

The art of medicine consists of amusing the patient while nature cures the disease." *Voltaire* "Wherever the art of Medicine is loved, there is also a love of Humanity" *Hippocrates*

ikawalit Approach to Acid Base Disorders Author Dr Issa A kawalit

Copyright © 2013 International Renal Care Group All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means electronic, mechanical, photocopying, recording or otherwise, without the prior written permission of the author.

Published by IRCG- International Renal Care Group 1201 Orange St.600, Wilmington 19899, Delaware, USA www.ircg.us.com

1201 Orange St.600, Wilmington 19899, Delaware, USA

Dedication

I dedicate this book to my inspirational wife Lara who have always been there for me, and have never doubted my dreams, no matter how crazy they might be. Also to my wonderful Kids Afif , Noor and Jana, they are the reason I get up every day and push myself to do more and be better than the day before. To my mother Tamara and my father Afif they are my inspiration in everything I do and every choice I make.

IKawalit Approach

Acid-base balance has earned a reputation as a difficult subject to understand. This should not be the case. Presented in a logical fashion, with proper attention paid to the basic physiologic and chemical principles involved, acid-base balance should in fact be quite easy to master. Ikawalit approach attempts to "demystify" the subject, an understanding of which is a necessity for those who practice in the critical care setting.

The text is divided into three sections. Section I deals with the basic chemistry and physiology of acid-base balance. Clinical acid-base disturbances are discussed in Section II. Finally, case studies are provided in Section III to give you practice dealing with some of the topics that were discussed.

This text focuses on the "basic science" of acid-base homeostasis, the chemistry and physiology involved in maintaining a stable plasma hydrogen ion concentration. As such, it cannot, and indeed should not, serve as a definitive guide for treatment of clinical acid-base and electrolyte disturbances. Many excellent texts are available for this purpose. It is hoped, however, that an understanding of the material presented here will provide those who care for patients suffering acid-base disturbances with a clearer focus on the subject, resulting in more effective treatment.



Content

(Section I) Acid Base Physiology	5	
Daily Acid Load	5	
Carbonic acids or volatile acid (respiratory acid)	5	
Noncarbonic acids or non-volatile (metabolic acid)	6	
Acid Buffering	7	
Renal Acid Excretion	8	
Hydrogen Secretion	8	
Bicarbonate Reabsorption	8	
Urinary Buffering	10	
Titratable Acidity	10	
Ammonium Excretion	11	
Ammoniagenesis	11	
The Role of Ammonium Excretion	12	
Medullary Recycling and Ammonium Trapping	13	
Pulmonary Acid Excretion	14	
(Section II) Acid Base Abnormalities	14	
Introduction acid base disorders	14	
Compensatory Responses	15	
Compensatory Responses: Metabolic Acidosis	15	
Compensatory Responses: Respiratory Acidosis	15	
Compensatory Responses: Metabolic Alkalosis	17	
Compensatory Responses: Respiratory Alkalosis	17	
	10	
Anion Gan	19	
Alloit Gap	19	
	20	
Onnelar Con	22	
Ostitulal Gap	22	
Stepwise approach to interpreting the arterial blood gas.		
Eliology of Acid Base Disturbances	20	
	20	
✓ Ketoacidosis		
✓ Diabetic Ketoacidosis		
✓ Alcoholic Ketoacidosis		
✓ Starvation/ Fasting		
✓ Renal Tubular Acidosis		
✓ Uremic Acidosis		
Metabolic Alkalosis	40	
✓ GI Hydrogen Loss and Reduction in ECV		
✓ Contraction Alkalosis and Hypokalemia		
✓ Hypokalemia		
✓ Mineralocorticoid excess		
Pospiratory Acidosis	15	
Respiratory Alkalosis	+J //7	
Mixed metabolic disorders		
Section III) Practice Cases	4J 51	
Deferences	57	
	57	

IKawalit Approach

To Acid Base Disorders

Acid-base balance has earned a reputation as a difficult subject to understand. This should not be the case. Presented in a logical fashion, with proper attention paid to the basic physiologic and chemical principles involved, acid-base balance should in fact be quite easy to master. Ikawalit approach attempts to "demystify" the subject, an understanding of which is a necessity for those who practice in the critical care setting.

The text is divided into three sections. Section I deals with the basic chemistry and physiology of acid-base balance. Clinical acid-base disturbances are discussed in Section II. Finally, case studies are provided in Section III to give you practice dealing with some of the topics that were discussed.

This text focuses on the "basic science" of acid-base homeostasis, the chemistry and physiology involved in maintaining a stable plasma hydrogen ion concentration. As such, it cannot, and indeed should not, serve as a definitive guide for treatment of clinical acid-base and electrolyte disturbances. Many excellent texts are available for this purpose. It is hoped, however, that an understanding of the material presented here will provide those who care for patients suffering acid-base disturbances with a clearer focus on the subject, resulting in more effective treatment.

I. Acid Base Physiology

Each day there is *always* a production of acid by the body's metabolic processes and to maintain balance, these acids need to be excreted or metabolised. The various acids produced by the body are classified as respiratory (or volatile) acids and as metabolic (or fixed) acids. The body normally can respond very effectively to perturbations in acid or base production.

Daily Acid Load

The daily acid load is constituted by one's diet, and is comprised primarily of foods containing acid, and the production of acid as a result of metabolism. The intake of alkali containing foods and the production of alkali as a result of metabolism offsets the daily acid load but the net effect is daily addition of acid to the body that must be buffered and excreted to maintain acid base balance.

There are 2 types of acids that can potentially contribute to the daily acid load; carbonic or volatile acid (H_2CO_3) and noncarbonic or nonvolatile acids.

Carbonic acids or volatile acid (respiratory acid)

The acid is more correctly carbonic acid (H_2CO_3) but the term 'respiratory acid' is usually used to mean carbon dioxide. But CO_2 itself is not an acid in the Bronsted-Lowry system as it does not contain a hydrogen so cannot be a proton donor.

However CO_2 can instead be thought of as representing a potential to create an equivalent amount of carbonic acid. Carbon dioxide is the end-product of complete oxidation of carbohydrates and fatty acids. It is called a volatile acid meaning in this context it can be excreted via the lungs. Of necessity, considering the amounts involved there must be an efficient system to rapidly excrete CO_2 .

The amount of CO_2 produced each day is huge compared to the amount of production of fixed acids. Basal CO_2 production is typically quoted at 12,000 to 13,000 mmols/day.

Basal Carbon Dioxide Production

Consider a resting adult with an oxygen consumption of 250 mls/min and a CO_2 production of 200 mls/min Daily CO_2 production = 0.2 x 60 x 24 litres/day divided by 22.4 litres/mole = 12,857 mmoles/day.

Increased levels of activity will increase oxygen consumption and carbon dioxide production so that actual daily CO_2 production is usually significantly more than the oft-quoted basal level. [Different texts quote different figures usually in the range of 12,000 to 24,000 mmoles/day but the actual figure simply depends on the level of metabolic activity and whether you quote basal or typical figures.]

Daily CO₂ production can also be calculated from the daily metabolic water production. The complete oxidation of glucose produces equal amounts of CO₂ and H₂0. The complete oxidation of fat produces approximately equal amounts of CO₂ and H₂O also. These two processes account for all the body's CO₂ production. Typically, this metabolic water is about 400 mls per day which is 22.2 moles (ie 400/18) of water. The daily typical CO₂ production must also be about 22,200 mmoles.

Before elimination by the lungs, most of the CO_2 is taken up by red blood cells, reacting with H_2O to form carbonic acid as shown below:

$CO_2 + H_2O \leftrightarrow H_2CO_3(CA) \leftrightarrow H^+ + HCO_3^-$

where (CA) is the very important enzyme carbonic anhydrase.

Intracellularly, carbonic acid dissociates to form hydrogen and bicarbonate ions. The latter is pumped out of the cell into plasma. At the alveoli, bicarbonate ions re-enter the RBC and the above equation is driven to the left, re-producing CO_2 which is then eliminated by the lung.

Under normal circumstances, CO_2 produced via metabolism is primarily eliminated via alveoli ventilation. Any increases in CO_2 production is matched by an increase in alveolar ventilation leading to a stable PCO_2 level.

Nonvolatile Acids	Volatile Acids (H ₂ CO ₃)
Metabolism of amino acids, producing HCL and H ₂ SO ₄	Metabolism of fats and carbohydrates producing CO ₂
Intake of acid containing foods-sulphates, phosphates	
Daily loss of alkali in feces (minimal unless diarrhea)	

Noncarbonic acids or non-volatile (metabolic acid)

This term covers all the acids the body produces which are non-volatile. Because they are not excreted by the lungs they are said to be 'fixed' in the body and hence the alternative term fixed acids. All acids other then H_2CO_3 are fixed acids.

These acids are usually referred to by their anion (eg lactate, phosphate, sulphate, acetoacetate or b-hydroxybutyrate). This seems strange at first because the anion is, after all, the *base* and not itself the acid. This useage is acceptable in most circumstances because the dissociation of the acid must have produced one hydrogen ion for every anion so the amount of anions present accurately reflects the number of H^+ that must have been produced in the original dissociation.

Another potentially confusing aspect is that carbon dioxide is produced as an endproduct of metabolism but is not a 'metabolic acid' according to the usual definition. This inconsistency causes some confusion: it is simplest to be aware of this and accept the established convention.

Net production of fixed acids is about 1 to 1.5 mmoles of H^+ per kilogram per day: about 70 to 100 mmoles of H^+ per day in an adult. This non-volatile acid load is excreted by the kidney. Fixed acids are produced due to incomplete metabolism of carbohydrates (eg lactate), fats (eg ketones) and protein (eg sulphate, phosphate).

A normal diet results in the generation of 50 -100 meq of H+ per day. Most of this comes from the metabolism of sulphur containing amino acids such as cysteine and methionine which yield sulphuric acid and from metabolism of lysine, arginine and histidine which yield hydrochloric acid.

The above total for net fixed acid production excludes the lactate produced by the body each day as the majority of the lactate produced is metabolised and is not excreted so there is no net lactate requiring excretion from the body.

The routes of excretion are the lungs (for CO_2) and the kidneys (for the fixed acids). Each molecule of CO_2 excreted via the lungs results from the reaction of one molecule of bicarbonate with one molecule of H⁺. The H⁺ remains in the body as H₂O.

Ingestion of alkali containing foods (e.g. citrate), and metabolism of amino acids such as aspartate and glutamate that lead to alkali production offset the daily acid load but the net effect is daily acid addition.

Acid Buffering

One of the major ways in which large changes in H+ concentration are prevented is by buffering. The body Buffers are weak acids or bases that are able to minimize changes in pH by taking up or releasing H⁺. Phosphate is an example of an effective buffer, as in the following reaction:

 $HPO_4^{2-} + (H^+) \leftrightarrow H_2 PO_4^{--}$

Upon addition of an H⁺ to extracellular fluids, the monohydrogen phosphate binds H⁺ to form dihydrogen phosphate, minimizing the change in pH. Similarly, when [H⁺] is decreased, the reaction is shifted to the left. Thus, buffers work as a first-line of defense to blunt the changes in pH that would otherwise result from the constant daily addition of acids and bases to body fluids.

Buffers are located in the extracellular fluid (ECF), intracellular fluid and bone.

Extracellular Buffers

The most important buffer in the ECF is HCO3- (bicarbonate) which combines with excess H+ ions to form carbonic acid.

Take for instance an acid load of H2SO4 produced via metabolism of methionine: H2SO4 + 2NaHCO3 \rightarrow NA2SO4 + 2H2CO3 \rightarrow 2CO2 + 2H2O + NA2SO4. Note in this buffering reaction that bicarbonate reacts with a strong acid to form a weaker acid(H2CO3) which then dissociates into CO2 and H2O. The CO2 produced here does not reform H2CO3 because it is then excreted by the lungs. Note that HCO3- is used up in this reaction. So that pH is not affected, the HCO3- used up in this process must be regenerated and the NA2SO4 must be excreted by the kidneys. The CO2/HCO3- buffer system is considered very effective because of the vast quantity of bicarbonate in the body and the ability to excrete the CO2 formed via ventilation.

Other less important buffers in the ECF are plasma proteins and inorganic phosphates.

Intracellular Buffers

The primary intracellular buffers are proteins, organic and inorganic phosphates and in the RBC, hemoglobin (HB-). Whereas buffering by plasma HCO3- occur almost immediately, approximately 2-4 hours is required for buffering by cell buffers due to slow cell entry.

Hemoglobin is a very important buffer in RBCs, particularly in the role of carbonic acid buffering. It should also be noted that transcellular uptake of hydrogen ions by cells result in the passage of Na+ and K+ ions out of cells to maintain electroneutrality. This process can substantially affect potassium balance.

Bone

An acid load, is associated with the uptake of excess H+ ions by bone which occurs in exchange for surface Na+ and K+ and by the dissolution of bone mineral, resulting in the release of buffer compounds, such as NaHCO3, CaHCO3, and CaHPO4.

Renal Acid Excretion

The process of renal acid excretion is complex. In order to conceptualize this process, lets consider the follow equation:

 $\text{HCI} + \text{NaHCO3} \iff \text{NaCI} + \text{H2CO3} \iff \text{CO2} + \text{H2O} + \text{NACI}.$

The above equation represents the process of buffering of the daily nonvolatile acid load. Buffering minimizes the effect that strong acids such as HCI would have on the pH. Nonetheless the pH will be affected if the bicarbonate lost in this process is not regenerated, because as we will learn; loss of bicarbonate from the ECF lowers the extracellular pH, leading to acidosis. One way to regenerate the lost bicarbonate would be for the kidney to reverse the above equation, and excrete HCI in the urine as free H+ ions. Unfortunately this would require a urine pH of 1.0, an impossible task since the minimum attainable urine pH is 4.0 to 4.5.

In order to maintain acid base balance, the kidney must accomplish two tasks:

1) Reabsorption of all filtered bicarbonate

2) Excrete the daily acid load

The kidney achieves these three tasks via the processes of hydrogen secretion, bicarbonate reabsorption and excretion of hydrogen ions with urinary buffers(titratable acids and ammonium).

Hydrogen Ion Secretion

The kidney is responsible for excreting the nonvolatile acid load, which is equivalent to about 50-100meq/L of hydrogen ions per day. Hydrogen ions are buffered in the blood and are not filtered by the kidney as free ions. Hydrogen ions are instead excreted in the urine via the process of hydrogen ion secretion. In the tubular fluid, the secreted hydrogen ions combine with urinary buffers to be

excreted as titratable acids and ammonium or combine with filtered bicarbonate leading to bicarbonate reabsorption.

