

Pathophysiological Approach to Acid Base Disorders

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1. Introduction

In this chapter, we are presenting the review of the acid base disorders. The emphasis is on the pathophysiology and the underlying concepts.

The complicated formulas and graphs are avoided and things are explained in the simple language. The basic acid base disorders namely metabolic acidosis, metabolic alkalosis, respiratory acidosis and respiratory alkalosis are discussed in detail. When appropriate the information is presented in the table forms to make it clear. Important references are also given for the interested readers.

2. Basic concepts

2.1 Acid and base

According to the standard definitions, acid is a substance which can donate H^+ ion and base is a substance which can accept H^+ ion (Ali, 1994; Boron, 2006; Kellum, 2007).

Acids are of two types.

1. Volatile acids for example carbon dioxide (CO_2) which is regulated by the alveolar ventilation in the lungs.
2. Non-volatile acids for example lactic acid, sulfuric acid, phosphoric acid, uric acid and, keto acid. These acids may not be converted to CO_2 and hence must be removed from the body by the kidneys to keep the acid base in balance.

Acids and bases are also categorized according to their chemical behavior in the blood. They are called strong and weak. The strong acids and bases are completely ionized at the pH of 7.4. The weak acids and bases are ionized only partially at the pH of 7.4, depending upon their dissociation constant (pKa). Hydrochloric Acid (HCl) is a strong acid and Sodium Hydroxide (NaOH) is a strong base. Sodium Bicarbonate ($NaHCO_3$) is a weak acid (Boron, 2006; DuBose & Hamm, 1999; Kellum, 2007).

2.1.1 Acidemia

Acidemia is defined as an increase in H^+ concentration of the blood. Acidemia may also be defined as a decrease in arterial pH.

2.1.2 Alkalemia

Alkalemia is defined as a decrease in the H^+ concentration of the blood. Alkalemia may also be defined as an increase in arterial pH.

2.2 Normal concentrations

The normal concentration of H^+ in plasma or serum is 40 nmol/liter and it varies inversely with the HCO_3^- concentration.

The pH (Plasma concentration of H^+) is the negative log of H concentration. Thus,

$$pH = -\log (H^+).$$

The normal arterial pH is 7.40, normal partial pressure of carbon dioxide (PCO_2) is 40 mmHg. Normal serum bicarbonate (HCO_3^-) concentration is 24 mEq/L.

Concentration of ions in a solution should be written in brackets. For example, for hydrogen ions as (H^+). However for the convenience it is often written with out brackets.

When coagulation factors are removed from the plasma, it is called serum. For practical purposes, plasma and serum are the same as far as the clinical medicine is concerned (DuBose & Hamm, 1999).

2.3 Buffers

Buffers are weak acids, i.e. they do not dissociate completely at the pH of 7.4. They accept or donate H^+ ions to prevent large changes in the free H^+ ion concentration.

The body buffers are divided into 3 groups:

(1) Extracellular (2) intracellular, and (3) bone

2.3.1 Extracellular buffers

Bicarbonate is the most important extracellular buffer due to its high concentration and also due to its ability to control the PCO_2 by alveolar ventilation. This system plays a central role in the maintenance of acid-base balance. HCO_3^- is regulated by renal H^+ excretion and PCO_2 by the ventilation of lungs. Clinically, the acid base status of a person is expressed in terms of the principal extracellular buffer, the bicarbonate/ CO_2 system.

Relationship between acid and base is expressed by the following equation:

$$(H^+) = 24 \times CO_2 \div (HCO_3^-)$$

Henderson-Hasselbalch equation is the modified form of the above simpler equation:

Henderson-Hasselbalch equation:

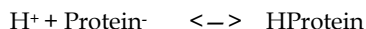
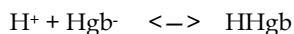
$$pH = 6.10 + \log (HCO_3^-) \div (0.03 \times PCO_2)$$

pH is $(-\log H^+)$, 6.10 is the pKa, 0.03 is solubility constant for CO_2 in the extracellular fluid, and PCO_2 is the partial pressure of carbon dioxide in the extracellular fluid.

Other, less important buffers in the extracellular fluid are phosphates and the plasma proteins.

2.3.2 Intracellular buffers

The intracellular buffers are phosphates, hemoglobin (Hgb), and proteins.



