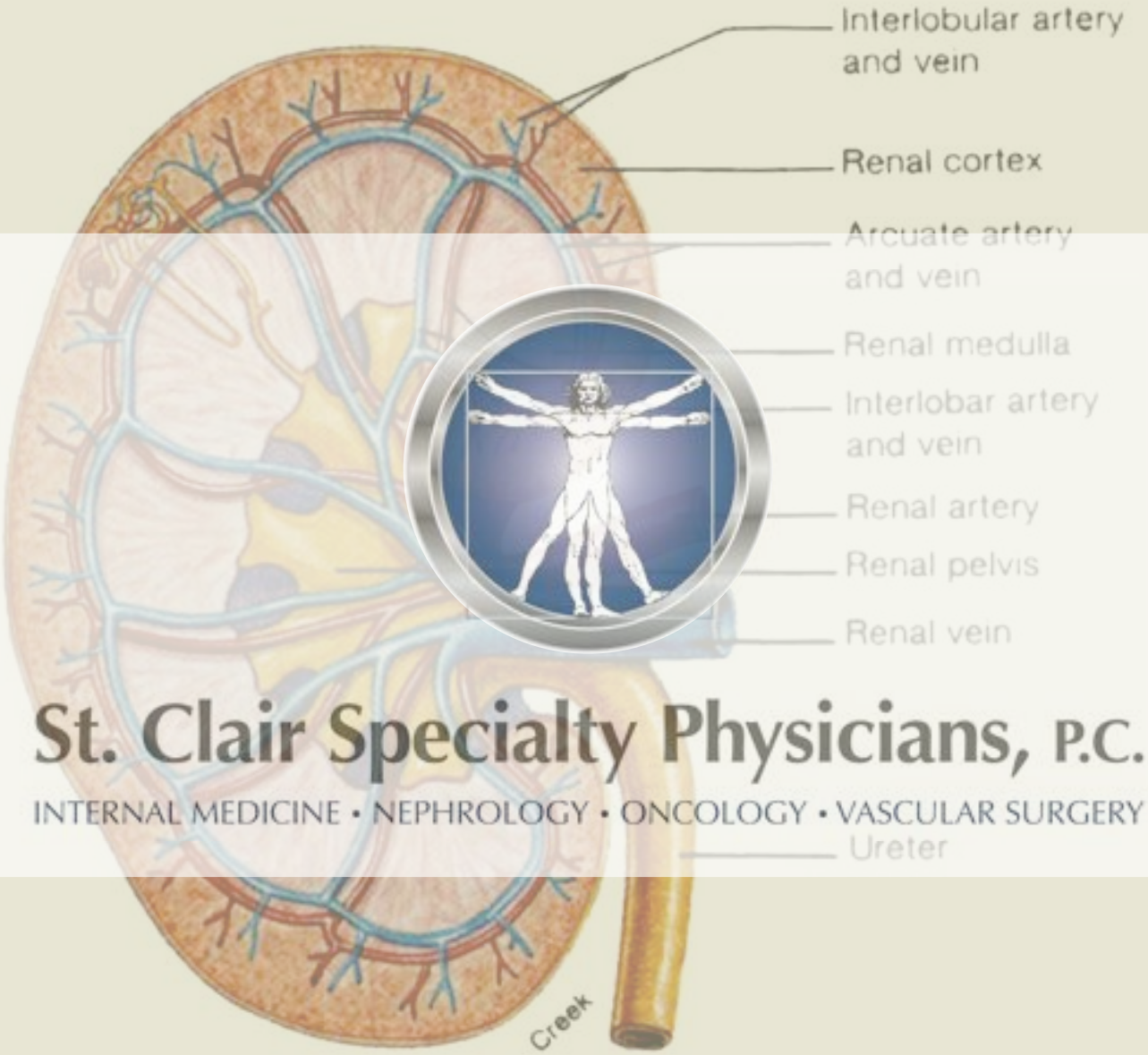
Acid Base Balance:
a Practical Workshop



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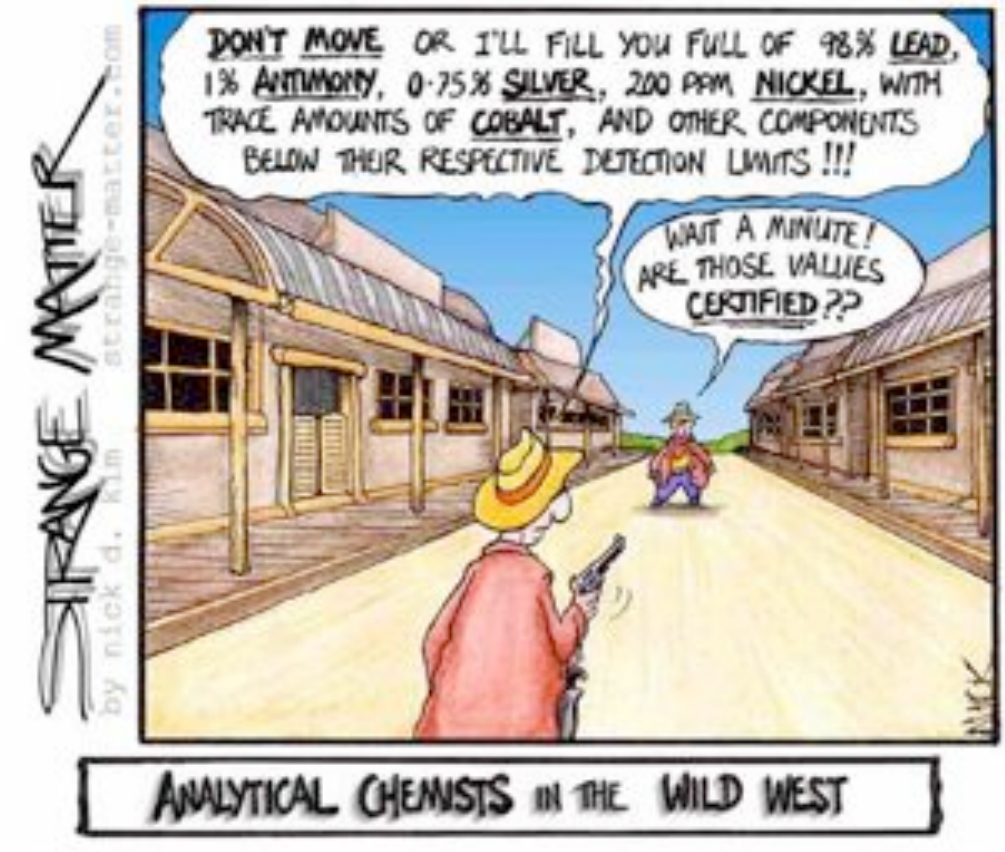

Introduction

Acid-base is a subject that is intimidating because the inorganic chemists screwed it up. While every other medically important ion is measured in straight forward, an easy to understand units, hydrogen ions are measured on a non-linear negative log rhythmic scale.