Bicarbonate Reabsorption

- The kidney filters approximately 4320 meq/day of HCO3- (24 meq/L ×180L/day). Under normal circumstances, the kidney is able to completely reabsorb all the filtered bicarbonate. This is vitally important, since any loss of bicarbonate in the urine would disturb acid base balance.
- The process of bicarbonate reabsorption occur predominantly in the proximal tubule (about 90%). The rest occur in the thick ascending limb and in the collecting tubule. All involve hydrogen ion secretion as shown in the diagram below. To completely reabsorb bicarbonate, the kidney must secrete 4320 meq/day of hydrogen ions in addition to the amount required to exrete the daily acid load.



- The primary step in proximal hydrogen secretion is the secretion of H+ by the Na+ - H+ antiporter in the luminal membrane. Hydrogen ions are generated by the intracellular breakdown of H20 to OH- and H+.
- Hydrogen ions secreted combine with filtered HCO3- ions to form carbonic acid and then CO2 + H2O, which are then passively reabsorbed.
- Technically, HCO3- ions reabsorbed in this process are not the same as the ones filtered. Note that a new HCO3- ion is generated from the intracellular breakdown of H20 to OH- and H+ and subsequent reaction of OH- with CO2 to form HCO3-. This new bicarbonate then crosses the basolateral membrane via a Na+ - 3HCO3- cotransporter.
- The net effect is one mol of bicarbonate ion returned to systemic circulation for every H+ ion that is secreted and reabsorption of virtually all filtered bicarbonate.
- Similar processes occur in the thick ascending loop of Henle and intercalating cells of the collecting duct. In contrast to the proximal

tubule, hydrogen ion secretion in the collecting tubule is mediated by a H+ ATPase pump in the luminal membrane and a CI-HCO3- exchanger in the basolateral membrane as shown in the diagram above. The H+ ATPase pump is influenced by aldosterone, which stimulates increased H+ secretion. Hydrogen ion secretion in the collecting tubule is the process primarily responsible for acidification of the urine, particularly during states of acidosis. The urine pH may fall as low as 4.0.

 Proximal reabsorption of bicarbonate can be affected by many factors, in particular, potassium balance, volume status and renin/angiotensin levels. Therefore these factors can have very significant effects on acid base balance. Their specific effects will be discussed later.

Urinary Buffering

The role of urinary buffering serves two purposes; to a) excrete the daily acid load and b) regenerate bicarbonate lost during extracellular buffering. It is a process whereby seceted hydrogen ions are buffered in the urine by combining with weak acids (titratable acidity) or with NH3 (ammonia) to be excreted. It is a necessary process because the kidney cannot easily excrete free hydrogen ions.

Titratable Acidity

• The major titratable acid buffer is HPO₄²⁻. Other less important buffers are creatinine and uric acid. In DKA, ketoanions also serve as a source of titratable acids. *Below is a diagram outlining this process.*



• Excretion of titratable acids is dependent on the quantity of phosphate filtered and excreted by the kidneys, which is dependent on one's diet, and also PTH levels. As such, the excretion of titratable acids is not regulated by acid base balance and cannot be easily increased to excrete the daily acid load. **Ammonium production** can however be regulated to respond to acid base status, as will be discussed next.

Ammonium Excretion

With increased acid load, there is increased hydrogen ion secretion, causing the urine pH to fall below 5.5. At this point, virtually all the urinary phosphate exist as H2PO4- and further buffering cannot occur unless there is an increase in urinary phosphate excretion. As mentioned previously, phosphate excretion is mainly dependent on dietary phosphate intake and PTH levels and is not regulated in response to the need to maintain acid base balance. Without further urinary buffering, adequate acid excretion cannot take place. The major adaptation to an increased acid load is increased ammonium production and excretion. The ability to excrete H+ ions as ammonium adds an important degree of flexibility to renal acid base regulation, because the rate of NH4+ production and excretion can be regulated in response to the acid base requirements of the body. Also of importance is the role of ammonium production in the further generation of bicarbonate ions.

The process of ammonium excretion takes place in 3 steps.

- Ammonium Formation (ammoniagenesis) (proximal tubule)
- Ammonium Reabsorption (Medullary Recycling)(thick ascending loop)
- Ammonium Trapping (collecting tubule)

Ammoniagenesis

- The process of ammoniagenesis occurs within proximal tubular cells. Glutamine made in the liver, is received from peritubular capillaries and is metabolized into alpha-keto glutarate and NH4+, in a reaction that involves the enzyme glutaminase.
- The ammonium is secreted into the tubular lumen by substituting for H+ on the Na+ H+ exchanger. In the tubular fluid, NH4+ circulates partly in equilibrium with NH3.
- The alpha-ketoglutarate is metabolized further into two HCO3- ions, which then leave the cell and enter systemic circulation by crossing the basolateral membrane.

Please note that the generation of new HCO3- ions is probably the most important feature of this process.



Below is a diagram outlining Ammonium formation.

The Role of Ammonium Excretion

What happens next to ammonium is somewhat complex. So before continuing , let us re-examine the rational behind ammonium excretion.

Now remember; free hydrogen ions are not filtered by the kidney. Instead, they are secreted into the tublar fluid. Because free hydrogens cannot be excreted in the urine easily, there are excreted with weak acids such as H2PO4- which function as urinary buffers. Now in the presence of an increased acid load, the phospate ions are used up and the kidney then increases its production of ammonium .

Notice that ammonium, not ammonia is produced in the proximal tubule. Therefore you might ask yourself, how does ammonium production increase hydrogen excretion if it cannot bind to hydrogen ions secreted in the proximal tubular lumen?

The answer to this is somewhat controversial in the literature. Below is one school of thought that has gained popularity.

As was mentioned previously, new bicarbonate ions are produced during ammoniagenesis. The generation of new bicarbonate ions conceptually is akin to inceased hydrogen excretion. Therefore the real function of ammoniagenesis is not as a urinary buffer of hydrogen ions as is commonly inaccurately described.

The real function of ammoniagensis is to increase the generation of new bicarbonate ions. For simplicity, this rational will be the basis of the remaining discussion on ammonium excretion.

Ammonium before it is excreted is first re-absorbed in the thick ascending limb, circulated in the medullary interstitium and then pumped back in the collected tubule as ammonia. In the collecting tubule, ammonia then takes up hydrogen ions secreted into the lumen by intercalated cells, to form ammonium.

Now the second question you might ask is why so many steps leading to the same result?

In order for ammoniagenesis to be effective in the generation of new HCO3-, the NH4+ produced must be excreted in the urine.

If NH4+ were to enter the circulation, it would end up in the liver where metabolism would lead to the formation of urea as showed in the following equation:

NH4+ + 2 HCO3- => urea + CO2 + 3 H2O

Notice that the formation of urea consumes 2 molecules of bicarbonate. Therefore, in essence, the bicarbonate generated in the proximal tubule would be negated or cancelled out, and ammoniagenesis would not increase net acid excretion.

As mentioned previously, NH4+ secreted in the proximal tubule is in equilibrium with a small quantity of NH3. This NH3 is capable of diffusing out of the lumen into the peritubular capillaries. If this were allowed to continually happen, a large quantity of ammonium would be lost to the circulation and its metabolism in the liver would consume the HCO3- generated.

This effect is minimized by having an acidic urine ph which keeps NH4+ in its protonated form. However, the urine does not become maximally acidified until the collecting tubule where secretion of hydrogen ions by intercalated cells significantly reduce the urine pH. Therefore the kidney prevents loss of ammonium by reabsorbing NH4+ in the thick ascending limb and pumping it into the collecting duct where the urine pH is very low, facilitating ammonia in its protonated form. This process is enhanced during periods of acidosis when hydrogen secretion by the intercalated cells is significantly increased.

Medullary Recycling and Ammonium Trapping

After ammoniagenesis, ammonium is taken up into the medullary interstitium via a process called medullary recycling. It is then pumped back into the tubular fluid at the level of the collecting duct, where it undergoes what is called ammonium trapping after which it is excreted. *Below is an outline of this process.*



- 1. Ammonium is first reabsorbed at the level of the thick ascending limb by substituting for K+ on the Na+ -K+ -2Cl- carrier.
- 2. The less acidic tubular cell then causes NH4+ to dissociate into NH3 and H+.
- 3. The luminal membrane in the thick ascending limb is impermeable to NH3 and thus NH3 cannot diffuse back into the lumen. It instead diffuses out into the medullary interstitium into those compartments which have the lowest NH3 concentration, i.e. the S3 segment of the proximal tubule and the medullary interstitium of the collecting tubule.
- 4. At the S3 segment of the proximal tubule, NH3 re-enters the lumen where it is protonated back to NH4 and is again recycled back into the medullary interstitium via reabsorption at the thick ascending limb. This leads to a high concentration of NH3 in the medullary interstitium.
- 5. Because of the very low NH3 concentration in the collecting tubular fluid (as a result of removal in the loop of Henle), and a maximally acidic urine pH in the collecting duct that further reduces tubular NH3, there is a large gradient for NH3 secretion into the collecting tubular lumen.
- 6. In contrast to the thick ascending limb, the tubular lumen is permeable to NH3 but not to NH4. As a result, NH3 secretion into the collecting duct lumen leads to "ammonium trapping" as NH4+ formed from the very acidic urine is unable to diffuse back into the cell.
- 7. NH4 is then excreted in the urine, usually with a CI- anion.

Note that this process is primarily dependent on acidification of the urine in the collecting tubule as a result of hydrogen secretion by intercalated cells. In states of acidosis, where hydrogen secretion is significantly increased in the collecting tubule, this process is greatly enhanced. In states of alkalosis, the process is appropriately hindered as a result of the alkalemic urine

Pulmonary Acid Excretion

The main physiologic stimuli to respiration are an elevation in the PCO2 and a reduction in the PO2 (hypoxemia). The CO2 stimulus to ventilation occurs in the chemosensitive areas in the respiratory center in the brain stem, which responds to CO2 induced changes in the cerebral interstitial pH. This effect is important in removing the 15 mol of CO2 produced daily from metabolism of fats and carbohydrates, via alveolar ventilation. In acid base disorders, the initial rise or fall in alveolar ventilation is mediated primarily by the peripheral chemoreceptors in the carotid or aortic bodies, which immediately sense the change in pH. Changes in PCO2 are sensed via central chemo-receptors as CSF ph is altered. In general, PCO2 is regulated by alveolar ventilation. Hyperventilation (increase in alveolar ventilation) enhances CO2 excretion and lowers the PCO2 while hypoventilation (reduction in ventilation) reduces CO2 excretion and raises the PCO2.

II. Acid Base Abnormalities

Introduction acid base disorders

In order to approach acid base disorders, consider the following equations: 1) Henderson Hasselbalch equation: pH = 6.1 + log [HCO3-]/ 0.03 PCO2where 6.1 is the pKa (negative logarithm of the acid dissociation constant) for carbonic acid (H2CO3) and 0.03, the factor which relates PCO2 to the amount of CO2 dissolved in plasma.

рН	[H+], nanomol/L
7.80	16
7.70	20
7.60	26
7.50	32
7.40	40
7.30	50
7.20	63
7.10	80
7.00	100
6.90	125
6.80	160

2) Kassirer-Bleich equation: $[H+] = 24 \times PCO2 / [HCO3-]$

Although cumbersome and somewhat difficult to use at the bedside, both equations represent a very important relationship. They predict that the ratio of dissolved CO2 to HCO3-, rather than their actual concentrations, determines hydrogen ion concentration and thus pH.

A drop or rise in PCO2 will result in a drop or rise in [H+] respectively.

[HCO3-] on the other hand is inversely related to H+ concentration whereby a drop in bicarbonate levels result in an increase in H+ concentration while a rise in bicarbonate levels result in a reduction in H+ concentration.

This buffer system is of physiologic importance because both the pulmonary and renal mechanisms for regulating pH work by adjusting this ratio. The PCO2 can be modified by changes in alveolar ventilation, while plasma [HCO3-] can be altered by regulating its generation and excretion by the kidneys.

Compensatory Responses

Acid Base disoders are associated with defense mechanisms referred to as compensatory responses that function to reduce the effects of the particular disorder on the pH. They do not restore the pH back to a normal value. This can only be done with correction of the underlying cause. In each of these disorders, compensatory renal or respiratory responses act to minimize the change in H+ concentration by minimizing the alteration in the PCO2 /[HCO3-] ratio.

Compensatory Responses: Metabolic Acidosis

Metabolic Acidosis is an acid base disturbance characterized by a reduction in bicarbonate ions leading to an elevation in the PCO2/HCO3- ratio and thus an elevation in hydrogen ion concentration according to the following equation: $[H+] = 24 \times (PCO2 / [HCO3-])$

In metabolic acidosis, this reduction in bicarbonate ions may result from increased extracellular buffering of an increased acid load or less commonly; loss of bicarbonate ions in the urine.

Remember that, HCO3- is the main buffer of nonvolatile or noncarbonic acids in the body and therefore in the presence of excess acid, its concentration will decrease. The body responds to metabolic acidosis by trying to restore the PCO2 / [HCO3-] ratio. (*This is done by reducing the PCO2*)

The reduction in PCO2 is accomplished by increasing alveolar ventilation. The drop in arterial pH stimulates both the central and peripheral chemoreceptors controlling respiration, resulting in an increase in alveolar ventilation. The inccrease in ventilation is characterized more by an increase in tidal volume than by an increase in respiratory rate, and may if the acidemia is severe, reach a maximum of 30L/min (nl = 5-6 L/min). In its most pronounced clinical manifiestation, the increase in ventilation is referred to as Kussmaul Respiration.

In general, respiratory compensation results in a 1.2 mmHg reduction in PCO2 for every 1.0 meq/L reduction in the plasma HCO3- concentration down to a minimum PCO2 of 10 to 15mmHg. For example, if an acid load lowers the plasma HCO3- concentration to 9 meq/L, then: Degree of HCO3- reduction is 24 (optimal value) – 9 = 15.

Therefore, PCO2 reduction should be $15 \times 1.2 = 18$.

Then PCO2 measured should be 40 (optimal value) - 18 = 22 mmHg.