2.3.3 Bone

It is an important buffer for acid and base loads with as much as 40 percent contribution in buffering (Halperin & Goldstein, 2002; Kellum, 2005).

3. Types of acid base disorders

There are four types of acid base disorders. A patient may present with one (simple) or more than one (mixed) disorder.

Metabolic Acidosis

Metabolic Alkalosis

Respiratory Acidosis

Respiratory Alkalosis

3.1 Acidosis

Acidosis is a process which tends to raise the hydrogen ion (H^+) concentration.

3.1.1 Metabolic acidosis

When the process of acidosis is primarily due to retention of non volatile acid or due to bicarbonate loss, it is called metabolic acidosis. The arterial pH is low as well as serum bicarbonate concentration (Kraut & Madias, 2010).

3.1.2 Respiratory acidosis

When the process of acidosis is primarily due to CO_2 retention, it is called respiratory acidosis. The arterial pH is low and PCO_2 is high (Corey, 2005).

3.2 Alkalosis

Alkalosis is a process which tends to lower the hydrogen (H^+) concentration.

3.2.1 Metabolic alkalosis

When the process of alkalosis is primarily due to loss of non volatile acid or due to retention of bicarbonate, it is called metabolic alkalosis. The arterial pH is high as well as serum bicarbonate concentration (Corey, 2005).

3.2.2 Respiratory alkalosis

When the process of alkalosis is primarily due to CO_2 loss, it is called respiratory alkalosis. The arterial pH is high and PCO_2 is low.

Acidosis and alkalosis are the processes. Acidemia and alkalemia are the end result of these processes. Acidosis induces acidemia and alkalosis induces alkalemia.

In the body, these processes of acidosis and alkalosis never stop and one should use the terms acidosis and alkalosis rather than acidemia and alkalemia.

3.3 Compensations

The body responds to acid and base disorder by changes to bring the pH towards normal value. In respiratory disorders, bicarbonate (HCO_3) changes to compensate. In metabolic disorders, partial pressure of carbon dioxide (P CO_2) changes to compensate. It is worthy of note that compensation always occurs in the same direction as the primary disorder (Adrogue & Madias, 1998; Corey, 2005).

4. Acute and chronic

Respiratory acidosis and respiratory alkalosis are divided into two groups, acute and chronic, on the basis of their compensation. There are no plasma buffers for respiratory acidosis or alkalosis. The role of intracellular buffers and bone buffers is minor. The renal compensation takes about 3 to 5 days to complete.

Hence the acute phase continues for 3 to 5 days. Once full renal compensation is in place, the respiratory acidosis and respiratory alkalosis are called chronic.

On the other hand, metabolic acidosis and metabolic alkalosis are not divided into acute and chronic groups. However, sometimes the terms acute metabolic acidosis or alkalosis, and chronic metabolic acidosis or alkalosis are used. They indicate the time period, and not the compensatory response. In the metabolic disorders, the plasma buffers act immediately and respiratory compensation occurs quickly with in minutes to hours, so the acute phase, if any, is very brief (Schrier, 2003).

5. Diagnosis of acid base disorders

Evaluation of any acid-base disorder requires measurement of arterial blood gases (ABGs) and serum bicarbonate (HCO_3) concentration. The Henderson-Hasselbalch equation shows that the pH is determined by the ratio of HCO_3 concentration to PCO_2 .

In metabolic acidosis, the primary event is a drop in the serum HCO_3 and P CO_2 drops as a secondary response. In respiratory alkalosis, the primary event is a drop in PCO_2 and bicarbonate drops as a secondary event. PCO_2 and HCO_3 both will be low in metabolic acidosis as well as in respiratory alkalosis. The pH will be low in metabolic acidosis and high in respiratory alkalosis (Boron, 2006; Corey, 2005; DuBose & Hamm, 1999; Kellum, 2007; Lowenstein, 1993).

Similarly, PCO_2 and HCO_3 will be high in metabolic alkalosis as well as in respiratory acidosis. The pH will be high in metabolic alkalosis and low in respiratory acidosis.