Goals

- Understand pH
- The Henderson Hasselbach formula
- The four primary acid-base disturbances.
- Compensation
  - Metabolic acidosis
  - Metabolic alkalosis
  - Respiratory acidosis
  - Respiratory alkalosis
- Anion Gap
- Anion gap metabolic acidosis
- Non-anion gap metabolic acidosis
- Delta-gap or gap-gap
- Osmolar gap
- Alkalosis and calcium
- Etiologies and management of the primary acid-base disturbances
  - Metabolic alkalosis
  - Metabolic acidosis
  - Respiratory acidosis
  - Respiratory alkalosis

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pH and the hydrogen ion concentration

Acid base physiology is the regulation of hydrogen ion concentration

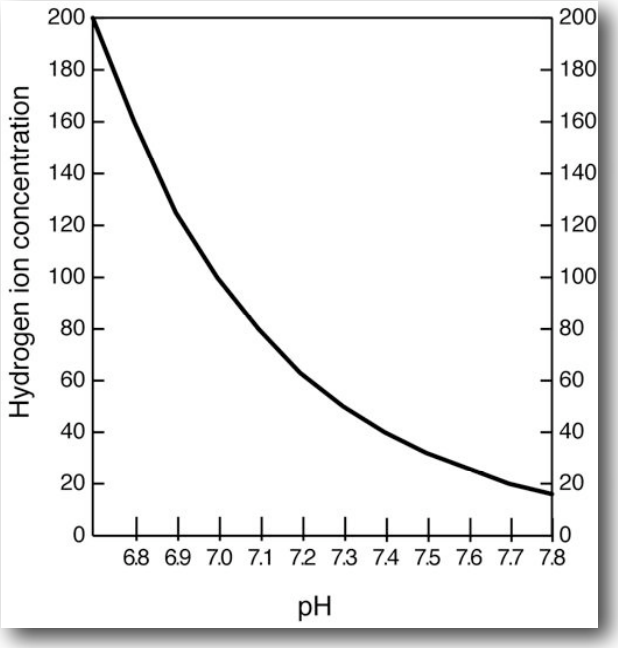
Hydrogen ions are similar and different from other physiologically important electrolytes. Like other electrolytes, hydrogen ion concentrations need to be regulated. If the concentration rises too high or falls too low there are physiologic consequences and illness. A normal hydrogen ion concentration is 40 nmol/L and that leads to the principle difference from other ions.

Hydrogen ions exist at such a minute concentrations that inorganic chemists decided to measure then on a negative logrhythmic scale so 0.00004 mmol/L converts to 7.4. Every move of one point is a factor of ten. a pH of 6.4 is 400 mmol/L and 8.4 is 4 mmol/L. On this scale every change of 0.3 pH units changes the hydrogen concentration by a factor of two.

40 nmol/L

is

0.00004 mmol/L



pH	H^+ concentration (nmol/L)
6.8	*160*
7.1	*80*
7.4	*40*
7.7	*20*

Henderson-Hasselbalch equation

The primary buffer in the body is bicarbonate which is in equilibrium with carbon dioxide and water. The relationship between hydrogen ions, bicarbonate and carbon dioxide is governed by the law of mass action. This mass action formula can be simplified to a simple relationship called the Henderson-Hasselbalch formula.

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

This equation represents the relationship of water, carbon dioxide, hydrogen and bicarbonate in the body.

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

$$H_2O + CO_2 \leftrightarrow H^+ + HCO_3^-$$

H_2CO_3 is rapidly broken down by carbonic anhydrase (the fastest enzyme in the body). Since it is so transient, it is dropped from the equation.

$$Ka = \frac{[H^+][HCO_3^-]}{[H_2O][CO_2]}$$

The Ka of bicarbonate is the ratio of the products (H^+ and HCO_3^-) to the reactants (H_2O and CO_2) of the above reaction.

$$[H_2O] \times Ka = \frac{[H^+][HCO_3^-]}{[H_2O][CO_2]} \times [H_2O]$$

Unlike H^+, HCO_3^- and CO_2, the concentration of water in the body does not change (i.e., it is a constant). By multiplying both sides of the equation by this constant, H_2O drops out of the right-hand side of the equation.

$$Ka' = \frac{[H^+][HCO_3^-]}{[CO_2]}$$

This simplified formula defines the relationship of bicarbonate to hydrogen and carbon dioxide in terms of its Ka. The term Ka' represents Ka × $[H_2O]$.

$$Ka' = \frac{[H^+][HCO_3^-]}{[CO_2]} = 800 \text{ nanomol/L}$$

Ka', the ratio of H^+ and HCO_3^- to CO_2, is a constant; its value is 800 nanomol/L.

$$Ka' = \frac{[H^+][HCO_3^-]}{[CO_2]}$$

This is the formula for the Ka of bicarbonate which defines the relationship of bicarbonate and hydrogen to carbon dioxide.

$$\frac{[CO_2]}{[HCO_3^-]} Ka' = \frac{[H^+][HCO_3^-]}{[CO_2]} \frac{[CO_2]}{[HCO_3^-]}$$

The initial equation can be solved for H^+ by multiplying both sides of the equation by: CO_2 / HCO_3^-.

$$\frac{[CO_2]}{[HCO_3^-]} Ka' = [H^+]$$

$$[H^+] = Ka' \frac{[CO_2]}{[HCO_3^-]}$$

The equation is rearranged so that H^+ is on the left side.

$$-\log \times [H^+] = Ka' \frac{[CO_2]}{[HCO_3^-]} \times -\log$$

After both sides of the equation are multiplied by a negative log, what results is…

$$pH = pKa' + \log \frac{[HCO_3^-]}{[CO_2]}$$

The Henderson-Hasselbalch equation.

$$pH = 6.1 + \log \frac{[HCO_3^-]}{0.03\ PCO_2}$$

Since carbon dioxide is typically measured in partial pressure, a conversion factor is added to the denominator. The value for pKa' (the negative log of 800 = 6.1) is also substituted.

The Henderson Hasselbalch formula Provides a critical relationship that governs all of acid base physiology. It is the Mantra of Acid Base physiology.

The pH is proportional to the serum bicarbonate over carbon dioxide. An increase in the numerator, bicarbonate, increases pH. A decrease in the denominator, carbon dioxide, also increases the pH. This relationship of bicarbonate, CO2 and pH is critical and you must have perfect knowledge of it to understand even the basics of acid-base physiology.

If the quantitative approach is not helpful one can understand the relationship from a simple qualitative approach. Bicarbonate is alkaline so increases in its concentration occur with increases in pH. The carbon dioxide is the acid so as its concentration rise the pH falls.

You are taking boards and they give you the following ABG:

$$pH = 6.8 \ / \ pCO_2 = 50 \ / \ HCO_3 = 15$$

You have been told that one question on the boards will require to use the Henderson-Hasselbalch equation to determine if the ABG is possible. Use the Henderson-Hasselbalch equation to determine if this ABG is possible.