Winter's Formula

To estimate the expected PCO2 range based on respiratory compensation, one can also use the Winter's Formula which predicts: $PCO2 = (1.5 \times [HCO3-]) + 8 \pm 2$ Therefore in the above example, the PCO2 according to Winter's should be $(1.5 \times 9) + 8 \pm 2 = 20-24$

Another useful tool in estimating the PCO2 in metabolic acidosis is the recognition that the pCO2 is always approximately equal to the last 2 digits of the pH.

Compensatory Responses: Respiratory Acidosis

Respiratory Acidosis is an acid base disturbance characterized by an elevation in the partial pressure of dissolved CO2 leading to an elevation in the $PCO2/[HCO_3-]$ ratio which subsequently increases the hydrogen ion concentration according to the following equation:

 $[H+] = 24 \times PCO2 / [HCO3-]$

In Respiratory Acidosis, the elevation in PCO2 result from a reduction in alveolar ventilation. Elevation in PCO2 is never due to an increase in CO2 production. In response to the increase in [H+] and reduction of the pH, the body responds by trying to increase the plasma [HCO₃-] to match the increase in PCO2 and thus maintain the PCO2/HCO₃- ratio. This is accomplished via two mechanisms; a) rapid cell buffering and b) an increase in net acid excretion.

Because these mechanisms occur at different moments in time, acute respiratory acidosis can be distinguished from chronic respiratory acidosis.

Acute Respiratory Acidosis

Cell buffering occur within minutes after the onset of respiratory acidosis. The elevation in CO2 levels lead to an increase in carbonic or volatile acid in the plasma. Unlike nonvolatile acids, carbonic acid (H_2CO_3) cannot be buffered by HCO_3 - in the extracellular fluid. Therefore, in contrast to metabolic acidosis, bicarbonate levels do not fall in respiratory acidosis.

In this setting, carbonic acid (H_2CO_3) can only be buffered by the limited intracellular buffers (primarily hemoglobin and proteins).

 $H_2CO_3 + Hb- \rightarrow HHb + HCO_3-$

As shown above, each buffering reaction produces HCO_3 -, which leads to an increase in plasma [HCO_3 -]. And due to this process, acutely, there is an increase in the plasma [HCO_3 -], averaging 1 meq/L for every 10 mmHg rise in the PCO2.

Chronic Respiratory Acidosis

In chronic respiratory acidosis, the persistent elevation in PCO2 stimulates increased excretion of titratable acid and ammonium, resulting in the addition of new HCO3- to the extracellular fluid.

This process is complete after 3-5 days resulting in a new steady state in which there is approximately a 3.5 meq/L increase in the plasma HCO3- concentration for every 10 mmHg increase in the PCO2.

To put into perspective the impact of cell buffering vs renal adaptation on protecting the pH in respiratory acidosis, consider the following examples:

If the PCO2 is acutely increased to 80 mmHg, there will be approximately a 4meq/L elevation in the plasma [HCO3-] to 28 meq/L and a potentially serious reduction in extracellular pH to 7.17.

Change in PCO2 = 80-40 = 40.

Therefore elevation in $[HCO3-] = 40/10 \times 1 = 4$

According to the Henderson-Hasselbach equation, $pH = 6.1 + \log[HCO3-]/0.03 PCO2$ Hence $pH = 6.1 + \log (28/0.03 \times 80) = 7.17$.

In another example: If the PCO2 were chronically increased to 80 mmHg, the plasma [HCO3-] should rise by 14 ([(80-40)/10] \times 3.5) to a new concentration of 38 meq/L (24+14)

The pH in this situation would be:

 $pH = 6.1 + log (38/0.03 \times 80) = 7.30$

Thus renal compensation offers more significant pH protection in the setting of chronic respiratory acidosis in contrast to intracellular buffering in the acute situation. Chronic respiratory acidosis is commonly caused by COPD. These patients can tolerate a PCO2 of up to 90-110 mmHg and not have a severe reduction in pH due to renal compensation.

Compensatory Responses: Metabolic Alkalosis

Metabolic alkalosis is an acid base disorder characterized by an elevation in [HCO3-] above the normal range, which leads to a reduction in the PCO2/[HCO3-] ratio and subsequently a reduction in hydrogen ion concentration according to the following equation:

[H+] = 24 ×(PCO2 / [HCO3-])

This elevation in bicarbonate ions is due to an addition in alkali to the body which then cannot be excreted by the kidney. Metabolic alkalosis is always associated with renal impairment of some kind because the kidney has a vast capacity in excreting excess alkali.

Please note, loss of acid from the body as occurs in vomiting induced metabolic alkalosis is equivalent to adding alkali to the body.

In response to the reduction in [H+] and elevation in pH, the body responds by trying to increase the PCO2 to match the increase in [HCO3-] and thus maintain the PCO2/[HCO3] ratio. Elevation in PCO2 is accomplished by lowering alveolar ventilation.

The development of alkalemia is sensed by central and peripheral chemoreceptors, resulting in a reduction in the rate of ventilation and a reduction in tidal volume and thus an elevation in the pCO2. This happens fairly quickly following the onset of metabolic alkalosis.

On average the pCO2 rises 0.7 mmHg for every 1.0 meq/L increment in the plasma [HCO3-]. For example, if an alkali load raises the the plasma HCO3- concentration to 34 meq/L, then: Degree of HCO3- elevation is 34 - 24 (optimal value)= 10. Therefore, PCO2 elevation should be $0.7 \times 10 = 7$. Then PCO2 measured should be 40 (optimal value) +7 = 47mmHg.

Compensatory Responses: Respiratory Alkalosis

Respiratory alkalosis is caused by an elevation in the frequency of alveolar ventilation and more importantly tidal volume that result in an increase in minute ventilation. The increase in ventilation leads to the excretion of CO2 at a rate greater than that of cellular CO2 production.

This leads to a net reduction in PCO2 and subsequently to a reduction in the PCO2 / $[HCO_3-]$ ratio which reduces the hydrogen ion concentration (and increases the pH) according to the following equation: $[H+] = 24 \times PCO2 / [HCO_3-]$

In response to the decrease in [H+] and elevation in pH, the body responds by trying to reduce the plasma $[HCO_3-]$ to match the reduction in PCO2 and thus maintain the ratio. There are two mechanisms responsible for this compensation to respiratory alkalosis; 1) rapid cell buffering and 2) a decrease in net renal acid excretion.

As in respiratory acidosis, these responses occur in different moments of time, distinguishing acute respiratory alkalosis from chronic respiratory alkalosis.

Acute Respiratory Alkalosis

About 10 minutes after the onset of respiratory alkalosis, hydrogen ions move from the cells into the extracellular fluid, where they combine with [HCO₃- to form carbonic acid in the following reaction:

 $H+ + HCO_3- \rightarrow H_2CO_3$ (CA)

The hydrogen ions are primarily derived from intracellular buffers such as hemoglobin, protein and phosphates. The reaction with bicarbonate ions in this reaction leads to a mild reduction in plasma $[HCO_3-]$.

In acute respiratory alkalosis, as a result of cell buffering, for every 10 mmHg decrease in the PCO2, there is a 2meq/L decrease in the plasma HCO3-concentration.

Please note that the cellular buffering does not offer adequate protection against respiratory alkalosis. For example:

If the PCO2, were reduced to 20 mmHg, the change in PCO2 would be 20 (40-20) and therefore the fall in plasma [HCO3-] would be 4 meq/L ($20/10 \times 2$). The new plasma [HCO3-] would be 20 meq/L (24-4).

The pH in this circumstance would be:

pH = 6.1 + log (20/ 0.03×20) = 7.63

Had no cell buffering occurred, then the pH would be

 $pH = 6.1 + log (24/0.03 \times 20) = 7.70$

As you can see, really not much of a change.

Chronic Respiratory Alkalosis

If respiratory alkalosis persist for longer than 2- 6 hours, the kidney will respond by lowering hydrogen secretion, excretion of titratable acids, ammonium production and ammonium excretion. There will also be an increase in the amount of HCO3excreted due to decreased reabsorption of filtered HCO_3 -.

Completion of this process occurs after 2-3 days after which a new steady state is achieved.

Renal compensation result in a 4 meq/L reduction in plasma [HCO_3 -] for every 10 mmHg reduction in PCO2.

In comparison, to acute respiratory alkalosis, this compensation offers a much better protection of the arterial pH. To put this into perspective, consider the same 20 mmHg fall in PCO2 as before in the acute scenario. Now, due to renal compensation, the plasma [HCO₃-] falls by 8 meq/L to 16 meq/L. The pH now in the chronic situation would be :

 $pH = 6.1 + \log (16/0.03 \times 20) = 7.53.$

Compensatory Responses: summary and take home points

Primary disorder	Initial chemical change	Compensatory response	Compensatory Mechanism	Expected level of compensation
Metabolic			Hyperventilation	PCO2 = (1.5 × [HCO3-]) + 8 ± 2
Acidosis	11003-	1 002	rigperventilation	↓PCO2 = 1.2 ×∆ [HCO3-]
				PCO2 = last 2 digits of pH
Metabolic Alkalosis	↑HCO3-	↑PCO2 Hypoventilation PCO2 = (↑PCO2 = (Hypoventilation	PCO2 = (0.9 × [HCO3-]) + 16 ± 2
				↑PCO2 = 0.7 × ∆ [HCO3-]
Respiratory Acidosis	↑PCO2	↑ HCO3-		
Acute			Intracellular Buffering (hemoglobin, intracellular proteins)	↑[HCO3-] = 1 mEq/L for every 10 mm Hg ∆PCO2
Chronic			Generation of new HCO3- due to the increased excretion of ammonium.	↑[HCO3-] = 3.5 mEq/L for every 10 mm Hg ∆PCO2
Respiratory Alkalosis	↓PCO2	↓HCO3-		
Acute			Intracellular Buffering	↓[HCO3-] = 2 mEq/L for every 10 mm Hg ∆PCO2
Chronic			Decreased reabsorption of HCO3-, decreased excretion of ammonium	↓[HCO3-] =4 mEq/L for every 10 mm Hg ∆PCO2

Below is table summarizing compensatory responses and their mechanisms.

Also: In acute respiratory acidosis, $\downarrow pH = 0.008 \times \Delta PCO2$ In chronic respiratory acidosis, $\downarrow pH = 0.003 \times \Delta PCO2$.

Calculations

There are various calculations that are commonly used diagnostically in interpreting acid base disorders and distinguishing between different causes of acid base disorders. Calculating the anion gap is an approach that must be taken in all cases of metabolic acidosis. Other calculations such as osmolar gap and urine anion gap, are used when clinically, the cause of an acid base disorder is in doubt.

This teaching module will discuss the various diagnostic calculations that can be useful in interpreting acid base disorders. Emphasis will be placed on the underlying rational behind each formula to increase comprehension and deduction and minimize memorization.

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 CI- and HCO3- concentrations from the plasma Na concentration.

Na + Unmeasured cations = CI- + HCO3- + Unmeasured anions Anion gap = [Na] - ([CI-] + [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 \pm 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 \rightarrow NaCl + H2CO3 \rightarrow CO2 + H2O

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

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

HA + NaHCO3 \rightarrow NaA + H2CO3 \rightarrow 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 = \triangle Anion gap/ \triangle [HCO3-] or \uparrow anion gap/ \downarrow [HCO3-] Delta Delta = <u>Measured anion gap – Normal anion gap</u> Delta del Normal [HCO3-] – Measured [HCO3-] Delta Delta = <u>(AG – 12)</u> 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 HCO3- . 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 [HCO3-]. 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 [HCO3-] 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 HCO3- is due to further buffering of an acid that does not contribute to the anion gap. (i.e addition of HCI to the body as a result of diarrhea)

A value above 2:1 indicates a lesser fall in [HCO3-] than one would expect given the change in the anion gap. This can be explained by another process that increases the [HCO3-],i.e. a concurrent metabolic alkalosis. Another situation to consider is a pre-existing high HCO3- 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

Urine Anion Gap

The three main causes of normal anion gap acidosis are:

- Loss of HCO3- from Gastrointestinal tract (diarrhea)
- Loss of HCO3- from the Kidneys (RTAs)
- · Administration of acid

Distinguishing between the above 3 groups of causes is usually clinically obvious, but occasionally it may be useful to have an extra aid to help in deciding between a loss of base via the kidneys or the bowel. Calculation of the urine anion gap may be helpful diagnostically in these cases.

The measured cations and anions in the urine are Na+, K+, and Cl-; thus the urine anion gap is equal to:

Urine anion gap = [Na+] + [K+] - [Cl-]

Urine anion gap = unmeasured anions – unmeasured cations

In normal subjects, the urine anion gap is usually near zero or is positive. In metabolic acidosis, the excretion of the NH4+ (which is excreted with CI-) should increase markedly if renal acidification is intact. Because of the rise in urinary CI-, the urine anion gap which is also called the urinary net charge, becomes negative, ranging from -20 to more than -50 meq/L. The negative value occurs because the CI-concentration now exceeds the sum total of Na+ and K+.

In contrast, if there is an impairment in kidney function resulting in an inability to increase ammonium excretion (i.e. Renal Tubular Acidosis), then CI- ions will not be increased in the urine and the urine anion gap will not be affected and will be positive or zero.

In a patient with a hyperchloremic metabolic acidosis: A negative UAG suggests GI loss of bicarbonate (eg diarrhea), a positive UAG suggests impaired renal acidification (ie renal tubular acidosis).

As a memory aid, remember 'neGUTive' - negative UAG in bowel causes. Remember that in most cases the diagnosis may be clinically obvious (severe diarrhea is hard to miss) and consideration of the urinary anion gap is not necessary

Osmolar Gap

The Osmolar Gap is another important diagnostic tool that can be used in differentiating the causes of elevated anion gap metabolic acidosis. The major osmotic particles in plasma are Na+, Cl-, HCO3-, urea and glucose and as such, plasma osmolarity can be estimated as follows:

Plasma osmolarity = 2(Na) + glucose/18 + BUN/2.8

Note that because CI- and HCO3- are always bound to Na, their contributions to osmolarity are estimated by doubling the Na concentration. Plasma osmolality (Posm) can also be measured directly by freezing point depression. The osmolar gap is the difference between the calculated serum osmolarity and the measured serum osmolarity.

Osmolar Gap = Measured Posm – Calculated Posm

The normal osmolar gap is 10-15 mmol/L H20 .The osmolar gap is increased in the presence of low molecular weight substances that are not included in the formula for calculating plasma osmolarity. Common substances that increase the osmolar gap are ethanol, ethylene glycol, methanol, acetone, isopropyl ethanol and propylene glycol.