Disorder	Primary Event	Secondary Event	pH
Metabolic Acidosis	HCO_3 Low	PCO_2 Low	Low
Metabolic Alkalosis	HCO_3 High	PCO_2 High	High
Respiratory Acidosis	PCO_2 High	HCO_3 High	Low
Respiratory Alkalosis	PCO_2 Low	HCO_3 Low	High

Table 1. Compensation in Simple Acid Base Disorders (Direction of primary and secondary event is always same)

The second step in the diagnosis of acid base disorders is to evaluate the degree of compensation. Once the disorder is diagnosed, the degree of compensation should be assessed. The expected degree of compensation is predefined on the basis of studies and experiments done by the scientists (Table 2).

Type of Disorder	Primary Change	Compensation Response	Expected pH
Metabolic Acidosis	Low HCO_3^-	1.2 mm Hg drop in PCO_2 for every 1 mEq/L drop in HCO_3^- (1.2 : 1) OR $\text{PCO}_2 = 1.5 \text{HCO}_3^- + 8 \pm 2$	Last 2 digits of PCO_2
Metabolic Alkalosis	High HCO_3^-	0.7 mm Hg rise in PCO_2 for every 1 mEq/L rise in HCO_3^- (0.7 : 1)	From Henderson-Hasselbalch equation
Acute Respiratory Acidosis	High PCO_2	1 mEq/L rise in HCO_3^- for every 10 mm Hg rise in PCO_2 (1 : 10)	0.08 drop in pH for every 10 mm Hg rise in PCO_2
Chronic Respiratory Acidosis	High PCO_2	3.5 mEq/L rise in HCO_3^- for every 10 mm Hg rise in PCO_2 (3.5 : 10)	0.03 drop in pH for every 10 mm Hg rise in PCO_2
Acute Respiratory Alkalosis	Low PCO_2	2 mEq/L drop in HCO_3^- for every 10 mm Hg drop in PCO_2 (2 : 10)	0.08 rise in pH for every 10 mm Hg drop in PCO_2
Chronic Respiratory Alkalosis	Low PCO_2	4 mEq/L drop in HCO_3^- for every 10-mm Hg drop in PCO_2 (4 : 10)	0.03 rise in pH for every 10 mm Hg drop in PCO_2

Table 2. Expected Degree of Compensatory Responses

5.1 Metabolic acidosis

The diagnosis of a simple metabolic acidosis requires low serum bicarbonate and a low extracellular pH.

5.1.1 Mechanism of acid production

The pathophysiology is better understood if we classify the metabolic acidosis on the basis of the mechanisms of acid production (Table 3).

(1) Increased Acid (H^+) Generation

In these disorders, there is either an increased H^+ generation due to deranged metabolism in the body or by the increased administration of chemicals which are the source of H^+ ions. Examples of the first are lactic acidosis, keto acidosis and examples of the later are methanol poisoning, ethylene glycol poisoning, and salicylate poisoning.

(2) Increased Loss of HCO_3^-

In these disorders, the primary event is loss of HCO_3^- , which in turn leaves behind H^+ ions. Examples are diarrhea, ureteral diversion, and proximal renal tubular acidosis (RTA type 2).

(3) Diminished Renal Acid (H^+) Excretion

In these disorders, there is decreased excretion of acid (H^+) from the kidneys. The kidneys are responsible for removing the daily non volatile acid load and to increase the H^+ excretion in case of metabolic acidosis. Obviously, when kidneys themselves are not competent, metabolic acidosis will occur. Examples of decreased acid (H^+) excretion are renal failure, distal renal tubular acidosis (RTA type 1), and RTA type 4.

Increased Acid (H⁺) Generation
Lactic acidosis Ketoacidosis Methanol Poisoning Ehylene Glycol Poisoning Salicylate Poisoning
Increased Loss Of HCO₃
Diarrhea Ureteral diversion Proximal renal tubular acidosis(Type 2)
Diminished Renal Acid (H⁺) Excretion
Renal failure Distal renal tubular acidosis (type 1) Renal tubular acidosis type 4

Table 3. Important Causes of Metabolic Acidosis (According to the Mechanism)

5.1.2 High and normal anion gap

Metabolic Acidosis may also be divided in two groups according to the serum anion gap.