Do the same for this ABG:

$$pH = 8.1 \ / \ pCO_2 = 10 \ / \ HCO_3 = 30$$

I guarantee you will get one of these questions on the boards. There will be one acid-base question where the right answer is some variance of:

E) There is a lab error.

or

B) This ABG is impossible.

One of the keys to the math on these problems is realizing that no one has a calculator and it is rather difficult to do logs in your head so the test writers try to keep the numbers easy to handle. The pCO_2 x 0.03 will always be a tenth of the bicarbonate (so the log is 1 and the pH should be 6.1+1=7.1) or a hundredth of the bicarbonate (so the log is 2 and the pH should be 6.1+2=8.1).

Remember: the Henderson-Hasselbalch equation is not just a good idea...Its the law.

The Mantra

$$pH = pKa + \log \frac{[HCO_3^-]}{[CO_2]}$$

$$pH \propto \frac{[HCO_3^-]}{[CO_2]}$$

$$\text{Acidity} = \frac{\text{Bicarbonate}}{\text{Carbon Dioxide}}$$

$$A = {}^{B}/_{CD}$$

There are four primary acid-base disturbances

Looking at The Mantra it becomes apparent there are four disturbances which can occur:

1. an increase in bicarbonate
2. a decrease in bicarbonate
3. an increase in carbon dioxide
4. a decrease in carbon dioxide

Any alteration of acid-base physiology requires at least one of these changes. The acid-base disturbances are categorized by the initial (i.e. primary) disturbance to The Mantra:

1. An increase in bicarbonate is a metabolic alkalosis
2. A decrease in bicarbonate is a metabolic acidosis
3. An increase in carbon dioxide is a respiratory acidosis
4. A decrease in the carbon dioxide is a respiratory alkalosis

Compensation

In order to remain in health, the body attempts to minimize changes in pH. Faced with a change in one component of The Mantra, the other factor changes in the same direction so that the fraction remains nearly constant. For example the body responds to a fall in bicarbonate by decreasing carbon dioxide. This minimizes changes in the ratio that determines the pH.

Acid-Base disorder	Primary disturbance	compensation
Metabolic acidosis	$\downarrow pH = \frac{\downarrow HCO_3}{CO_2}$	$\downarrow pH = \frac{\downarrow HCO_3}{\downarrow CO_2}$
Metabolic alkalosis	$\uparrow pH = \frac{\uparrow HCO_3}{CO_2}$	$\uparrow pH = \frac{\uparrow HCO_3}{\uparrow CO_2}$
Respiratory acidosis	$\downarrow pH = \frac{HCO_3}{\uparrow CO_2}$	$\downarrow pH = \frac{\downarrow HCO_3}{\downarrow CO_2}$
Respiratory alkalosis	$\uparrow pH = \frac{HCO_3}{\downarrow CO_2}$	$\downarrow pH = \frac{\uparrow HCO_3}{\uparrow CO_2}$

The important thing to recognize is that the primary disturbance without any compensation is a theoretical construct. In real patients, compensation occurs simultaneously with the primary defect. This complicates trying to sleuth out what is disease and what is compensation.

In metabolic disorders: pH, HCO_3 and pCO_2 all move in the same directions

For example: a decrease in bicarbonate and carbon dioxide could be due to a primary decrease in bicarbonate with a compensatory decrease in carbon dioxide or a primary decrease in carbon dioxide with a compensatory decrease in bicarbonate.

The key to this mystery is the fact that compensation does not completely erase the primary change in pH. In metabolic acidosis the pH falls, and the compensatory decrease in carbon dioxide minimizes the change in pH but does not erase it. So, a primary decrease in bicarbonate (metabolic acidosis) will decrease the pH while a primary decrease in carbon dioxide (respiratory alkalosis) will increased the pH.

In respiratory disorders: pH, HCO_3 and pCO_2 move in discordant directions

The quick method

Since bicarbonate is proportional to pH, any ABG with pH and bicarbonate moving in concordant directions will be a primary metabolic disease. Then all you need to do is determine if the pH is elevated, metabolic alkalosis, or decreased, metabolic acidosis. Additionally since the compensatory changes in carbon dioxide are in the same direction as the bicarbonate, all three Henderson-Hasselbalch variables will move in the same direction in a metabolic acid-base disturbance.

Conversely, since carbon dioxide is inversely related to pH, in a respiratory acid-base disturbance the carbon dioxide and pH move in discordant directions. Again since compensation is always in the same direction as the primary disorder, in a respiratory acid-base disturbance the three Henderson-Hasselbalch variables will move in discordant directions.

Determine the primary acid-base disturbance:

1. pH = 7.27 / pCO_2 = 34 / HCO_3 = 15

2. pH = 7.34 / pCO_2 = 50 / HCO_3 = 26

3. pH = 7.45 / pCO_2 = 48 / HCO_3 = 32

4. pH = 7.32 / pCO_2 = 28 / HCO_3 = 14

5. pH = 7.37 / pCO_2 = 50 / HCO_3 = 28

6. pH = 7.36 / pCO_2 = 80 / HCO_3 = 44

7. pH = 7.32 / pCO_2 = 36 / HCO_3 = 18

8. pH = 7.36 / pCO_2 = 48 / HCO_3 = 26

9. pH = 7.43 / pCO_2 = 45 / HCO_3 = 29

10. pH = 7.47 / pCO_2 = 54 / HCO_3 = 38

11. pH = 7.45 / pCO_2 = 18 / HCO_3 = 12

Rapid interpretation of ABGs

A pH of 7.1 in methanol intoxication is an ominous sign.

A pH of 7.1 following a grand-mal seizure is routine and without significant morbidity.

A pH of 7.6 due to anxiety-hyperventilation syndrome is benign.

A pH of 7.6 in patients on digoxin and diuretics predisposes to serious arrhythmia.

From the above examples it should be clear that it is the disease, not the pH that determines morbidity. Because of this, it is imperative to rapidly determine the etiology of an acid-base disturbance. The ABG and electrolyte panel allow one to easily narrow the differential diagnosis. It also allows the cagey physician to detect and categorize multiple, simultaneous, primary acid-base disorders.

You have already learned how to determine the primary disorder, there are a few more steps to narrowing the differential:

1. Determine if there is a second primary acid-base disorder affecting compensation
2. If the patient has an a metabolic acidosis, determine if there is an anion gap
3. If the patient has an anion gap metabolic acidosis, determine if there was a pre-existing non-anion gap metabolic acidosis or metabolic alkalosis

Multiple primary acid-base disturbances

Patients are complex and often have multiple simultaneous primary acid-base disturbances. Think of the patient with gastroenteritis with diarrhea causing metabolic acidosis and vomiting causing metabolic alkalosis. Uncovering these complex cases can be done mathematically or graphically. My suggestion to you is to get a computer. Patients are too important and you are too bad at math to do the calculation reliably, especially late at night.