In a patient suspected of poisoning, a high osmolar gap (particularly if \geq 25) with an otherwise unexplained high anion gap metabolic acidosis is suggestive of either methanol or ethylene glycol intoxication.

"One must correlate an elevated osmolar gap with other clinical findings because it is a relatively nonspecific finding that is also commonly seen in alcoholic and diabetic ketoacidosis, lactic acidosis and in chronic renal failure. Elevation in the osmolar gap in these disease states is thought to be due in part to elevations of endogenous glycerol, acetone, acetone metabolites, and in the case of renal failure, retention of unidentified small solutes."

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. See table.

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

- If elevated (> than 16), then acidosis due to KULT. (Ketoacidosis, Uremia, Lactic acidosis, Toxins). See table.

- 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. *See table.*

7. If anion gap is elevated, then calculate the Delta-Ratio (Δ/Δ) to assess for other simultaneous disorders.

- $\Delta\!/\!\Delta$ 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. (neGUTive in diarrhea)

Etiology of Acid Base Disturbances

This teaching module will give an overview of common causes of specific acid base disoders. Also included are conditions or scenarios that commonly lead to mixed acid base disorders.

• 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) Lactic Acidosis Uremia	Loss of Bicarbonate: Diarrhea Carbonic anhydrase inhibitors Type 2 RTA (proximal) Pancreatic ileostomy Pancreatic, biliary, intestinal fistula Exogenous Administration: ammonium chloride or HCL Decreased Renal Acid Excretion: Type 1(distal) ,4 RTA Renal Failure
Intoxications: Methanol, Ethylene Glycol, Paraldehyde, Salicylates, INH	Miscellaneous: Hyperkalemia Recovery from DKA

✓ Lactic Acidosis

A commonly encountered cause of elevated anion gap metabolic acidosis,

particularly in the ICU is lactic acid. Lactic acidosis is characterized by a pH < 7.36 and lactate level > 5mmol/L

Lactic acid is produced under normal aerobic states in cells of the brain, retina, and erythrocytes. Under normal circumstances, lactate is circulated to the liver, and to a lesser degree the kidney, where it is converted into glucose or CO2 and H2O. Lactate + $3O2 \rightarrow HCO3$ - + 2CO2 + 2H2O

2 Lactate + 2CO2 + 2H2O \rightarrow 2HCO3- + glucose.

In hypoxic states (low O2 supply) such as in strenuous muscle activity (seizure) or in low tissue perfusion states from circulatory failure, lactic acid is also produced anaerobically during glycolysis. This occurs via the following reaction:



This conversion of pyruvate to lactate in anaerobic conditions is promoted by the accumulation of NADH and the depletion of NAD+ which is needed as an electron acceptor so that glycolysis can continue. The conversion to lactate results in the regeneration of NAD+ so that minimal amounts of ATP can be made indefinitely from glycolysis in states of very low tissue oxygenation.

Lactate accumulation and lactic acidosis results because in states of low tissue perfusion such as shock, or in states of mitochondrion dysfunction, lactate cannot be recycled to the liver for conversion back to glucose or for further breakdown because both of these reactions as shown above require oxygen and both take place in the mitochondrion.

There are primarily 2 types of lactic acidosis: Type A – Due to tissue hypoperfusion and hypoxia Type B – Not due to tissue hypoperfusion and hypoxia.

Type A Lactic Acidosis

Most cases of lactic acidosis are due to reduced oxygen delivery as a result of reduced tissue perfusion from shock or cardiopulmonary arrest. Other conditions such as acute pulmonary edema, can cause severe hypoxemia leading to reduced O2 delivery. Other causes are carbon monoxide poisoning and severe anemia. Other causes of type A lactic acidosis which may not necessarily involve generalized tissue hypoxia are severe seizure, severe exercize and hypothermic shivering. All of which result in localized skeletal muscle hypoxia leading to increased lactic acid production. The clinical signs usually indicate reduced tissue perfusion and include severe hypotension, tachypnea, oliguria or anuria, peripheral vasoconstriction and deteriorating mental status. Sepsis, particularly in critically ill patients is a very important cause of lactic acidosis and is often associated with fever (>38.5°C) or hypothermia (35°C). Kussmaul hyperventilation (deep sighing respiration) may be observed if the severity of the acidosis is sufficient to elicit a degree of respiratory compensation. Lactic acidosis is usually associated with laboratory abnormalities indicating organ failure or compromise such as abnormal liver function tests, elevated BUN and elevated creatinine. Lactate levels are usually greater than 5 meg/L. Upper limit of nl is 1.6 in plasma. Anion gap is classically elevated, > 16.

Type B Lactic Acidosis

Usually without clinically apparent tissue hypoxia and can be due to any number of conditions:

- Underlying diseases: DM, uremia, liver disease, infections, malignancies
- Drugs and toxins: ethanol, methanol, ethylene glycol, salicylates, metformin
- Inborn errors of metabolism: pyruvate dehydrogenase deficiency, glycogen storage disease, pyruvate carboxylase deficiency, etc.

• Other : D-Lactic acidosis (short bowel syndrome) *, idiopathic Typical picture includes acute onset after nausea and vomiting, altered state of consciousness and hyperventilation. Laboratory findings are variable depending on underlying cause.

D-Lactic Acidosis

Easily missed diagnosis, because the isomer responsible for the acidosis is the Disomer which is not detected by the standard assay for lactate. This unique form of lactic acidosis can occur in patients with jejunoilelal bypass, or less commonly, small bowel resection or other causes of the short bowel syndrome.

In these settings, the glucose and starch are metabolized in the colon into D-lactic acid, which is then absorbed into the systemic circulation. The ensuing acidemia tends to persist, since D-lactate is not recognized by L-lactate dehydrogenase, the enzyme that catalyzes the conversion of the physiologically occurring L-lactate into pyruvate.

Two factors that tend to contribute to the accumulation of D-lactate systemically are 1) an overgrowth of gram positive anaerobes, such as lactobacilli that are most able to produce D-lactate and 2) increased delivery of glucose and starch to the colon in the presence of a shorter small bowel transit.

Patients typically present with recurring episodes of metabolic acidosis, usually after a carbohydrate meal, and characteristic neurologic abnormalities including confusion, cerebella ataxia, slurred speech, and loss of memory.

Criteria for D-lactic acidosis:

- Presence of short bowel syndrome with an intact colon.
- An acute episode of encephalopathic symptoms, such as confusion, slurred speech , ataxia, unsteady gait, abusive behavior and/or nystagmus
- Metabolic acidosis with an increased anion gap
- Normal L-lactate levels
- Serum D-lactate levels > 3 mmom/L
- Abnormal colonic flora, with a predominance of Gram positive anaerobic bacteria (Lactobacilli, which produce large amounts of lactic acid)

Treatment for Lactic Acidosis

Treatment of lactic acidosis requires identification of the primary illness and therapy directed toward correction of that disturbance. Restoration of tissue oxygen delivery through hemodynamic and/or respiratory support is the key therapeutic goal in type A lactic acidosis, which will reduce further lactate production and allow metabolism of excess lactate to HCO3-.

Unlike other forms of metabolic acidosis, the use of sodium bicarbonate in lactic acidosis is controversial, particularly in patients with circulatory and respiratory failure. Proponents argue that raising the arterial pH may improve tissue perfusion, by reversing acidemia induced vasodilatation and impaired cardiac contractility, and may diminish the risk of serious arrhythmias. Others argue that the NaHCO3 administration may actually worsen acidosis, particularly in patients with respiratory compromise due to the generation of CO2 from the metabolism of NaHCO3. It is thought that this CO2 accumulates in tissues leading to worsening intracellular acidosis. The intracellular acidosis leads to reduced lactate utilization in hepatic cells and a decline in cardiac contractility leading to reduced cardiac output and paradoxically further promotion of lactic acid production. Others also argue that NaHCO3 administration carries with it a risk of volume overload and overshoot metabolic alkalosis after normal hemodynamic has been restored. Despite the controversy most physicians support administration of NaHCO3 for very severe acidemia and will give small amounts of NaHCO3 to maintain the arterial pH above 7.10, since a pH beyond this value will promote the development of arrhythmias and cardiac depression.

Treatment for D-Lactic acidosis

Spontaneous regeneration of HCO3- does not occur in D-lactic acidosis, since Dlactate cannot be metabolized. Therapy for D-lactic acidosis consists of sodium bicarbonate administration to correct the acidemia and oral antibiotics to decrease gram positive anaerobic colonic bacteria. A low carbohydrate diet is also helpful in the reducing carbohydrate delivery to the colon.

✓ Ketoacidosis

Ketoacidosis is a common form of elevated anion gap metabolic acidosis seen in patients with insulin requiring diabetes mellitus, alcoholics and pts undergoing fasting or starvation and is due to the overproduction of ketone bodies (Ketosis) leading to accumulation of ketones in plasma (Ketonemia) and urine (Ketonuria).

The basic mechanism for the development of Ketonemia is as the following. In starvation states where plasma glucose levels are low or in states of low plasma insulin where uptake of glucose by cells is diminished, fatty acids will be mobilized and transported to tissues (brain, skeletal muscle, heart) for fatty acid oxidation and energy production. Fatty acids are also transported to the liver, where due to diminished citric cycle activity resulting from gluconeogenesis, acetyl CoA from fatty acid oxidation can not be oxidized and is instead converted to the generation of ketone bodies. These ketone bodies (acetoacetate and β -hydroxybutyrate) serve as a source of fuel for other tissues, in particular, the brain. Ketonemia arises when this process is prolonged due to prolonged states of glucose unavailability, as the hepatic production of ketone bodies overwhelms the capacity of extrahepatic tissues to oxidize them. Accumulation and ionization of ketones in plasma result in the release of excess hydrogen ions which then lead to acidosis.

✓ Diabetic Ketoacidosis (DKA)

Uncontrolled type 1 diabetes mellitus is the most common cause of ketoacidosis. The lack of insulin contributes to this condition not only via decreased glucose uptake but also by promoting lipolysis (triglyceride breakdown) and fatty acid oxidation. It is a state that also includes an increase in counter-regulatory hormones (ie, glucagon, cortisol, growth hormone, epinephrine) which contribute to hyperglycemia by promoting further gluconeogenesis and to ketonemia by promoting acetyl –COA migration into mitochondrion where they can be converted into ketones.

Progressive rise of blood concentration of these acidic organic substances initially leads to a state of ketonemia. Natural body buffers can buffer ketonemia in its early stages. When the accumulated ketones exceed the body's capacity of extracting them, they overflow into urine (ie, ketonuria). If the situation is not treated promptly, more accumulation of organic acids leads to frank clinical metabolic acidosis (ie, ketoacidosis), with a drop in pH and bicarbonate serum levels. Hyperglycemia usually exceeds the renal threshold of glucose absorption and results in significant glycosuria. Consequently, water loss in the urine is increased (polyuria) due to osmotic diuresis induced by glycosuria. This incidence of increased water loss results in severe dehydration, thirst, tissue hypoperfusion, and, possibly, lactic acidosis. In addition, beta hydroxybutyrate induces nausea and vomiting that consequently aggravate fluid loss. Typical free water loss in DKA is approximately 6 liters or nearly 100 mL/kg of body weight.

Hyperglycemia, osmotic diuresis, serum hyperosmolarity, and metabolic acidosis result in severe electrolyte disturbances. The most characteristic disturbance is total body potassium loss. Total body potassium loss is usually present despite normal or high serum potassium levels. Potassium levels may appear to be high due to the transcellular shift of potassium out of cells. This is not due to ketoacidosis directly but rather is due to insulin deficiency and hyperosmolality. A large part of the shifted extracellular potassium is lost in urine because of osmotic diuresis. Also, when ketoacids are excreted, they are usually excreted with Na or K in the urine, leading to

further K loss. Vomiting may also contribute to potassium loss in these patients. Patients with initial hypokalemia are considered to have severe and serious total body potassium depletion.

In addition, hyponatremia is usually present, and is usually due to the dilutional effect of hyperosmolality as water is shifted from intracellular to extracellular compartments. The direct effect of hyperosmolarity is often counteracted by the glucosuria-induced osmotic diuresis. The diuresis results in water loss in excess of sodium and potassium, which will tend to raise the plasma sodium concentration and plasma osmolality unless there is a comparable increase in water intake. As such, hyponatremia is usually mild.

The combined effects of serum hyperosmolarity, dehydration, and acidosis result in increased osmolarity in brain cells that may clinically manifest as an alteration in the level of consciousness.

<u>History</u>

- 25% of patients present with DKA as first presentation of their diabetes mellitus.
- Usually triggered by illness: UTI, infection, stress (medical or emotional), MI
- May also be due to poor compliance, or missed injections due to vomiting
- Insidious increased thirst (ie, polydipsia) and urination (ie, polyuria) are the most common early symptoms of DKA.
- Nausea and vomiting may occur associated with diffuse abdominal pain
- Lethargy, somnolence, confusion may develop
- Dyspnea

<u>Signs</u>

- Signs of dehydration Weak and rapid pulse, dry tongue and skin, hypotension, and increased capillary refill time
- Oral odor Characteristic fruity odor (from acetone, a product of acetoacetate metabolism
- Signs of acidosis Deep sighing breathing, abdominal tenderness, and disturbance of consciousness
- Body temperature may be within the reference range or low, even in the presence of intercurrent infection.