1. High Serum Anion Gap Metabolic Acidosis
2. Normal Serum Anion Gap Metabolic Acidosis (Table 4)

The terms gap and non gap metabolic acidosis are used sometimes. There is always an anion gap, normal, high, low, or negative. The gap/no gap terminologies should be abandoned.

Increased Anion Gap
Advaned Renal Failure Lactic acidosis Ketoacidosis Methanol Poisoning Ehylene Glycol Poisoning Salicylate Poisoning
Normal Anion Gap
Early Stages of Renal Failure Renal Tubular Acidosis (all types) Diarrhea Ureteral diversion

Table 4. Important Causes of Metabolic Acidosis (According to the Serum Anion Gap)

Serum Anion Gap (Serum AG) is the difference between the routinely measured cations i.e. sodium (Na) and sum of routinely measured anions i.e. chloride (Cl) and bicarbonate (HCO_3^-). It can be calculated from the following formula:

Serum AG = Routinely Measured Cations - Routinely Measured Anions

$$\text{Serum AG} = \text{Na} - (\text{Cl} + \text{HCO}_3^-)$$

Although, serum potassium (K) is also routinely measured but it is omitted from calculations. The reasons for omission of K from calculation are twofold. First, its serum concentration range is small, and second, if it is changed drastically, patient will succumb to its consequences before the change in the anion gap is considered.

The serum anion gap may also be written as following.

Serum AG = Unmeasured anions - Unmeasured cations

Unmeasured anions are albumin, lactate, sulfate, urate, phosphate, and other anions. Unmeasured cations are potassium, magnesium, calcium, and other cations. Serum AG will increase when there is a rise in the unmeasured anions or fall in the unmeasured cations.

The serum anion gap (AG) will not increase if the H^+ ion is accompanied by chloride. Serum AG will increase if acid H^+ accompanies an anion other than chloride.

The normal range of the serum AG is 10 ± 3 meq/L. Negatively charged serum albumin contributes most of the serum AG. One g/dL of serum albumin is equal to 2.5 meq/L of anion gap.

Examples of normal AG metabolic acidosis are diarrhea and RTA.

Examples of high AG metabolic acidosis are lactic acidosis, keto acidosis, renal failure, methanol poisoning, and ethylene glycol poisoning (Corey, 2005; Emmett & Narins, 1997; Fidkowski & Helstrom, 2009).

5.1.3 Delta anion gap/delta bicarbonate

The ratio of increase in serum Anion Gap to decrease in plasma bicarbonate is called Delta AG (ΔAG)/Delta HCO_3^- (ΔHCO_3^-) ratio, or just Δ/Δ ratio. It is a useful tool in sorting out the cause of metabolic acidosis.

In case of high anion gap metabolic acidosis, the drop in HCO_3^- should match the rise in the AG. In other words, the Δ/Δ ratio should be 1:1. In lactic acidosis, AG increases more than the drop in serum HCO_3^- and Δ/Δ ratio may be as high as 1.6:1.

The reason for this discrepancy is buffering of the part of the H^+ by the intracellular and bone buffers. The part of the H^+ which is taken care by the intracellular and bone buffers does not lower the serum HCO_3^- concentration. The accompanied anion (lactate) remains in the extracellular fluid and raises the AG.

In ketoacidosis, the $\Delta \text{AG}/\Delta \text{HCO}_3^-$ ratio is usually 1:1 due to partial excretion of ketones from the kidneys which balance out the intracellular and bone buffering. In mixed high anion gap and normal anion gap metabolic acidosis, the $\Delta \text{AG}/\Delta \text{HCO}_3^-$ ratio will be less than one (Fidkowski & Helstrom, 2009; Kellum, 2007; Rastegar, 2007).

In mixed metabolic alkalosis and metabolic acidosis, the $\Delta \text{AG}/\Delta \text{HCO}_3^-$ ratio will be more than 2. In this case, the drop in HCO_3^- is much less than the rise in AG due to concomitant metabolic alkalosis.

In the following paragraphs urinary anion gap, urinary osmolar gap, and serum osmolar gap are explained. These are the commonly used investigations in solving the complicated acid base disorders.