ABGpro for the PalmOS correctly dissects the ABG and provides all the primary acid-base disorders. Check out the correctly diagnosed triple disorder pictured below

The best program for the PalmOS is ABGpro which is free from http://www.stacworks.com.

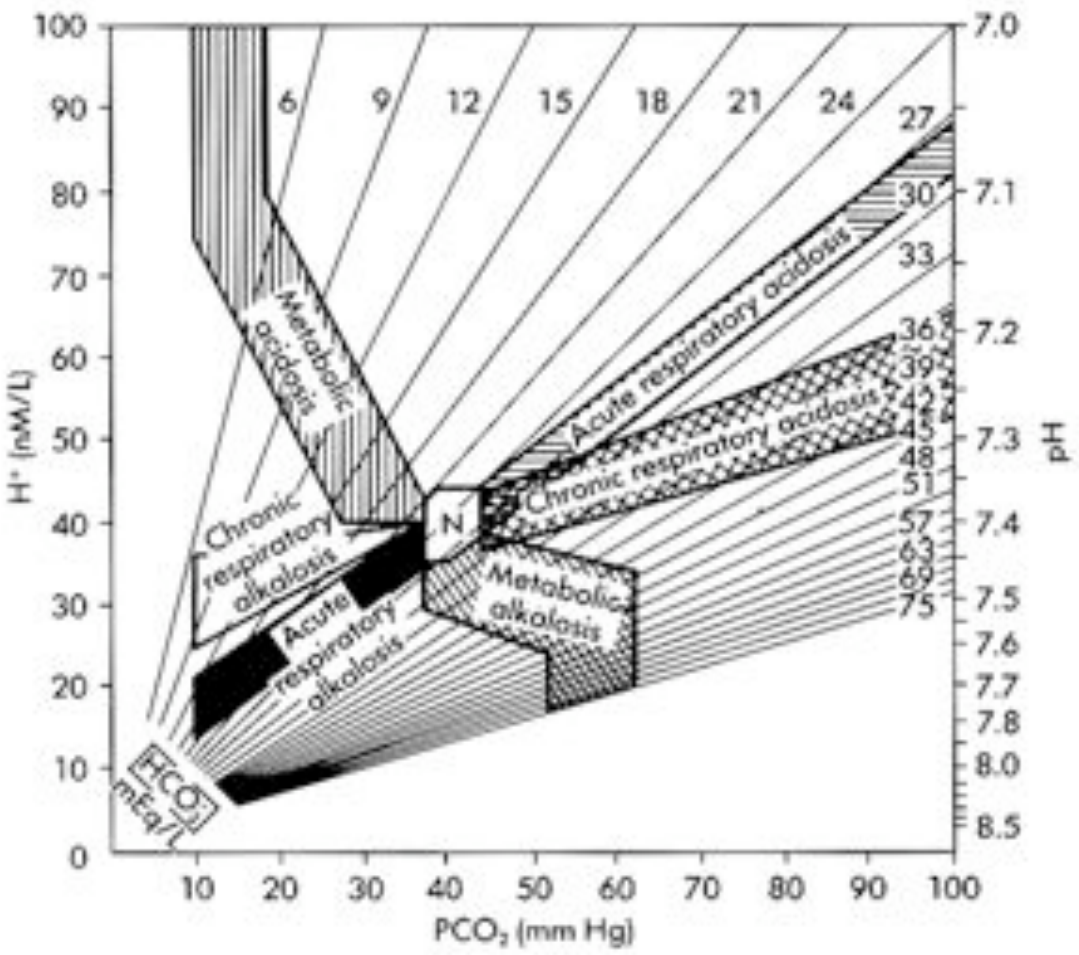
On the iPhone and iPod Touch there is a free program called ABG which will do this for you.

For windows based Pocket PCs I have not found a good computer program. You can purchase StyleTap (http://styletap.com) which allows you to run any Palm application on your windows PPC. If you use a Windows PPC the only equivalent program I am aware of is Acid-Base and Blood Gas Interpreter 1.1 which costs $29.99.

Medical applications available for the iPhone and iTouch. Epocrates Rx is a free medication reference, Mediquations is an inexpensive medical calculator ($4.99) with 91 medical equations. ABG is a free ABG interpreter. Medical Calc is free medical calculator which has the key formulas but is not as polished as Mediquations.

Alternatively one can use an Acid-Base nomogram which are accurate and easy to use. Just draw a line connecting the pH and pCO2 or connect the pCO2 and the bicarbonate (the diagonal lines).

Unfortunately neither computers nor nomograms are available on the boards. For this reason you need to be able to fully interpret an ABG on your own.



Looking for second primary acid base disturbances the old fashioned way

As discussed earlier, compensation occurs in every acid-base disturbance. In the absence of a second primary-disorder the degree of compensation can be determined solely by the severity of the primary disturbance (and by the duration in the case of metabolic compensation).

We use the predictability of compensation to determine if additional primary disorders are present. If the degree of compensation falls in the predicted range then there is no additional acid-base disturbance.

Each primary acid-base disturbance has its own equation to calculate the predicted degree of compensation. See the table below.

Disorder	Primary disturbance / Compensation	How to predict compensation
Metabolic acidosis	*decrease in bicarbonate* *decrease in carbon dioxide*	*$CO_2 = 1.5 \times HCO_3 + 8 \pm 2$* *Winter's formula*
Metabolic alkalosis	*increase in bicarbonate* *increase in carbon dioxide*	*CO_2 increases 0.7 for every 1 mmol increase in HCO_3*
Respiratory acidosis	*increase in carbon dioxide* *increase in bicarbonate*	**Acute:** *HCO_3 increases 1 for every 10 mmHg of CO_2* **Chronic:** *HCO_3 increases 3 for every 10 mmHg of CO_2*
Respiratory alkalosis	*decrease in carbon dioxide* *decrease in bicarbonate*	**Acute:** *HCO_3 decreases 2 for every 10 mmHg of CO_2* **Chronic:** *HCO_3 decreases 4 for every 10 mmHg of CO_2*

If the prediction equation explains the compensation then you have a simple acid-base disorder. If the prediction equation does not explain the compensation then a second primary disorder exists.

In metabolic disorders, if the actual pCO_2 is less than the predicted pCO_2 there is an additional respiratory alkalosis. If the actual pCO_2 is greater than the predicted pCO_2 there is an additional respiratory acidosis.

In respiratory disorders, if the actual HCO_3 is greater than the predicted HCO_3 there is an additional metabolic alkalosis. If the actual HCO_3 is less than the predicted

HCO_3 there is an additional metabolic alkalosis.

Using the prediction equations

Metabolic acidosis

Suppose a patient has a pH of 7.37, HCO_3 of 10 and a pCO_2 of 18.

- All three variables are lower than normal so the patient has a metabolic disturbance.
- The pH is decreased so this is metabolic acidosis.