Laboratory

- Urine dipstick highly positive for glucose, ketones (dipstick detect acetoacetate but not beta-hydroxybutyrate which is the predominant ketone, therefore test not always positive initially for ketones)
- Serum ketones present
- ABG : low bicarbonate, low PCO2, pH < 7.35
- Anion gap > 16
- Serum K normal, high or low.
- Serum Na low phos low.
- Serum phosphate: usually phosphate depleted due to urine losses but are normal or high by labs due to transcellular shift out of cells in the setting of acidosis and insulin deficiency. After treatment with Insulin, phosphate levels usually low
- Serum glucose usually > 300 mg/dl but below 800mg/dl (unlike NKH, where > 1000 mg/dl)
- Leukocytosis, even in the absence of infection
- Bun/Cr high due to prerenal azotemia

<u>Treatment</u>

The major goals of treatment are 1) rapid fluid volume expansion, 2) correction of hyperglycemia and hyperketonemia, 3) prevention of hypokalemia during treatment, and 4) identification and treatment for any associated bacterial infection

- 1. Fluids: IVF, in adults, rapid infusion of 1L of 0.9% NS (e.g. over 30 min), repeat bolus as necessary to prevent shock. When BP is stable and urine output adequate, can switch to 0.45% NS at a slower rate. This is done to replace the free water loss induced by the osmotic diuresis.
- 2. Insulin infusion: 10-20 unit bolus (0.15 u/kg), then 5-7 units/hr (0.1 unit/kg/hr). This stops the lipolysis and gluconeogenesis and allows for the conversion of ketones to bicarbonate. BS should not be allowed to fall below 250 in the first 4-5 hours of treatment. If does, change rate to 0.03 u/kg/hr. When anion gap normal, initiate SQ insulin, overlap for 1-2hr with insulin infusion. When blood sugar less than 180, can add 5-10% dextrose to IVF.
- 3. Potassium replacement: If initial K >6, then withhold replacement. If K< 4.5, then administer 10-20 meq/hr of K. If initial K < 3, then administer 40 meq/hr.
- 4. Bicarb replacement: If pH < 7.1 and/or cardiac instability present, then give bicarb
- 5. Phosphate replacement: Give K-phos if initial P< 1.0mg/dl. (usually high initially, due to the transcellular shift of phosphate outside the cell in the setting of acidosis and insulin deficiency)

✓ Alcoholic Ketoacidosis

Alcoholic ketoacidosis (AKA) is an acute metabolic acidosis that typically occurs in people who chronically abuse alcohol and have a recent history of binge drinking, little or no food intake, and persistent vomiting. AKA is characterized by elevated serum ketone levels, high anion gap and a normal or only slightly high plasma glucose

Pathophysiology: AKA is a result of prolonged starvation with glycogen depletion, increase in counter-regulatory hormone production, dehydration, and the metabolism of ethanol itself.

Due to a physical complaint (abdominal pain, vomiting), dietary intake usually ceases in these patients leading to starvation and the development of increased ketoacid production. The body's response to starvation is a decrease in insulin activity and an increase in the production of counter-regulatory hormones such as glucagon, epinephrine, growth hormone and cortisol. Decrease in insulin plus an increase in the concentration of counter-regulatory hormones, primarily glucagon, result in increased lipolysis, fatty acid mobilization and transfer of fatty acids to the liver. These fatty aids are taken up by the liver and undergo fatty acid oxidation in the mitochondrion which results in the accumulation of acetyl-CoA. As mentioned previously, the liver during states of starvation is actively undergoing gluconeogenesis, diminishing the citric cycle by using up intermediates. Acetyl-CoA which normally enters the citric cycle for further oxidation, accumulates and is instead converted to ketoacids; β hydroxybutyrate and acetoacetate.

The metabolism of ethanol leads to an accumulation in reduced nicotinamide adenine dinucleotide (NADH), which then result in 2 processes: 1) Impaired conversion of lactate to pyruvate or preferential conversion of pyruvate to lactate, both resulting in increased lactic acid levels, and 2) a shift in the β -hydroxybutyrate to acetoacetate equilibrium toward β -hydroxybutyrate.

As a result, β -hydroxybutyrate is by far, the predominant ketone in AKA. The standard nitroprusside test for detecting ketones unfortunately only detects acetoacetate and in AKA may be falsely negative or only minimally positive, and can lead to a an underestimation of the degree of ketoacidosis.

Acid base disorders in AKA

These patients frequently may present with a mixed acid base disturbance:

- Elevated anion gap metabolic acidosis secondary to Ketoacidosis
- · Metabolic alkalosis as a result of persistent vomiting
- Chronic respiratory alkalosis as a result of liver disease.
- Mild degree of lactic acidosis may also be present, contributing to the elevated anion gap acidosis.

<u>History</u>

- Chronic alcoholic who goes on drinking binge
- Develops pancreatitis, gastritis, which leads to abdominal pain, nausea and persistent vomiting
- Symptoms leads to cessation of alcohol consumption and poor oral intake 1 to 3 days prior to presentation
- Symptoms may also include that of liver disease or portal hypertension : melena, hematochezia, hematemesis, fatigue, dyspnea
- Alcoholic withdrawal: tremors, seizure, hallucinations, delirium tremens
 s

<u>Signs</u>

- Tachycardia, tachypnea, Kussmaul respiration, hypotension (possibly)
- Abdominal tenderness (particularly if pancreatitis present)
- Heme-positive stools
- Physical exam findings may include that of chronic liver disease: spider nevi, ascitis, hepatomegaly, caput medusa, palmar erythema, varices, jaundice, gynecomastia

Laboratory findings

- ABG: pH may be low high or normal depending on acid base disturbances present. PCO2 will be low, HCO3- high. Anion gap will be elevated, >16
- Serum ketones may be falsely negative, or only weakly positive.
- Serum glucose may be low, normal or only slightly elevated (in contrast to DKA were glucose levels are significantly elevated)
- Serum lactate may be elevated
- Mg, phos, depleted low due to increased urinary excretion and poor nutrition. Phos may appear normal or high due to transcellular shift in the setting of acidosis.
- Bun and Cr elevated due to prerenal axotemia
- Anemia may be present due to alcohol induced bone marrow suppression, hyperspenism, or GI bleed
- Hct may be falsely elevated due hemoconcentration secondary to volume loss.
- Alcohol levels absent or low
- LFTs may be abnormal if liver disease present. Amylase, lipase elevated if pancreatitis present

Treatment

- Establish ABCs. If the patient's mental status is diminished, consider administration of oxygen, thiamine, dextrose, and naloxone. Remember thiamine must be given prior to dextrose to prevent Wernicke Korsakoff.
- Once the diagnosis of AKA is established, the mainstay of treatment is hydration with 5% dextrose in normal saline (D5NS.) Carbohydrate and fluid replacement reverse the pathophysiologic derangements that lead to AKA by increasing serum insulin levels and suppressing the release of glucagons and other counter-regulatory hormones. Dextrose stimulates the oxidation of NADH and aids in normalizing the NADH/NAD+ ratio. Fluids alone do not correct AKA as quickly as fluids and carbohydrates together.

- Insulin contraindicated, because may lead to life threatening hypoglycemia particularly as the patient's endogenous insulin levels rise with carbohydrate and fluid repletion.
- Bicarbonate only given if pH < 7.1, and acidosis not responding to IVF.

✓ Starvation/ Fasting

Starvation, as mentioned previously can result in ketoacidosis due to the increase in counter-regulatory hormones and a decrease in insulin, a balance which promotes fatty acid oxidation, gluconeogenesis, and ketone production. However in comparison to the potentially severe ketoacidosis that develops in uncontrolled diabetes and alcoholic states, ketoacid levels do not exceed 10 meg/L

with fasting. This limitation in the ketone formation may reflect the ability of ketonemia to promote insulin secretion, eventually limiting the release of free fatty acids and thus ketoacidosis

✓ Renal Tubular Acidosis

Renal Tubular Acidosis (RTA) refer to a group of disorders intrinsic to renal tubules characterized by an impairment in urinary acidification which result in retention of H+ ions, reduction in plasma [HCO3-] and a hyperchloremic metabolic acidosis with a normal serum anion gap. There are 3 distinct types of RTA, each having a different pathophysiology leading to decreased acid excretion. The urinary anion gap ([Na + K] – CI-) is usually positive in RTA due to an inability to excrete H+. This distinguishes RTA from the other causes of normal anion gap metabolic acidosis

This distinguishes RTA from the other causes of normal anion gap metabolic acidosis such as diarrhea which will have a negative urinary anion gap.

Type 1 (Distal) RTA

Type 1 or distal RTA is referred to as the classic RTA and is a disorder of acid excretion involving the collecting tubules. The disorder is characterized by a hypokalemic, hyperchloremic metabolic acidosis.

Pathophysiology

The disorder is due to defective H+ ion secretion in the distal tubule. Impairment in H+ ions secretion result in an inability to acidify the pH beyond 5.5 which retards the excretion of titratable acids (H_2PO_4) and NH_4^+ ions, thus resulting in a reduction in net acid excretion. The plasma bicarbonate is significantly reduced and may fall below 10 meq/L.

The impairment in H+ ions secretion is most commonly thought to be due to a defect in the luminal H+ -ATPase pump located in the intercalating cells of the collecting tubule. The H+ -ATPase pump is primarily responsible for the hydrogen secretion in the distal nephrons.

These patients tend to have urinary K+ wasting and hypokalemia. The etiology of the hypokalemia is unclear but is thought to be due to increased potassium secretion by distal tubular cells in the setting of diminished H+ ion secretion.

Hypercalciuria, hyperphosphatemia, nephrolithiasis (calcium phosphate stones) and nephrocalcinosis are frequently associated with untreated type 1 RTA. The

hypercalciuria is thought to be due to 1) increased calcium phosphate release from bone as a result of bone buffering of excess acid and 2) reduction in tubular calcium reabsorption secondary to chronic acidosis. The hypercalciuria, alkaline urine, and reduced excretion of citrate in the urine (which normally prevents calcium

crystallization) promote the precipitation of calcium phosphate and stone formation. The hypocitraturia is thought to be due to the effects of acidosis and hypokalemia on proximal tubule reabsorption.

Causes

Many different conditions have been associated with type I RTA. See table below. The most common identifiable causes in adults are autoimmune disorders, such as Sjogren's syndrome . In children, RTA is most often a primary hereditary condition.

Symptoms

The loss of calcium salts from bones in these patients can result in failure to thrive, rickets and stunting of growth in children and osteomalacia or osteopenia in adults. Patients may otherwise be asymptomatic or may present with symptoms of severe acidosis or hypokalemia (polyuria, polydypsia, weakness and fatigue)

Major causes of distal RTA

Idiopathic or sporadic in children Familial Autosomal dominant Autosomal recessive

Secondary (Acquired) Sjogren's Hypercalciuria Rheumatoid Arthritis , SLE Hyperglobulinemia Ifosfamide, Amphotericin , Lithium carbonate Sickle cell anemia Cirrhosis, renal transplant

Type 2 (Proximal) RTA

Type 2 RTA is characterized by an impairment in proximal HCO3- reabsorption resulting in a hypokalemic hyperchloremic metabolic acidosis.

Pathophysiology

This condition usually appears as part of a generalized disorder of proximal tubular function known as Fanconi syndrome which also include defects in the absorption of glucose, amino acids, phosphate, uric acid, and other organic anions such as citrate. The reduction in HCO3- reabsorption leads to an increase in bicarbonate loss in the urine. Remember that a loss of a single bicarbonate ion is akin to adding one hydrogen ion to the plasma, therefore this bicarbonate loss in the urine leads to increased hydrogen ion concentration and a subsequent reduction in arterial pH. Usually about 90% of the filtered HCO3- is absorbed by the proximal tubule, the rest is absorbed by the distal nephrons. In the setting of proximal impairment of HCO3-, the distal nephrons become overwhelmed by an increase in HCO3- delivery and cannot compensate for the loss in proximal function. However as urinary HCO3- loss progresses, plasma HCO3- drops to 15-18 meg/L. This causes the level of filtered HCO3- to fall and thus there is reduced delivery of HCO3- ions to the distal nephrons. At that point, the distal nephrons are no longer overwhelmed and can regain function, leading to a reduction in bicarbonaturia and a urine which can now be acidic. This is in contrast to type 1 RTA, where urine acidification is limited to a minimum urinary pH of 5.5.

Thus type 2 RTA is a self limiting disorder in which the plasma HCO3- concentration is usually between 14 and 20 meq/L due to the establishment of a new steady state. Urinary K+ wasting and hypokalemia are common in type 2 RTA and is due to persistent hyperaldosteronism, leading to increased K secretion by the distal nephrons. Hyperaldosteronism in these patients are related to the defect in proximal reabsorption of filtered HCO3- which in effect leads to decreased proximal NaCl reabsorption and a tendency for salt wasting.

The factors responsible for the defects in proximal transport are incompletely understood. There are three features of the proximal tubules that are vital to proximal reabsorption of HCO3- : 1) the Na+- H+ exchanger in the luminal membrane, 2) the Na+-K+ ATPAse pump in the basolateral membrane and 3) the enzyme carbonic anhydrase, which is located both intracellularly where it results in the generation of H+ and HCO3- , and in the lumen, where it facilitates HCO3- reabsorption. It has been proposed that one or more of these factors must be impaired to account for the defect in type 2 RTA.

Causes

Below is a table showing some of the known causes of type II RTA. A variety of congenital and acquired disorders can cause type 2 RTA. Idiopathic RTA and cystinosis are most common in children; carbonic anhydrase inhibitors and multiple myeloma are most often responsible in adults.

Complications

As in type 1 RTA, bone disease also occurs due to an increase in bone buffering of excess acid and the release of calcium salts from bone. Also contributing to this problem is acquired vitamin D deficiency, since the proximal tubule is a major site of formation of calcitriol.

Defects in proximal transport may also result in phosphate wasting and hypophosphatemia leading to decreased deposition of mineral in bone. Rickets in children and osteomalacia or osteopenia in adults are relatively common in type 2 RTA, occurring in up to 20% of cases.

In contrast to type 1 RTA, nephrocalcinosis and nephrolithiasis does not occur, and this is due to normal levels of urinary citrate in this condition (in contrast to type 2) and the ability to acidify the urine which increases the solubility of calcium phosphate.

Major Causes of type 2 RTA

Idiopathic or sporadic in children

Hereditary

- A. Cystinosis
- B. Galactosemia
- C. Tyrosinemia
- D. Glycogen storage disease, type 1
- E. Wilson's disease

Acquired disorders

- A. Multiple Myeloma
- B. Hypocalcemia and vitamin D deficiency
- C. Drugs and Toxins: (Acetazolamide or other carbonic anhydrase inhibitor, Ifosfamide, Streptozocin, Lead, Cadmium, Mercury, outdated tetracycline)
- D. Amyloidosis
- E. Renal transplant rejection

Type 4 RTA

Type IV RTA is the only type characterized by a hyperkalemic, hyperchloremic acidosis. The defect is thought to be Aldosterone deficiency or resistance.

Pathophysiology

Aldosterone deficiency or resistance impairs the secretion of hydrogen and potassium ion resulting in acidosis and hyperkalemia. The hyperkalemia is usually very prominent in this condition and has an important role in metabolic acidosis by impairing ammonium production and acid excretion in the urine. The hyperkalemia in this setting impairs NH4+ production in the proximal tubule by inducing a state of intracellular alkalosis within the tubular cell. This occurs due to the transcellular exchange of potassium for hydrogen resulting in the exit of hydrogen ion from the cell.