5.1.4 Urinary anion gap

The urinary anion gap is the difference between major urinary cations (sodium and potassium) and major urinary anions (chloride). It is calculated as follows:

$$\text{Urinary Anion Gap} = (\text{Na} + \text{K}) - (\text{Cl})$$

Urinary AG is an indirect measurement of urinary ammonium (NH_4^+) excretion. Negative value means chloride concentration of urine is higher than the sum of sodium and potassium. Negative urine AG is an appropriate response to metabolic acidosis. An increased NH_4^+ excretion results in enhanced acid removal from the kidney, for example, in diarrhea (DuBose TD Jr, et al. 1991; Oh & Carrol, 2002; Rose et al., 2001; Schoolwerth, 1991). Positive value means chloride concentration of urine is less than the sum of sodium and potassium. Positive urine anion gap indicates decreased NH_4^+ excretion, and decreased acid removal from the kidney, for example in renal tubular acidosis (Battlle et al., 1988).

5.1.5 Urinary osmolar gap

Just like urinary AG the urine osmolar gap (UAG) is a measure of urinary NH_4^+ excretion. An advantage of urine osmolar gap is that, it is not dependent on urinary chloride. It takes account of all the urinary anions accompanied with ammonium. It is calculated as follows:

$$\text{Urinary Osmolar Gap} = \text{Measured urine osmolality} - \text{Calculated urine osmolality}$$

$$\text{Calculated urine osmolality} =$$

$$2 \times (\text{Na} + \text{K}) + \frac{\text{Urine Urea Nitrogen}}{2.8} + \frac{\text{Urine Glucose}}{18}$$

In the above formula, 2 indicates the anions accompanying sodium and potassium. Na and K are in meq/L, Urea Nitrogen and glucose are in mg / dl. (Kamel et al., 1990).

5.1.6 Serum osmolar gap

It is the difference between measured serum osmolality and calculated serum osmolality. Measured serum osmolality includes all the serum osmoles. Calculated osmolality includes only some selected ones (Kamel et al., 1990).

Calculated Serum Osmolality =

$$2 \times \text{Na} + \frac{\text{Blood Urea Nitrogen mg/dl}}{2.8} + \frac{\text{Blood Glucose mg/dl}}{18}$$

In the above formulas, 2 indicates the anions accompanying sodium.

Normal serum osmolar gap is about 5 to 10. Examples of high osmolar gap metabolic acidosis are methanol and ethylene glycol intoxication. There are conditions when serum osmolar gap is high with out acidosis, eg. mannitol infusion and ethanol ingestion (Lynd et al., 2008).

6. Stewart approach

Traditionally, the hydrogen ion concentration (pH) of blood is expressed as a function of the ratio of PCO_2 and serum HCO_3^- based upon Henderson-Hasselbalch equation.

An alternative approach was proposed by Stewart, which is called Stewart's approach or strong ion difference (SID) approach.

The SID is the difference between the concentration of strong cations and concentration of strong anions in the plasma. Major strong cations are Na^+ , K^+ , Ca^{++} , Mg^{++} , and the major strong anions are Cl^- and lactate.

According to SID approach, there are six primary acid-base disturbances. These are respiratory acidosis, respiratory alkalosis, strong ion acidosis, strong ion alkalosis, nonvolatile buffer ion acidosis, and nonvolatile buffer ion alkalosis.

Stewart proposed that the serum bicarbonate concentration is not independent and does not play an active role in the determination of the H^+ concentration. According to Stewart's theory of SID, the plasma concentrations of nonvolatile weak acids and PCO_2 are independent variables. Nonvolatile total weak acids are phosphate and charges of albumin. The pH depends upon these three variables and not on $\text{HCO}_3^- / \text{PCO}_2$ ratio.

The SID method was presented by Stewart as an alternative to serum AG method for solving the acid-base problems. However, it did not get the popularity. Many physiologists believe that Stewart's method does not give any additional information if serum AG is corrected for serum albumin concentration (Fidkowski & Helstrom, 2009; Kellum et al., 1995).

7. Modified base excess method

Base excess is the amount of acid or base that must be added to the solution to bring the pH to 7.4 at PCO_2 of 40 mmHg and temperature of 37° C. Negative base excess means there is acidemia and positive base excess means there is alkalemia. The modified or sometimes called "standardized base excess method" is based upon Stewart's theory. It may be defined as the amount of strong acid or strong base required to bring the pH to 7.4 and PCO_2 to 40 mmHg (Fidkowski & Helstrom, 2009; Kraut & Madias, 2007; Rastegar, 2009).