To look for a second primary condition the first step is to use Winter's formula to see if the compensation is appropriate.

- With a bicarbonate of 10, Winter's formula predicts a pCO_2 of 23±2.
- The actual pCO_2 is 18, below the predicted pCO_2 so this patient has an additional primary respiratory alkalosis.
- If the actual pCO_2 was 24, then the patient would have physiologically compensated metabolic acidosis without a second primary respiratory disorder.
- If the actual pCO_2 was 28 then the patient would have a pCO_2 that was higher than predicted or an additional primary respiratory acidosis.

Metabolic alkalosis

Suppose a patient has a pH of 7.50, HCO_3 of 36 and pCO_2 of 48.

- All three variables are higher than normal so the patient has a metabolic disturbance.
- The pH is increased so this is metabolic alkalosis.

To look for a second primary condition first determine what the expected compensation should be. In metabolic alkalosis the pCO_2 rises 0.7 for every 1 mmol/L increase in HCO_3.

- An HCO_3 of 36 is an increase of 12 from normal. This should be compensated by an increase in pCO_2 of 8.
- The actual pCO_2 is 48, so this patient has an isolated metabolic alkalosis with appropriate respiratory compensation.
- If the pCO_2 was 58, the patient would have an additional respiratory _____.
- If the pCO_2 was 28, the patient would have an additional primary respiratory _____.

Respiratory acidosis

Suppose a patient has a pH of 7.35, HCO_3 of 30 and a pCO_2 of 56.

- The pH is decreased and both the HCO_3 and pCO_2 are elevated. Since the variables move in discordant direction it is a respiratory disturbance.
- The pH is decreased so this is respiratory acidosis.

To look for a second primary condition the first step is to determine the expected bicarbonate.

- The pCO_2 is 16 above normal which corresponds to an expected increase in HCO_3 of 2 in acute respiratory acidosis and 5 in chronic respiratory acidosis.
- So the expected bicarbonate is 26 if the respiratory acidosis is acute and 29 if it is chronic. The actual HCO_3 is 30 so there is an additional metabolic alkalosis if the patient has acute disease and a pure res-

piratory acidosis if the condition is chronic.

It is important to understand that the compensation equation can not tell you if the patient has acute or chronic disease. The physician must determine that.

Respiratory alkalosis

Suppose a patient has a pH of 7.56, HCO_3 of 23 and a pCO_2 of 22.

- The pH is increased and the HCO_3 and pCO_2 are both decreased. Since the variables move in discordant direction it is a respiratory disturbance.
- The pH is increased so this is respiratory alkalosis.

To look for a second primary condition the first step is to determine the expected bicarbonate.

- The pCO_2 is 18 below normal which corresponds to an expected decrease in HCO_3 of 4 in acute respiratory alkalosis and 8 in chronic respiratory alkalosis.
- So the expected bicarbonate is 20 if the respiratory acidosis is acute and 16 if it is chronic. The actual HCO_3 is 23 so this is a respiratory alkalosis with metabolic alkalosis regardless if it is acute or chronic.

	Respiratory acidosis	**Respiratory alkalosis**
Acute	***10:1***	***10:2***
Chronic	***10:3***	***10:4***
	For every rise of 10 in the pCO2 the HCO3 will rise by 1 or 3	***For every fall of 10 in pCO2 the HCO3 will fall by 2 or 4.***

Brittany has been out partying and wakes up vomiting. After six hours she is still vomiting and calls her personal Concierge Physician who gets the following ABG:

7.71 / 33 / 94 with an HCO_3 of 40 on the electrolyte panel.

John Daley presents to the ED stuporous. His catty says he has been taking nips from a little bottle all day. His labs reveal the following:

7.22 / 17 / 112

147	104	38
4.2	7	1.8

Hunter Thompson is dragged in to your office by his attorney. Mr. Thompson is incomprehensible but does not appear toxic. An ABG and lytes are drawn:

7.28 / 30 / 88

130	112	16
2.8	14	0.8

John Wayne is admitted to a surgery center for a colonoscopy. During the procedure the oxygen saturation monitor malfunctions so the gastroenterologist gets an ABG to confirm good oxygenation.

7.32 / 60 / 145 / 31

The anion gap

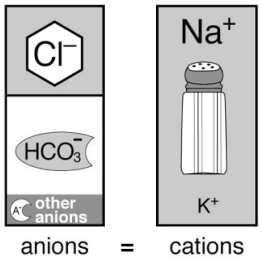
In respiratory acidosis the acid is known, by definition its carbon dioxide. In metabolic acidosis the acid (anion) can be anything and what it is can have profound implications for your patient.

Metabolic acidosis is categorized by the type of acid which is consuming the bicarbonate. The acid has two components a proton, which reacts with bicarbonate and an anion which accumulates in the body. The identity of the anion is how we name the different metabolic acidosis.

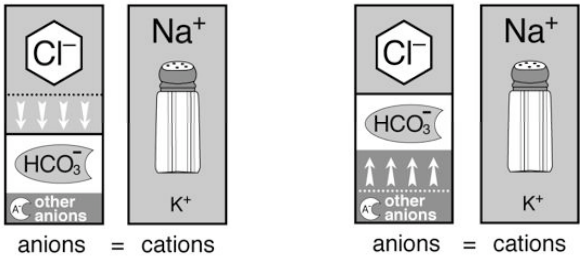
In all of clinical medicine there are only two types of anions:

Its either chloride
or
Its not chloride

The anion-gap is a construct which allows one to rapidly determine if the excess anion is chloride or not. The total number of anions in the blood must equal the total number of cations (otherwise touching blood would give you a shock).



In metabolic acidosis bicarbonate (an anion) is decreased, so to keep the anions in balance with the unchanged cations another anion must fill the void. This is either chloride as seen on the left or another anion as seen on the right.



The anion gap is a way quantify this relationship. Since the bicarbonate, sodium and chloride are all measured on routine electrolytes we can create an equation:

$$Cl^- + HCO_3 + \text{Other anions} = Na^+ + \text{Other cations}$$

Then rearrange it to solve for the *other ions:*

$$\text{Other anions} - \text{Other cations} = Na^+ - (Cl^- + HCO_3)$$

The *other anions* minus the *other cations* is called the anion gap.

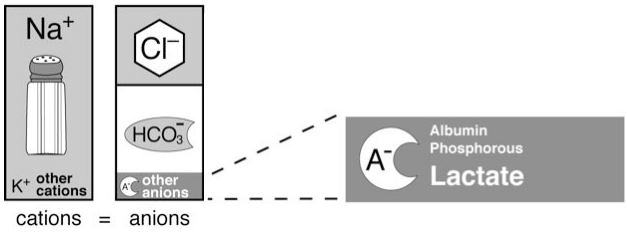
$$\text{Anion gap} = Na^+ - (Cl^- + HCO_3)$$

On average the anion gap is 6±3 with the upper limit of normal being 12. With metabolic acidosis, the bicarbonate falls and either the chloride rises to compensate or the anion gap will increase. If the anion gap is over twelve then the increase in other anions is causing an anion gap metabolic acidosis.