The development of intracellular alkalosis reduces NH4+ secretion by the proximal tubular, which in combination with decreased hydrogen secretion distally, result in decreased ammonium excretion and decreased net acid excretion. Reversing this process by correcting the hyperkalemia often leads to increased NH4+ excretion and correction of the metabolic acidosis

The metabolic acidosis seen with hypoaldosteronism is generally mild, with the plasma [HCO3-] usually above 15 meq/L. Despite the impairment in distal H+ secretion, the urine pH in this disorder is generally but not always below 5.3, in contrast to type 1 RTA. The ability to acidify the urine in this condition is due to the inadequate amount of NH3 available for buffering of protons. Even if only a few protons are secreted distally, urinary pH will fall in the absence of buffers. This is in contrast to type 1 RTA where distal H+ secretion is impaired and any protons secreted will be buffered by available NH3, thus maintaining an alkaline urine.

Causes

Type 4 RTA due to aldosterone deficiency has multiple etiologies. Hyporeninemic hypoaldosteronism is the most common cause and is usually associated with mild to moderate renal insufficency. It is most commonly found in diabetes nephropathy and chronic interstitial nephritis. NSAIDS, ACE inhibitors, trimetoprim and heparin can all reduce aldosterone production and produce a type 4 RTA. Drug-induced type 4 RTA is usually seen in patients with pre-existing renal insufficiency.

Patients with tubular resistance to aldosterone will present very similarly to hyporeninemic hypoaldosteronism. It is thought to be due to a tubulointerstial process that damages the distal tubule causing retention of hydrogen and potassium ions despite adequate aldosterone. BPH and sickle cell disease are the most common causes. Spironolactone has also been known to cause an aldosterone resistant state.

Symptoms

Type IV RTA is usually asymptomatic with only mild acidosis, but cardiac arrhythmias or paralysis may develop if hyperkalemia is extreme.

Diagnosis of RTA

Type I RTA

The findings of hypokalemic, normal anion gap metabolic acidosis with an inappropriately high urine pH (>5.5) and postive urine anion gap confirm the diagnosis. In patients with a normal plasma bicarbonate concentration, the failure to

lower urinary pH to less than 5.5 after an acute acid challenge with NH4Cl defines the syndrome of incomplete classic distal RTA

<u>Type II RTA</u>

The diagnosis of type 2 RTA is made by measurement of the urine pH and fractional bicarbonate excretion during a bicarbonate infusion. The plasma bicarbonate concentration is raised toward normal (18-20 meq/L) with an intravenous infusion of sodium bicarbonate at a rate of 0.5 to 1.0 meq/kg/hour. The urine pH , even if initially acidic, will rise rapidly once the reabsorptive threshold for bicarbonate is exceeded. As a result, the urine pH will be above 7.5 and the fractional excretion of bicarbonate will exceed 15%.

Type IV RTA

The findings of hyperkalemic, normal anion gap metabolic acidosis with an appropriately low urine pH (<5.5) and positive urine anion gap confirm the diagnosis. The diagnosis is further supported by a bicarbonate fractional excretion of less than 10% in the setting of bicarbonate infusion.

Comparison of RTA				
Finding	Type 1 RTA	Type 2 RTA	Type 4 RTA	GI Bicarbonate loss
Basic defect	Decreased distal acidification	Diminished proximal HCO3- reabsorption	Aldosterone deficiency or resistance	
Normal Anion-gap acidosis	Yes	Yes	yes	Yes
Urine anion gap	Positive	Positive	Positive	Negative
Minimum urine ph	> 5.5	Variable, > 5.5 if given an alkali load	< 5.5	5 to 6
Serum K	Low	Low	High	Low
% filtered bicarbonate excreted	< 10	> 15	< 10	< 10
Plasma [HCO3-], untreated	May be below 10 meq/L	Usually 14- 20 meq/L	Usually above 15 meq/L	
Daily acid excretion	Low	Normal	Low	High
GFR	Normal	Normal	Low	NA
Stones/nephrocalcinosis	Yes	No	No	No
Fanconi syndrome	No	Yes	No	No

Treatment of RTA

Type 1 RTA

Treatment of acidosis is generally indicated in type 1 RTA to allow normal growth to occur in children, to minimize stone formation, nephrocalcinosis, and possible osteopenia due to calcium loss from bone, and to diminish inappropriate urinary K losses.

Alkali supplement is the standard therapy. Enough alkali is usually prescibed to titrate the fraction of daily acid load that is not excreted. In adults, this is usually 1-2 meq/kg/day.

Patients are generally treated with NaHCO3 or sodium citrate. Many patients do not need potassium replacement since correction of acidemia leads to marked improvement in potassium wasting. However patients with significant hypokalemia, calcium stones, or nephrocalcinosis require potassium and are treated with potassium citrate or Polycitra (potassium citrate plus sodium citrate).

Type 2 RTA

Alkali therapy is required for normal growth in children and to prevent or treat osteopenia/osteomalacia in adults. Reversal of acidemia is difficult since the exogenous alkali is rapidly excreted in the urine. As a result, much higher doses of alkali are required in comparison to type 1 and 4 RTA. About 10-15 meq/kg/day of alkali is typically required to stay ahead of urinary excretion.

The preferred therapy is potassium citrate which also helps with potassium losses in this disorder. Thiazides are also sometimes used with low salt diet to reduce the amount of alkali required. Thiazides induced volume contraction can be used to enhance proximal HCO3- reabsorption leading to improvement in bicarbonaturia and renal acidification. If hypophosphatemia is present, vitamin D and phosphate supplement is also required.

Type 4 RTA

Therapy is aimed mainly at reducing serum potassium, as acidosis will usually improve once the hyperkalemic block of ammonium production is removed. All patients should be placed on a low potassium diet. Any drugs that suppresses aldosterone production or blocks aldosterone effects should be discontinued. Mineralocorticoid replacement with fludrocortisone will improve hyperkalemia and acidosis but is not appropriate with patients with hypertension or a history of heart failure. These patients are instead treated with a low potassium diet and a loop diuretic.

✓ Uremic Acidosis

Metabolic acidosis is a common complication of renal disease and results from an inability of the diseased kidney to excrete the daily dietary acid load. To understand the effects of acid base with progressive renal failure, it is first necessary to review the normal handling of acids.

The daily dietary acid load is primarily due to the generation of H2SO4 from the metabolism of sulphur containing amino acids. This acid is rapidly buffered by HCO3- and other buffers, leading to the formation of sodium sulphate salts.

H2SO4 + 2NaHCO3 ----- NA2SO4 + 2H2CO3 ----- 2CO2 + 2H2O + NA2SO4.

To maintain the steady state, both the 2H+ and the SO42- must be excreted in the urine. The excretion of H+ occurs via the excretion of titratable acids and more importantly, NH4+. Whilst, the excretion of SO42- anions depends on the capacity of the kidney to filter and reabsorb the anions.

In initial stages of chronic renal disease, as the number of functioning renal tubules are reduced, the tubular functions of the kidney are diminished and the kidney's

ability to produce NH4+ ions is affected, thus resulting in a reduction of hydrogen ions excreted and an increase in the amount of HCO3- ions excreted. The excretion of bicarbonate ions results in a reduction in plasma [HCO3-] and thus metabolic acidosis. On the other hand, initially in CKD, ultrafiltration occurs and glomerular filtration rate reduces at a much slower pace than is the loss of tubular function. Therefore, the excretion of sulphate and other organic and inorganic acid anions is not affected as their filtration by the kidney is maintained. In addition, the kidneys lose the capacity to reabsorb these anions due to loss in tubular function leading to further anion excretion. To maintain electroneutrality, the kidneys retain CI- with each bicarbonate ion lost and thus early renal disease is associated with a hyperchloremic metabolic acidosis. The anion gap is not affected due to the continued excretion of organic acids by the kidneys.

In advanced kidney disease as GFR falls below 20ml/min, the kidneys capacity to filter the anions of organic acids is significantly diminished and thus there is retention of phosphates, sulphates, urate and hippurate anions in the plasma that significantly raise the anion gap resulting in an elevated anion gap metabolic acidosis. *To summarize*: Early chronic kidney disease is associated with a hyperchloremic normal anion gap metabolic acidosis while end stage renal disease (uremia) is associated with an elevated anion gap metabolic acidosis.

In some cases of end stage renal disease, patients may also present with elevated anion and normal anion gap acidosis simultaneously. The acidosis associated with renal disease is usually not severe and this is due to the increased buffering of retained H+ ions by bone. This process is manifested by the release of calcium salts from bone and their excretion in urine. This calcium loss over time can lead to osteopenia.

Treatment

To prevent bone loss and possible osteopenia, alkali therapy is generally recommended even for mild metabolic acidosis associated with chronic renal disease. It is assumed that alkali replacement will prevent the harmful effects of prolonged positive H+ balance, including the persistent buffering of H+ ions by bone. Oral alkali is typically used to maintain the [HCO3-] over 20 meq/L. This can be accomplished with relatively modest amounts of alkali (1.0 to 1.5 mEq/kg per day). Usually this is amount of new bicarbonate generated each day.

Therapies include sodium bicarbonate and Shohl (sodium citrate). Sodium citrate (Shohl solution) has been shown to enhance the absorption of aluminum from the gastrointestinal tract and should never be administered to patients receiving aluminum-containing antacids because of the risk of aluminum intoxication.

• 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.

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

✓ GI Hydrogen Loss and Reduction in ECV

Loss of hydrogen ions leading to metabolic acidosis most commonly occurs via the GI tract in the form of vomiting or nasogastric suction. Gastric juice contains a high concentration of HCL and lesser concentration of KCL. Each meq of H+ ion secreted generates 1 meq of HCO3- which is then absorbed in the plasma. Under normal conditions the increase in the plasma HCO3- concentration is only transient, since the entry of acid into the duodenum stimulates an equal amount of HCO3- secretion from the pancreas. However there is no stimulus to HCO3- secretion if gastric juice is removed during vomiting and NG suction. The net result is an increase in the plasma [HCO3-] and metabolic alkalosis.

Under normal conditions, the excess HCO3- generated would be excreted in the urine by the kidney and thus alkalosis would not be maintained. However vomiting or nasogastric suction also results in a decrease in the extracellular fluid compartment

and the effective circulating volume (ECV). The reduction in the ECV leads to decreased GFR (less bicarb filtered), and also serves as a stimulus to increase angiotensin and aldosterone production leading to an increase in Na and HCO3-reabsorption by the proximal tubules. An increase in Na reabsorption leads to increased HCO3- reabsorption because of the increase in hydrogen secretion as Na is exchanged for H+ across the Na-H+ transporter in the proximal tubule. The secreted hydrogen ions combine with filtered HCO3- leading to reabsorption as previously described. Aldosterone primarily acts distally to increase H+ and K secretion resulting in increased acid and potassium excretion. The net result is a hypokalemic metabolic alkalosis. The almost complete reabsorption of HCO3- in the setting of reduced ECV, leads to the paradoxical finding of an acidic urine despite the presence of extracellular alkalosis.

✓ Contraction Alkalosis and Hypokalemia

Contraction alkalosis occurs whenever there is a loss in bodily fluid that does not contain HCO3- . In this setting, which is most commonly due to diuretics, the extracellular volume contracts around a fixed quantity of HCO3- resulting in a rise in [HCO3-]. Note that in this setting, the total body bicarbonate is the same as shown in the figure below.

The direct effect of contraction is largely minimized by the release of H+ from cell buffers, thereby lowering the plasma [HCO3-] toward normal. However, if ECF reduction by diuretics result in hypovolemia, then as in vomiting, the release of angiotensin and aldosterone will be stimulated. This then leads to an increase in HCO3- absorption and increased H and K secretion. The increase in potassium secretion result in the development of hypokalemia which also plays a very important role in maintaining the alkalosis.



✓ Hypokalemia

Hypokalemia is very commonly associated with metabolic alkalosis. This is due to 2 factors: 1) the common causes of metabolic alkalosis (vomiting, diuretics, mineralocorticoid excess) directly induce both H+ and K loss (via aldosterone) and thus also cause hypokalemia and 2) hypokalemia is a very important cause of metabolic alkalosis. Hypokalemia causes metabolic alkalosis by three mechanisms. The initial effect is by causing a transcellular shift in which K leaves and H+ enters the cells, thereby raising the extracellular pH. The second effect is by causing a

transcellular shift in the cells of the proximal tubules resulting in an intracellular acidosis, which promotes ammonium production and excretion. Thirdly, in the presence of hypokalemia, hydrogen secretion in the proximal and distal tubules increases. This leads to further reabsorption of HCO3-. The net effect is an increase in the net acid excretion.

✓ Posthypercapnia

The normal stimulus to respiratory acidosis is a compensatory increase in HCO3reabsorption by the kidney and thus an increase in plasma [HCO3-]. Treatment with mechanical ventilation in this disorder leads to a rapid reduction in the pCO2. The plasma HCO3- will however remain elevated, resulting in the development of metabolic alkalosis. The maintenance of alkalosis in this setting is unclear. However chronic respiratory acidosis is thought to be associated with CI- loss in the urine leading to hypovolemia and hypochloremia. Restoration of CI- and volume balance tends to correct the disorder.

✓ Mineralocorticoid excess

The common causes of metabolic alkalosis cause and maintain metabolic alkalosis due to hypovolemia induced secondary hyperaldosteronism which leads to increased acid excretion and hypokalemia. Conditions of mineralocorticoid excess such as Conn's syndrome, excess steroid administration and Cushing's syndrome produce a state of hyperaldosteronism which also leads to metabolic alkalosis and hypokalemia. In these conditions, the extracellular volume is expanded and the patient may have hypertension. In these patients, metabolic alkalosis is perpetuated by the effects of hypokalemia (not hypovolemia) which leads to increased ammonium production, hydrogen secretion and bicarbonate reabsorbtion

Diagnosis of Metabolic Alkalosis

Once it has been determined that a patient has metabolic alkalosis, the etiology is usually obvious from the history. If there is no pertinent history, then one can assume that the alkalosis is due to one of the three most common causes: 1) vomiting, 2) diuretics, 3) mineralocorticoid excess. To differentiate between these conditions, it is usually helpful to measure the urinary chloride concentration.

In causes of metabolic alkalosis associated with a reduction in the ECV, there will be a stimulus for avid Na and CI reabsorption to replenish extracellular volume. In these setting urinary CI should be expected to be very low, less than 25 meq/L.

Urinary Na is not a reliable measure of extracellular volume in this setting because if the alkalosis is such that not all of the filtered HCO3- can be reabsorbed, then some will be excreted with Na and the urinary Na may be high. Thus, it may appear that the volume status is euvolemic or hypervolemic when it is not.

If the urinary CI is low, indicating a hypovolemic state, then administration of NaCI and water to replenish the extracellular volume should stop the stimulus for aldosterone production and in turn should lead to appropriate excretion of excess HCO3- and improvement of hypokalemia. Thus, leading to correction of the metabolic alkalosis. Such causes of metabolic alkalosis are said to be saline responsive. *See table below.*

In contrast, states of mineralocorticoid excess are associated with an expanded volume and sometimes hypertension. The urinary CI will be high (> 40 meq/L). In these patients, administration of saline would further expand the extracellular volume and worsen hypertension. It would not correct the alkalosis which is primarily due to hypokalemia. Such causes of metabolic alkalosis are said to be saline resistant.

Urine Cl < 25 meq/L	Urine Cl > 40 meq/L
Saline Responsive	Saline Unresponsive
Vomiting or nasogastric suction Diuretics Posthypercapnia Cystic Fibrosis Low chloride intake	Primary mineralocorticoid excess Exogenous Alkali load Barrter's or Gitelman's syndrome Severe Hypokalemia (K< 2.0)

Causes of saline resistant metabolic alkalosis can further be distinguished based on whether or not the patient is hypertensive. Mineralocorticoid excess states tend to be associated with hypertension while exogenous alkali load, Barrters and Gitelman's syndrome are associated with normal blood pressure.

Treatment

Saline - Responsive metabolic alkalosis

- Re-expand volume with Normal Saline (Primary Therapy)
- Supplement with Potassium to treat hypokalemia (alkalosis associated with severe hypokalemia will be resistant to volume resuscitation until K is repleted)
- H+ blockers or PPIs if vomiting/NG suction to prevent further losses in H+ ions
- Discontinue diuretics
- Acetazolamide if NS contraindicated due to CHF. (Monitor for hypokalemia)
- HCI or NH4CI in emergency. (HCI can cause hemolysis, NH4CI should not be used in liver disease)
- Hemodialysis in patients with marked renal failure

Saline – Unresponsive metabolic alkalosis (Mineraldocorticoid excess)

- Surgical removal of mineralocorticoid producing tumor
- Aldosterone inhibitor
- ACE inhibitor.
- Discontinue steroids
- Potassium repletion (only intervention needed to treat the alkalosis)

• Respiratory Acidosis

Respiratory acidosis is a clinical disorder characterized by a low arterial pH (< 7.36), an elevation in the pCO2 (hypercapnia) and a compensatory increase in the plasma [HCO3-]. Hypercapnia also occurs in metabolic alkalosis, but this is rather a response to the high arterial pH, which distinguishes the two. Pathophysiology

As mentioned previously, breakdown of carbohydrates and fats result in the endogenous production of up to 20 mol of CO2. This CO2, if not excreted via ventilation will combine with H2O to form carbonic acid in the following reaction:

 $CO2 + H2O \leftrightarrow H2CO3 (CA) \leftrightarrow H+ + HCO3$ -Any increase in PCO2 due to increased CO2 production is rapidly handled by increased alveolar ventilation. Because of the lung's excellent capacity to excrete excess CO2, increases in PCO2 are always due to hypoventilation and never to increased CO2 production.

Hypoventilation can occur with any interference in the respiratory process. Common etiologies are neuromuscular disorders, CNS depression, disorders of the chest wall, chronic obstructive lung disease and acute airway obstruction.

Causes of respiratory acidosis

A) CNS depression

- 1. Opioids
- 2. Oxygen in patient with chronic hypercapnia
- 3. Central sleep apnea
- 4. CNS lesion
- 5. Extreme obesity (Pickwickian syndrome)

B) Neuromuscular disorders

- 1. Myasthenia gravis
- 2. Guillain-Barre
- 3. ALS
- 4. Poliomyelitis
- 5. Muscular dystrophy
- 6. Multiple Sclerosis
- C) Chest wall or Thoracic Cage Abnormality
 - 1. Kyphoscoliosis
 - 2. Flail Chest
 - 3. Myxedema
 - 4. Rib Fracture
 - 5. Scleroderma
- 4) Disorders affecting gas exchange
 - 1. COPD
 - 2. Severe asthma or pneumonia
 - 3. Pneumothorax or Hemothorax
 - 4. Acute pulmonary edema
- 5) Airway obstruction
 - 1. Aspiration of foreign body
 - 2. Obstructive sleep apnea
 - 3. Laryngospasm

Symptoms

Symptoms are caused by acute respiratory acidosis and not by chronic respiratory acidosis and usually include neurologic abnormalities. Initial symptoms include headache, blurry vision, restlessness, and anxiety, which can progress to tremors, asterixis, delirium, and somnolence or coma (CO2 narcosis). Severe hypercapnia increases cerebral blood flow and cerebrospinal fluid pressure. Signs of increased intracranial pressure such as papilledema may be seen.

The tendency to develop neurologic abnormalities in acute respiratory acidosis is due to the rapid reduction in CSF pH. CO2 is lipid soluble and rapidly crosses the blood brain border, leading to a decline in CSF pH. In contrast, HCO3- is a polar compound that does not readily cross the blood border and thus is not available to counteract the actions of CO2. Thus acute respiratory acidosis promotes a greater fall in CSF pH than acute metabolic acidosis, which may explain why neurologic abnormalities are seen less often in the latter. In chronic respiratory acidosis, the CO2 accumulates at a much slower rate, allowing renal compensation to return the arterial pH and ultimately CSF pH toward normal. Therefore neurologic abnormalities are also seldom seen in chronic respiratory acidosis.

Treatment

- Treat underlying disorder
- Supply oxygen
- Corticosteroids and bronchodilators to reduce airway inflammation and resistance.
- Mechanical ventilator if ventilation fails.

• Respiratory Alkalosis

Respiratory Alkalosis is an acid base disturbance characterized by elevated arterial pH, hyperventilation resulting in a low pCO2 and a usually compensatory decrease in plasma HCO3- concentration.

Pathophysiology

Respiratory Alkalosis results from an elevation in alveolar ventilation that causes a fall in the partial pressure of dissolved carbon dioxide. The fall in PCO2 causes a compensatory fall in plasma HCO3- concentration as was decribed previously. The causes of Respiratory Alkalosis are shown in the table below. It is very commonly induced by what the body or patient perceives as a stressor. The stressor which is often associated with anxiety, pain, and infection stimulates the CNS leading to hyperventilation. Other common causes are hypoxemia, sepsis, liver failure and PE. Aspirin intoxication is an interesting cause of respiratory alkalosis which can also cause an elvated anion gap acidosis.

A) CNS stimulation

- 1. pain
- 2. Anxiety, Psychosis
- 3. Fever
- 4. CVA

5. Meningitis, encephalitis

6. Tumor, trauma

7. Drugs: Salicylate (also causes metabolic acidosis), methylaxanthines, theophylline, aminophyllines.

8. Pregnancy, progesterone

B) Hypoxemia or tissue hypoxia

1. High altitude

2. Pulmonary disease: pneumonia, interstitial fibrosis, PE, pulmonary

edema

- 3. CHF
- 4. Hypotension
- 5. Severe anemia
- 6. Aspiration
- C) Chest Receptors stimulation
 - 1. Flail Chest
 - 2. Hemothorax
 - 3. PE

4) Miscellaneous disorders

- 1.Gram negative septicemia (very early clinical sign of septicemia)
- 2. Hepatic failure
- 3. Mechanical hyperventilation
- 4. Heat exposure
- 5. Recovery from metabolic acidosis

Clinical Manifestations

Clinical manifestations of respiratory alkalosis vary according to duration and severity and depend on the underlying disease process.

In acute respiratory alkalosis, acute onset of hypocapnia can cause cerebral vasoconstriction. Therefore, an acute decrease in PCO2 reduces cerebral blood flow and can cause neurologic symptoms, including dizziness, mental confusion, syncope, seizures, paresthesias, numbness around the mouth. This acute drop in PCO2, result in a substantial drop in CSF pH not seen in chronic respiratory alkalosis or metabolic alkalosis. In metabolic alkalosis, the change in CSF pH occurs much slower due to the relative inability of HCO3- to cross the blood brain barrier in comparison to CO2.

In addition some complaints may be unrelated to the change in pH. For example, patients with psychogenic hyperventilation often complain of chest tightness, headache, dyspnea, and other somatic symptoms that may be related to anxiety and not alkalemia.

Acute respiratory alkalosis also causes intracellular shift of potassium and phosphates potentially resulting in hypokalemia and hypophosphatemia. The hypokalemia is usually mild. Hypocalcemia typically results, due to an increase in albumin bound calcium and may lead to tetany and a positive Chvostek or Trousseau sign.

Treatment

- Treat the underlying cause: oxygen, diuretics, etc.
- For anxious patient, reassurance, rebreathing into paper bag (raises the inspired PCO2).
- Teach breath holding techniques during episodes.
- If intubated, reduce minute ventilation by adjusting rate, tidal volume.

Usually self limited since muscles weakness will suppress ventilation.

If the PaCO2 is corrected rapidly in patients with chronic respiratory alkalosis, metabolic acidosis may develop due to the previous compensatory drop in serum bicarbonate

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.

• Mixed metabolic disorders

1. 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
- 2. 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. 3. 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 apequately 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.

- 1. 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
- 2. Chronic Respiratory Acidosis and Anion Gap Metabolic Acidosis Example:
 - COPD patient who develops shock and lactic acidosis
- 3. 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)
- 4. Respiratory Alkalosis and Metabolic Acidosis
 - Example:
 - Salicylate intoxication
 - Gram negative sepsis
 - Acute cardiopulmonary arrest
 - Severe pulmonary edema

Please note that it is impossible to have more than one respiratory disorder in the same mixed disorder(i.e. concurrent respiratory alkalosis and respiratory acidosis)

III. Practice Cases

<u>Case 1</u>

Rami is a 40 year old moderately dehydrated man , who 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?

Answer (using the step by step approach)

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) = 10Since gap is less than 16, it is therefore normal.

5. Is compensation adequate? Calculate the estimated PCO2.

Using Winter's formula; $PCO2 = 1.5 \times [HCO3-]) + 8 \pm 2 = 1.5 \times 16 + 8 \pm 2 = 30-34$. 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.

<u>Case 2</u>

Rania is a 22 year old female with type I DM, who presented to the emergency department with a 1 day history of nausea, vomiting, polyuria, polydypsia and vague abdominal pain. On physical examination she had deep sighing breathing, orthostatic hypotension, and dry mucous membranes.

Labs: Na 132, K 6.0, Cl 93, HCO3- 11 glucose 720, BUN 38, Cr 2.6.

UA: pH 5, SG 1.010, ketones negative, glucose positive . Plasma ketones trace. ABG: pH 7.27 HCO3- 10 PCO2 23

What is the acid base disorder?

Answer (using the step by step approach)

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

- · Elevated anion gap acidosis secondary to DKA, or
- Elevated anion gap acidosis secondary to lactic acidosis in the setting of vomiting and polyuria which may lead to hypovolemia, and/or
- Metabolic alkalosis in the setting of vomiting

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 but not yet ruled out.

Again, need to distinguish the initial change from the compensatory response. A low HCO3- represents acidosis and is consistent with the pH, therefore it must be the initial change. To maintain the PCO2/HCO3-, the PCO2 is reduced in response. 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 - (CI + HCO3) = 132 - (93 + 11) = 28Since gap is greater than 16, it is therefore abnormal.

5. Is compensation adequate? Calculate the estimated PCO2.

Using Winter's formula; PCO2 = 1.5 × [HCO3-]) + 8 ± 2 = 1.5 ×11 + 8 ± 2 = 22.5 - 26.5.

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. 6. **Since anion gap elevated,** calculate the delta-ratio to rule out concurrent metabolic alkalosis.

Delta ratio = \triangle Anion gap = (AG - 12) ppppp= (28 - 12) pp= 16 = 1.2 Deppppppp \triangle [HCO3-]pa(24 - [HCO3-])ppppp(24 - 11) pp 13

Since the delta gap is between 1 and 2, we can deduce that this is a pure metabolic acidosis.

Assessment: Compensated elevated anion gap acidosis most likely secondary to DKA.

Note the absence of ketones in the urine. This is sometimes seen in early DKA due to the predominance of beta-hydroxybutyrate. The dipstick test for ketones detect acetoacetate but not beta-hydroxybutyrate.

Case 3

A previously well 55 year old woman is admitted with a complaint of severe vomiting for 5 days. Physical examination reveals postural hypotension, tachycardia, and diminished skin turgor. The laboratory finding include the following:

Electroyes: Na 140 , K 3.4, Cl 77 HCO3- 9, Cr 2.1

ABG: pH 7.23 , PCO2 22mmHg

What is the acid base disorder?

Answer (using the step by step approach)

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

- Elevated anion gap acidosis secondary to lactic acidosis in the setting of severe persistent vomiting which may lead to hypovolemia, and/or
- Metabolic alkalosis in the setting of persistent vomiting

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 but not yet ruled out.

Again, need to distinguish the initial change from the compensatory response. 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-) = 140 - (77 + 9) = 54Since gap is greater than 16, it is therefore abnormal. 5. Is compensation adequate? Calculate the estimated PCO2.

Using Winter's formula; $PCO2 = 1.5 \times [HCO3-]) + 8 \pm 2 = 1.5 \times 9 + 8 \pm 2 = 19.5 - 23.5$.

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. 6. **Since anion gap elevated,** calculate the delta-ratio to rule out concurrent metabolic alkalosis.

Delta ratio = \triangle Anion gap = (AG - 12) ppppp = (54- 12) pp = 36 = 3 Deppppppp \triangle [HCO3-]pa(24 - [HCO3-])ppppp(24 - 9) pp 14

Since the delta ratio is greater than 2, we can deduce that there is a concurrent metabolic alkalosis. This is likely due to vomiting.

Another possibility is a pre-existent high HCO3- level due to compensated respiratory acidosis. But we have no reason to suspect respiratory acidosis based on the history. Also you can calculate the underlying Metabolic alkalosis by adding the anion gap to the initial HCO3 measured when the patient was admitted to the hospital which is 54 plus 9 equal 63, which it means the bicarbonate was around 63 (metabolic alkalosis) before developing Metabolic acidosis .