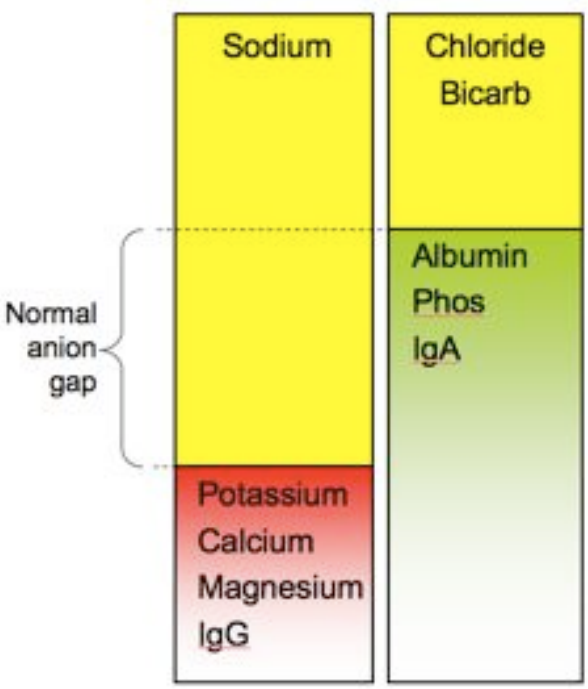
Calculate each individuals maximum normal anion gap

The other upper limit of normal for the anion gap, 12, is just an average. In some patients it may be lower. This is due to these patient's physiologic *other anions* (as opposed to the pathologic other anions from exogenous acids). These physiologic *other anions* include albumin and phosphorous. If these are abnormally low then the upper limit for a normal anion gap should be decreased. To calculate an individual's maximum normal anion gap use this equation:

Max anion gap = (Albumin x 2.5) + (Phos x 0.5)



If the albumin and/or phosphorous are low a lactic acidosis can hide in a normal anion gap. Calculate an individual maximum anion gap to avoid this.



An abnormally low anion gap

Sometimes you will find a patient with a low an abnormally low anion gap. Though not related to an acid-base disturbance it could signal disease. Causes of a low anion gap include:

- Increased chloride
  - Hypertriglyceridemia
  - Bromide
  - Iodide
- Decreased "Unmeasured anions"
  - Albumin
  - Phosphorous
- Increased "Unmeasured cations"
  - Hyperkalemia
  - Hypercalcemia
  - Hypermagnesemia
  - Lithium
  - Increased cationic paraproteins
  - IgG

Anion gap metabolic acidosis (AGMA)

The classic nemonic MUD PILES is outdated. The new nemonic is GOLD MARK. Know it.

G Glycols: ethylene glycol one of the four toxic alcohols (ethylene glycol, methanol, ethanol and isopropyl alcohol), of which, only two cause AGMA

O Oxoproline: Pyroglutamic Acid a newly recognized cause of high anion gap (30s) metabolic acidosis. It is associated with acetaminophen, hypotension and infection.

L L-lactic acidosis. Standerd run of the mill lactic acidosis. Associated with hypoperfusion (Type A) and toxin-induced impairment of cellular metabolism (metformin, malignancy, HIV nucleoside reverse transcriptase inhibitors, cyanide toxicity (Type B). The anion gap is insensitive for lactic acidosis with a sensitivity of only 58.2%.

D D-Lactic acidosis: Bacteria metabolize glucose and carbohydrate to D-lactic acid, which is then systemically absorbed. Lactate dehydrogenase only metabolizes L-lactate. The anion gap is usually small and transient because D-lactate is rapidly cleared by the kidneys. Treatment consists of fluid resuscitation, restriction of simple sugars, and the judicious use of antibiotics (such as metronidazole). The latter requires some caution, because antibiotics can precipitate the syndrome by permitting overgrowth of lactobacilli.

M Methanol

A Aspirin. The anion is actually lactate in ASA toxicity.

R renal failure

K Ketoacidosis: DKA, starvation, hypoglycemia

5-oxoproline (pyroglutamic acid)

The gamma-glutamyl cycle produces glutathione, an antioxidant substance that is involved in many important biologic functions, including inactivation of free radicals, detoxification of many compounds, and amino acid membrane transport (Figure 1).

Glutathione synthetase (GS) deficiency and 5-oxoprolinase (5-OPase) deficiency are two rare inherited enzyme defects that affect the gamma-glutamyl cycle and result in massive urinary excretion of 5-oxoproline (pyroglutamic acid). Patients with GS deficiency develop:

- Severe metabolic acidosis
- Hemolytic anemia
- Central nervous system dysfunction

Heterozygous patients do not usually develop metabolic acidosis or severe 5-oxoprolinuria. Moderately increased urine excretion of 5-oxoproline also has been described in patients with propionic acidemia.

Acquired 5-oxoprolinuria has been reported in infants who were fed the low-lactose preparation Nutramigen and in patients who were taking acetaminophen; the anticonvulsant vigabatrin; or several antibiotics, including flucloxacillin and netilmicin.

Increasingly people are recognizing acquired 5-oxoprolinuria as a cause of high anion gap metabolic acidosis.

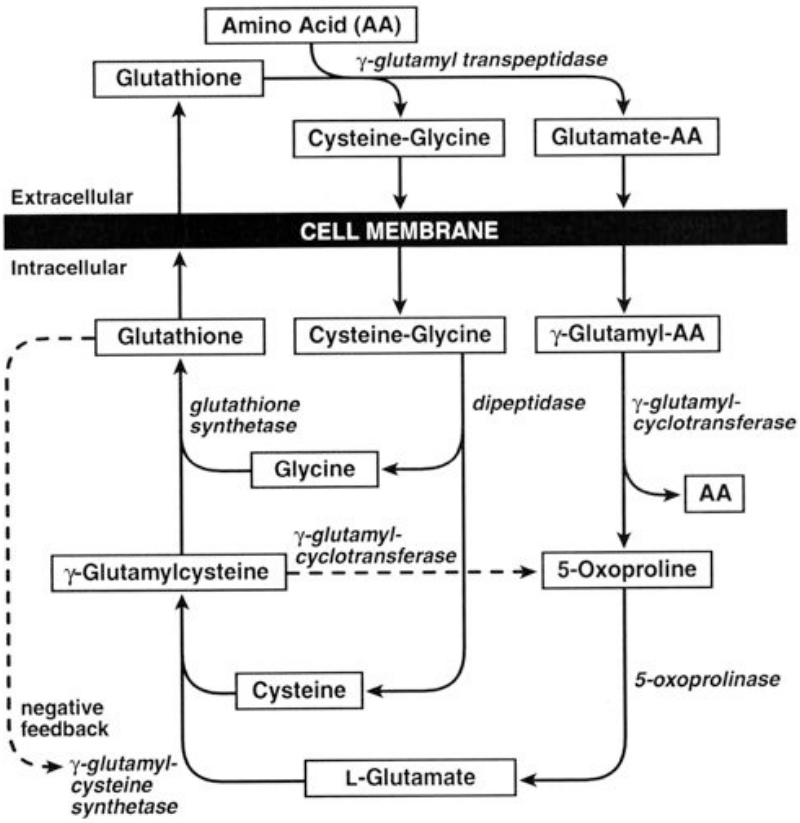


Figure 1

Table 1. Patient demographics and clinical characteristics of 20 patients with 5-oxoproline–induced high anion gap metabolic acidosis[a]