Assessment: Mixed elevated anion gap metabolic acidosis and metabolic alkalosis likely due to lactic acidosis

Case 4

Kamel is a 70 year old man with history of CHF presents with increased shortness of breath and leg swelling.

ABG: pH 7.24, PCO2 60 mmHg, PO2 52 HCO3- 27

What is the acid base disorder?

Answer (using the step by step approach)

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

- · Acute respiratory acidosis secondary to acute pulmonary edema
- 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 but not yet ruled out.

Need to distinguish the initial change from the compensatory response. HCO3- is on the high side of normal and is not consistent with the pH. PCO2 is high and represents acidosis and is consistent with the pH. Therefore it must be the initial change. The high normal HCO3- must be the compensatory response. Since the primary change involves PCO2, this is a respiratory process, i.e. Respiratory Acidosis.

4. Is respiratory process acute or chronic, estimate expected extent of compensation.

If acute, expected compensation is \uparrow [HCO3-] = 1 mEq/L for every 10 mm Hg $\Delta PCO2$.

Change in PCO2 = 60- 40 = 20.

Therefore elevation in $[HCO3-] = 20/10 \times 1 = 2$.

This should increase the [HCO3-] to 26. Since the actual PCO2 is close to the estimated value, we can conclude that this is acute respiratory acidosis. Based on the PCO2, we may also calculate the expected pH in acute respiratory acidosis.

 $\Delta \text{ pH} = 0.008 \times \Delta \text{PCO2} = 0.008 \times (60 - 40) = 0.16$ Therefore expected pH = 7.4 - 0.16 = 7.24. Since the actual pH is consistent with expected value, acid base disorder likely due solely to acute respiratory acidosis and other acid base disorders are most likely not present.

Assessment: Acute respiratory acidosis likely secondary to pulmonary edema.

<u>Case 5</u>

Reem is a 28 year old female with history of Sjogren's syndrome presents to her PCP for a check up visit. In review of systems, she reports a 2 day episode of watery diarrhea 2 days ago. She is otherwise doing well. Physical examination is unremarkable. She is noted to have the following serum chemistry:

Na 138, K 4.2, CI 108, HCO3- 14

Because of her history, the physician decides to check her urine electrolytes. Urine chemistry: K 31, Na 100, Cl 105

What is the acid base disorder? What is the likely cause? Answer

1. **History**: Note that in this scenario, we are not given an arterial blood gas. Therefore we must deduce the diagnosis primarily from the history and the limited workup available.

The patients presents to an outpatient visit very asymptomatic. Besides the history of diarrhea, there is nothing else in the history to suggest an active acid base disorder. However, her serum electrolytes indicate a low HCO3- concentration which suggests acidosis.We can safely rule out a chronic respiratory alkalosis as basis of the low HCO3- since hyperventilation would be evident on exam. In the absence of other data, we have to assume that the patient has a metabolic acidosis.

We are not given serum electrolytes and therefore we cannot calculate the anion gap, but based on the history, we can assume that the patient does not have lactic acidosis, ketoacidosis, uremia and has not ingested any toxins.

Assuming the patient has normal anion gap acidosis, our differential becomes diarrhea vs RTA. We have to consider RTA in this patient, because of the history of Sjogren's.

2. Urine Anion Gap. We are given urine electrolytes and thus to distinguish between RTA and diarrhea, we can calculate the urine anion gap, otherwise known as the Urinary Net Charge. Remember that the UAG is an indirect measure of ammonium excretion, which should be very high in the presence of acidosis if renal function is not impaired.

UAG = Na + K - CI

UAG = 100 + 31 - 105 = 26.

A positive UAG suggest RTA because in the setting of diarrhea, ammonium chloride concentration in the urine would be high and the UAG would be negative. A postive value suggests that the kidney is unable to adequately excrete ammonium, leading to a reduction in net acid excretion and thus metabolic acidosis.

Assessment: Metabolic acidosis likely secondary to renal tubular acidosis.

Note that further workup is needed in order to distinguish the different types of RTA. Sjogren's is most commonly seen in type I RTA and is associated with hypokalemia and a urine pH that that does not fall beyond 5.3, even in the setting of increased acid load. Checking the urine pH after administration of NH₄Cl would establish the diagnosis.

<u>Case 6</u>

Mark is a 72 year old man with history of COPD presents to the hospital with alcoholic ketoacidosis.

Serum chemistry: Na 136, K 5.1, Cl 85, HCO3- 25, BUN 28, Cr 1.4, ABG: pH 7.20, PCO2 60, HCO3- 25, PO2 75

Urine ketones 2+

If the patient's previous anion gap was 12, what was his bicarbonate concentration prior to the onset of ketoacidosis?

Answer

The patient is acidemic, with a high PCO2 and a HCO3- that is slightly elevated. This would seem to suggest an acute respiratory acidosis. However we are told that the patient has developed alcoholic ketoacidosis which should produce an elevated anion gap metabolic acidosis. In that case we would expect the bicarbonate level to be very low, but it is not. This would suggest that the patient either has a concurrent metabolic alkalosis or that the bicarbonate level was very high prior to the onset of metabolic acidosis.

The patient is not vomiting or taking diuretics and there is no reason to supect a metabolic alkalosis. We are told of the history of COPD, which is commonly associated with chronic respiratory acidosis. In these patients, bicarbonate levels are very high due to renal compensation. Therefore we suspect that the patient had a high bicarbonate level prior to the onset of AKA. The metabolic acidosis from AKA caused a drop in his bicarbonate level, down to a normal level.

The anion gap is Na - (CI + HCO3) = 136 - (85 + 25) = 26, this confirms our suspicion of an elevated anion gap metabolic acidosis.

In patients with ketoacidosis, we suspect a 1:1 change in the elevation of the anion gap vs the reduction of the bicarbonate level. That is, the elevation in the anion gap will be matched by an equal reduction in bicarbonate. See delta ratio.

If the previous anion gap was 12, then change in AG = 26 - 12 = 14.

The change in bicarbonate should also be 14, therefore the previous bicarbonate level should be 14 + 25 = 39.

<u>Case 7</u>

Hanna is a 60 year old homeless man presents with nausea, vomiting and poor oral intake 2 days prior to admission. The patient reports a 3 day history of binge drinking prior to symptoms.

Labs : Serum chemistry: Na 132, K 5.0, Cl 104, HCO3- 16 , BUN 25, Cr 1.3, Glu 75 ABG: pH 7.30, PCO2 29, HCO3- 16, PO2 92

Serum albumin 1.0

Does the patient have an abnormal anion gap? Answer

The patient is acidemic with a low bicarb and low PCO2, suggesting metabolic acidosis. The patient is hyponatremic with a history of nausea, vomiting and poor intake. In this scenario, the metabolic acidosis may either be due to normal anion gap acidosis secondary to vomiting and/or lactic acidosis, ketoacidosis secondary to extreme volume loss and poor intake. To rule out lactic acidosis and ketoacidosis, we need to calculate the anion gap.

Anion gap = (Na-(Cl +HCO3-) = 132 -(104 +16) = 12

Note that the anion gap appears to be normal, and thus lactic acidosis appears unlikely. However, note also that the patient is severely hypoalbuminemic with a serum albumin of 1.0.

Because the anion gap is primarily determined by negatively charged plasma proteins such as albumin, we must adjust the normal value of the anion gap to more accurately reflect the albumin deficiency. 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) Therefore in this scenario, the normal anion gap should be:

Decline in albumin = 4 - 1 = 3 g/dl

Reduction in normal anion gap = $3 \times 2.5 = 7.5$

Adjusted anion gap = 12 - 7.5 = 4.5.

Note now that a calculated anion gap of 12 is high when compared to the adjusted anion gap of 4.5 .

Assessment: This patient has an elevated anion gap metabolic acidosis which may be due to lactic acidosis or ketoacidosis.

<u>Case 8</u>

Jean is a 50 year old insulin dependent diabetic woman was brought to the ED by ambulance. She was semi-comatose and had been ill for several days. Current medication was digoxin and a thiazide diuretic for CHF. Lab results

Serum chemistry: Na 132, K 2.7, Cl 79, HCO3-19 Glu 815, Lactate 0.9 urine ketones 3+

ABG: pH 7.41 PCO2 32 HCO3- 19 pO2 82

What is the acid base disorder?

Answer (using the step by step approach)

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

- · Elevated anion gap acidosis secondary to DKA
- Metabolic alkalosis in the setting of thiazide diuretics use.
- 2. Look at the pH.

Note that the pH is normal which would suggest no acid base disorder. But remember, pH may be normal in the presence of a mixed acid base disorder.

3. What is the process? Look at the PCO2, HCO3-.

PCO2 is low indicating a possible respiratory alkalosis. The HCO3- is also low indicating a possible metabolic acidosis. Because the pH is normal, we are unable to distinguish the initial, primary change from the compensatory response. We suspect however that the patient has DKA, and therefore should have a

metabolic acidosis with an anion gap that should be elevated. We can confirm this by calculating the anion gap.

4. Calculate the anion gap

The anion gap is Na - (Cl + HCO3-) = 132 -(79 + 19) = 34

Since gap is greater than 16, it is therefore abnormal and confirms the presence of metabolic acidosis.

Why is the pH normal? If the patient has metabolic acidosis, we suspect a low ph unless there is another process acting to counteract the acidosis, i.e alkalosis.

5. To rule out a metabolic alkalosis, let us check the delta ratio.

```
Delta ratio = \Delta Anion gap = (AG - 12) pppppp= (34 - 12) pp = 22 = 4.4
```

Deppppppp∆ [HCO3-]pa(24 - [HCO3-])ppppp(24 - 19) pp 5

Since the delta ratio is greater than 2, we can deduce that there is a concurrent metabolic alkalosis. This is likely due to to the use of thiazide diuretic. Note that DKA is often associated with vomiting, but in this case;vomiting was not mentioned. Another possibility is a pre-existent high HCO3- level due to compensated chonic respiratory acidosis. But we have no reason to suspect chronic respiratory acidosis based on the history.

Assessment: Mixed elevated anion gap metabolic acidosis and metabolic alkalosis likely due to DKA and thiazide diuretics.

References

- Shaw, Patricia, ed. Fluids & Electrolytes Made Incredibly Easy! Springhouse, PA: Springhouse
- Bernards WC. Interpretation of Clinical Acid-Base Data. Regional Refresher Courses in Anesthesiology. 1973 Vol 1 Chap. 2.
- Brackett NC et al. Carbon Dioxide Titration Curve of Normal Man. New Engl J Med. 1965; 272: 6-12
- Brackett NC et al. Acid Base Response to Chronic Hypercapnia in Man. New Engl J Med. 1969; 280: 124-130.
- Brivet F et al. Hyperchloraemic Acidosis during Grand Mal Seizure Lactic Acidosis. Intensive Care Med. 1994; 20: 27-31.
- Brimioulle S et al. Hydrochloric Acid Infusion for Treatment of Metabolic Alkalosis associated with Respiratory Acidosis. Crit Care Med. 1989; 17: 232-236.
- Bunker J. The Great Trans-Atlantic Acid-Base Debate. Anesthesiology 1965; 25: 591-4.
- Burrows FA. Con: pH-stat Management of Blood Gases is Preferable to Alpha-stat in Patients undergoing Brain Cooling for Cardiac Surgery. J Cardiothorac Vasc Anesth. 1995; 9: 219-221.
- Cohen RD & Woods HF. Lactic Acidosis Revisited. Diabetes 1983; 32: 181
- Lim VS et al. Acid-base Regulation in Pregnancy. Am J Physiol, 1976; 231: 1764
- Lu HC et al. Phenformin-associated Lactic Acidosis due to Imported Phenformin. Diabetes Care. 1996; 19: 1449-1450.
- Maren TH. Carbonic anhydrase: Chemistry, Physiology and Inhibition. Physiol. Rev. 1967; 47: 595-725.
- Munro JF et al. Euglycaemic Diabetic Ketoacidosis. Br Med J. 1973; 2: 578-80.
- Narins RG & Cohen JJ. Bicarbonate Therapy for Organic Acidosis: The Case for Its Continued Use. Ann Int Med. 1987;106: 615-618.
- Narins RG & Emmett M. Simple and Mixed Acid-Base Disorders: A Practical Approach. Medicine. 1980; 59: 161-187.
- O'Dwyer C et al. Determinants of Cerebral Perfusion during Cardiopulmonary Bypass. J Cardiothorac Vasc Anesth. 1996; 10: 54-64; quiz 65
- Oh MS & Carroll HJ. The Anion Gap. New Engl J Med 1977; 297: 814-817.
- Oh MS et al. Hyperchloremic Acidosis During the Recovery Phase of Diabetic Ketosis. Ann Int Med. 1978; 89: 925-7.
- Oster JR & Epstein M. Acid-Base Aspects of Ketoacidosis. Am J Nephrol. 1984; 4: 137
- Severinghaus JW. Siggaard-Andersen and the Great Trans-Atlantic Acid-Base Debate. Scand J Clin Lab Invest 1993; 53 Suppl 214: 99-104
- Severinghaus JW & Astrup PB. The Development of Electrochemistry. Int Anes Clin. 1987; 25: 1-25.
- Stephan H et al. Acid-base Management during Hypothermic Cardiopulmonary Bypass Does Not AffectCerebral Metabolism But Does Affect Cerebral Blood Flow and Neurological Outcome. Br J Anaesth. 1992; 69: 51-57.
- Stewart PA. Independent and Dependent Variables of Acid-Base Control. Resp Physiol 1978; 33: 9-26.
- Stewart PA. How to Understand Acid-Base. New York: Elsevier, 1981.
- Stewart PA. Modern Quantitative Acid-Base Chemistry. Can J Physiol Pharmacol. 1983; 61: 1444-1461.
- Swan RC & Pitts RF. Neutralization of Infused Acid by Nephrectomized Dogs. J Clin Invest. 1955; 34: 205-212.
- Tallman RD. Acid-Base Regulation, Alpha-stat and the Emporer's New Clothes. J Cardiothorac Vasc Anesth. 1997; 11: 282-288
- Walmsley RN & White GH. Normal Anion Gap (Hyperchloremic) Acidosis. Clin Chem 1985;31: 309-313.
- Walmsley RN & White GH. Mixed Acid-Base Disorders. Clin Chem. 1985; 31: 321-325.
- Worthley LIG. Hydrogen Ion Metabolism. Anaesth Intens Care. 1977; 5: 347-360.