Patient	Reference	Age (yr)	Gender	Nutritional Status	Infection	Hypo-tension	Nausea/ Vomiting
1	Creer *et al.* (7)	52	F	Alb low, s/p Billroth II	None	+	None
2	Pitt *et al.* (8)	34	F	Vegetarian	Post mortem lung culture *S. Pneumonia*	−	+
3	Pitt and Hauser (9)	33	F	Pregnant	Blood culture *S. Pneumonia*	−	−
4	Pitt and Hauser (9)	54	F	Alcohol abuse	UTI	−	+
5	Pitt and Hauser (9)	60	F	Subtotal gastrectomy	None	−	+
6	Pitt and Hauser (9)	57	F	Multiple abdominal operations	None	−	+
7	Pitt and Hauser (9)	17	F	Spina bifida	Infected V-P shunt	+	−
8	Pitt and Hauser (9)	73	F		None	+	−
9	Pitt and Hauser (9)	84			SBE	+	−
10	Pitt and Hauser (9)	57		Alcohol abuse	None	−	−
11	Dempsey *et al.* (10)	80	F	Chronic infection	Septic arthritis, bilateral psoas abscess	+	−
12	Dempsey *et al.* (10)	60	F	Gastrectomy	None	−	
13	Dempsey *et al.* (10)	64	F	Lymphoma	None	−	
14	Dempsey *et al.* (10)	54	F	Alcohol abuse	None	+	−
15	Humphreys *et al.* (11)	41			None	−	−
16	Yale and Mazza (12)	44	F		None	−	−
17	Tailor *et al.* (13)	40			None	+	+
18	Foot *et al.* (14)	57	F	Kidney transplant, sepsis	Yes	+	+
19	Current report	36	F	Metastatic cancer	None	−	−
20	Current repoet	46	F	Intractable nausea	None	+	+
21	Current report	74	F	Alcohol abuse	None	+	+
22	Current report	55	F	Low albumin, poor oral intake	None	−	+

Table 2. Biochemical data of 20 patients with 5-oxoproline–induced high anion gap metabolic acidosis and significant acetaminophen exposure[a]

Patient	pH	Anion Gap	Lactic Acid (mmol/L)	Alkaline Phosphatase	GGT	Renal Insufficiency (Cr)	Urine 5-Oxoproline (mmol/mmol Cr)[b]	Plasma 5-Oxoproline (mmol/L)[c]	Acetaminophen Exposure
1 (7)	7.17	27	2.2	158/344	344	(2.1)	15	12.6	1 mo
2 (8)	7.17	N/A	N/A	N/A	N/A	N/A	13	16	+
3 (9)	7.12	33	N/A	520	N/A	N/A	17	N/A	2 wk
4 (9)	7.23	26	N/A	227	732	N/A	13.8	6.7	3 d
5 (9)	7.14	39	N/A	240	692	N/A	11	6.6	Acute
6 (9)	7.16	31	N/A	147	197	N/A	10	6.6	1 wk
7 (9)	7.38	31	N/A	N/A	304	+	20.4	N/A	Approximately 22 d
8 (9)	7.31	31	N/A	126	N/A	N/A	22	16	Long history 4 g/d
9 (9)	7.15	21	N/A	158	137	N/A	23.6	11.3	+
10 (9)	7.09	37	N/A	218	254	N/A	5.7	2.3	1 wk
11 (10)	7.27	35	0.5	109	27	(1.5)	Elevated	Elevated	+
12 (10)	7.14	38	1.6	240	692	(1.1)[d]	13.7	6.6	+
13 (10)	6.80	33	1.0	N/A	N/A	(2.6)	4.0	8.0	+
14 (10)	7.26	22	1.1	N/A	N/A	(2.7)	13.8	6.7	+
15 (11)	N/A	29	Normal	N/A	N/A	(1.5)	Elevated	N/A	20.8 g/10 d
16 (12)	N/A	25	0.9	N/A	N/A	N/A	0.55	N/A	+
17 (13)[e]	7.24 to 7.32	20 to 36	1.5 to 5.2	N/A	N/A	1.2 to 2.3	8.9 to 20.7	N/A	+/+/+
18 (14)	6.99	31	1.6	240	158	3.4	(370 mm/L)	N/A	+
19	N/A	47	N/A	N/A	N/A	(5.9)	7	N/A	1 mo +
20	6.88	33	N/A	N/A	N/A	(2.0)	N/A	6.4	+
21	7.16	24	2.5	138	N/A	(1.8)	1	2.8	+
22	7.44	35	4.3	223	N/A	(2.2)	24.7	10.5	2.7 g/d

[a]Cr, creatinine; GGT, γ-glutamyl transferase; N/A, not applicable.
[b]Reference range <0.070 mmol/mmol Cr.
[c]Reference range <0.1 mmol/L.
[d]History of chronic renal insufficiency.
[e]Six sequential admissions, three with documented high urine oxoproline levels.

Osmolar Gap

In patients with metabolic acidosis and a large anion gap, consideration should be given to ethylene glycol and methanol toxicity. Laboratory confirmation may take 24 hours. The osmolar gap allows one to infer the presence of these low molecular weight toxins.

If a patient has ingested ethylene glycol or methanol, treatment must be initiated rapidly. Usually therapy is begun prior to confirming the diagnosis with a specific assay for the alcohol. One of the keys to building the clinical suspicion is demonstrating an osmolar gap.

The osmolar gap demonstrates an increase in the serum osmolality that can not be explained by the usual suspects: electrolytes, glucose, urea and ethanol. Because the molecular weight of methanol and ethylene glycol are low, a few grams equals many osmoles and will increase the measured osmolality without affecting the calculated osmolality. This provides the gap.

If the calculated osmolality is significantly less than the measured osmolality you have an osmolar gap. Elevated osmolar gap is found with:

- Ethylene glycol
- Methanol
- Isopropyl alcohol
- Ketoacidosis
- Lactic acidosis
- Mannitol infusion
- Hypertriglyceridemia

Calculated osmolality:

$2 \times Na + glucose/18 + BUN/2.3 + EtOH/46$

Problems: figure out the anion gap, calculated osmolality, and osmolar gap in the following patients

1. 148 | 111 | 10 / 4.8 | 12 | 0.8 — Ethanol: 0 Glucose: 40 Osmolality: 337 — Anion gap: Calculated Osm: Osmolar gap:

2. 146 | 105 | 14 / 4.8 | 18 | 0.8 — Ethanol: 0 Glucose: 80 Osmolality: 311 — Anion gap: Calculated Osm: Osmolar gap:

3. 138 | 112 | 28 / 4.8 | 14 | 1.8 — Ethanol: 0 Glucose: 120 Osmolality: 302 — Anion gap: Calculated Osm: Osmolar gap:

4. 146 | 106 | 196 / 4.8 | 12 | 8.8 — Ethanol: 0 Glucose: 335 Osmolality: 400 — Anion gap: Calculated Osm: Osmolar gap:

5. 141 | 95 | 85 / 4.8 | 8 | 2.4 — Ethanol: 0 Glucose: 165 Osmolality: 338 — Anion gap: Calculated Osm: Osmolar gap:

6. 135 | 105 | 45 / 4.8 | 7 | 2.2 — Ethanol: 48 Glucose: 223 Osmolality: 309 — Anion gap: Calculated Osm: Osmolar gap:

7. 138 | 112 | 62 / 4.8 | 10 | 2.2 — Ethanol: 86 Glucose: 40 Osmolality: 333 — Anion gap: Calculated Osm: Osmolar gap:

8. 146 | 114 | 127 / 4.8 | 14 | 6.3 — Ethanol: 112 Glucose: 48 Osmolality: 380 — Anion gap: Calculated Osm: Osmolar gap:

9. 130 | 94 | 8 / 4.8 | 6 | 0.6 — Ethanol: 0 Glucose: 90 Osmolality: 313 — Anion gap: Calculated Osm: Osmolar gap:

10. 148 | 120 | 18 / 4.8 | 15 | 1.0 — Ethanol: 0 Glucose: 656 Osmolality: 344 — Anion gap: Calculated Osm: Osmolar gap:

Additional metabolic acid-base conditions

There is a trick for patients with anion-gap metabolic acidosis that allows physicians to go back in time prior to developing the anion gap and see what the bicarbonate was at that time. From that you can deduce if the patient had either a pre-existing metabolic alkalosis or pre-existing non-anion gap metabolic acidosis.

Earlier we looked at compensation to determine if a patient has a second primary acid-base disorder. Now we will look at the anion gap to determine if the patient has an additional primary acid-base disorder.

In order to use the anion gap to look for additional acid-base disorders we assume that for every increase in the anion gap over 12 the serum bicarbonate falls by one. We can establish a formula to represent this:

$$\Delta HCO3 = \Delta \text{Anion Gap}$$

$$HCO3_{before} - HCO3_{now} = AG_{current} - AG_{normal}$$

$$HCO3_{before} = HCO3_{now} + (AG_{current} - 12)$$

By using the last formula we can actually infer what the bicarbonate was prior to developing the anion gap. If this bicarbonate is low we call this a pre-existing non-anion gap metabolic acidosis. If the bicarbonate is elevated then the patient had pre-existing metabolic alkalosis.

Questions

A patient presents to the ER appearing toxic, hypotensive with these initial labs:

7.28 / 18 / 88 glucose: 875

128	106	16
5.6	8	1.8

What is the primary acid-base disturbance:

1.

Is there a second primary acid-base disturbance, what is it?

2.

What is the anion gap:

3.

Calculate the bicarbonate before:

4.

A patient with fever and diarrhea presents to the ER, hypotensive with these initial labs:

7.28 / 30 / 88 glucose: 128

142	102	16
3.2	18	1.8

What is the primary acid-base disturbance:

1.

Is there a second primary acid-base disturbance, what is it?

2.

What is the anion gap:

3.

Calculate the bicarbonate before:

4.

Calculate the bicarb prior to the AGMA:

1. 130 | 110 — 4.8 | 18 — Anion Gap: — Bicarb before:

2. 134 | 104 — 4.8 | 12 — Anion Gap: — Bicarb before:

3. 138 | 114 — 4.8 | 6 — Anion Gap: — Bicarb before:

4. 146 | 114 — 4.8 | 16 — Anion Gap: — Bicarb before:

5. 141 | 105 — 4.8 | 18 — Anion Gap: — Bicarb before:

6. 135 | 94 — 4.8 | 19 — Anion Gap: — Bicarb before:

7. 138 | 101 — 4.8 | 14 — Anion Gap: — Bicarb before:

8. 146 | 114 — 4.8 | 16 — Anion Gap: — Bicarb before:

9. 130 | 96 — 4.8 | 6 — Anion Gap: — Bicarb before:

10. 148 | 106 — 4.8 | 14 — Anion Gap: — Bicarb before:

Answers

Determine the primary acid-base disturbance:

1. Metabolic Acidosis
2. Respiratory acidosis
3. Metabolic alkalosis
4. Metabolic Acidosis
5. Respiratory acidosis
6. Respiratory acidosis
7. Metabolic Acidosis
8. Respiratory acidosis
9. Metabolic alkalosis
10. Metabolic alkalosis
11. Respiratory alkalosis

Multiple Acid-base disturbances. Case vignettes

Ms. Spears: both a primary metabolic alkalosis and respiratory alkalosis

Mr. Daley: isolated metabolic acidosis

Mr. Thompson: isolated metabolic acidosis

Mr. Wayne: isolatedchronic respiratory acidosis or an acute respiratory acidosis and metabolic alkalosis

Problems: figure out the anion gap, calculated osmolality, and osmolar gap in the following patients

1. Anion gap: 25 Calc Osm: 302 gap: 35
2. Anion gap: 23 Calc Osm: 301 gap: 10
3. Anion gap: 12 Calc Osm: 293 gap: 9
4. Anion gap: 28 Calc Osm: 381 gap: 19
5. Anion gap: 38 Calc Osm: 322 gap: 16
6. Anion gap: 23 Calc Osm: 309 gap: 0
7. Anion gap: 16 Calc Osm: 322 gap: 11
8. Anion gap: 18 Calc Osm: 364 gap: 16
9. Anion gap: 30 Calc Osm: 268 gap: 45
10. Anion gap: 13 Calc Osm: 339 gap: 5

Gap-Gap case vignettes:

1. metabolic acidosis

2. None

3. 14

4. 10

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1. metabolic acidosis

2. respiratory alkalosis

3. 22

4. 28

Calculate the bicarb prior to the AGMA:

1.Anion Gap: 20 Bicarb before: 26

2.Anion Gap: 18 Bicarb before: 18

3.Anion Gap: 18 Bicarb before: 12

4.Anion Gap: 16 Bicarb before: 20

5.Anion Gap: 18 Bicarb before: 24

6.Anion Gap: 22 Bicarb before: 29

7.Anion Gap: 23 Bicarb before: 25

8.Anion Gap: 16 Bicarb before: 20

9.Anion Gap: 28 Bicarb before: 22

10.Anion Gap: 28 Bicarb before: 30