Arterial Blood Gas machine gives a calculated base excess value. Any therapeutic decision can not be taken on this calculated value because of two reasons. First, it may give a false value of zero when metabolic acidosis and metabolic alkalosis coexist. Second, it is impossible to predict the PCO_2 level and pH after correcting the base excess or deficit.

This standardized base excess method does not give any advantage over traditional Henderson-Hasselbalch equation based methods.

In the following paragraphs important causes of metabolic acidosis are discussed.

8. Chronic and acute renal failure

The new name for chronic renal failure is chronic kidney disease and the new name for acute renal failure is acute kidney injury. Metabolic acidosis in renal failure results from reduced number of functioning nephrons. The single nephron function is intact.

The initial stages of renal dysfunction give rise to normal anion gap and later stages give rise to high anion gap metabolic acidosis. The anions accompanying the acid are sulfate, phosphate and urates. In early stages of renal failure, these anions are excreted without problem; thus the anion gap remains normal.

In latter stages of renal failure, there is retention of these unmeasured anions and high anion gap metabolic acidosis develops (Kraut & Kurtz, 2005; Narins & Emmett, 1980).

9. Methanol and ethylene glycol intoxication

Methanol and ethylene glycol are ingested for pleasure as a substitute for ethanol, and also in the suicidal attempts, or taken accidentally. Moonshine is a nick name of methanol when it is made illegally or locally using the radiators of the motor vehicles. Antifreeze solution contains high concentration of ethylene glycol (Lynd et al., 2008).

9.1 Methanol

Methanol is oxidized to formate by alcohol dehydrogenase and aldehyde dehydrogenase. Formate causes retinal injury with optic disc edema, blindness which may be permanent and basal ganglia injury.

High anion gap metabolic acidosis develops, due to accumulation of formate (formic acid). Serum AG is increased. (Kraut & Kurtz, 2008). Serum osmolar gap is increased.

9.2 Ethylene Glycol

Ethylene Glycol is metabolized to glycolate (glycolic acid), oxalate (oxalic acid), and glyoxylate by alcohol dehydrogenase and aldehyde dehydrogenase. Renal failure occurs due to renal tubular damage by glycolic acid and precipitation of oxalate crystals in the kidneys. High anion gap metabolic acidosis develops due to accumulation of glycolic acid and oxalic acid. Serum AG is increased. (Kraut & Kurtz, 2008). Serum osmolar gap is increased.

10. Lactic acidosis

Lactic acidosis is one of the most common causes of metabolic acidosis. Lactic acid is derived from the metabolism of pyruvic acid, which is generated from glucose and amino acids. Increased anaerobic metabolism lead to increased lactate production. The lactate produced in lactic acidosis is L-Lactate type, the accumulation of which gives rise to high anion gap.

The causes of lactic acidosis can be divided into type A, and type B. Type A lactic acidosis is associated with obviously impaired tissue oxygenation, for example, in shock, sepsis, hypovolemia, and cardiac failure.

In type B lactic acidosis, the impairment in oxygenation is not apparent. There is mitochondrial dysfunction due to toxins and drugs like metformin and nucleoside reverse transcriptase inhibitors (NRTIs).

10.1 D-lactic acidosis

D-lactate is produced in the colon from metabolism of starch and glucose by the gram-positive anaerobes. In the setting of short bowel syndrome and malignancy, over production of D-lactate with severe metabolic acidosis may occur. Diagnosis may be difficult because the usual assays used in laboratories detect only L-lactate.

11. Ketoacidosis

Ketoacids are derived from metabolism of fatty acids in the liver. Normal metabolism of fatty acids give rise to formation of triglycerides, CO₂, water, and ketoacids. However in the absence of insulin, ketoacids are produced out of proportion and cause acidosis.

Ketoacids are; (1) β -Hydroxy butyric acid, and (2) Acetoacetic acid. Acetone is often grouped with Ketoacids but it is not an acid.

Uncontrolled Diabetes Mellitus is the most common cause of Ketoacidosis. Starvation and excessive alcohol intake may also give rise to mild to moderate ketoacidosis. Diagnosis of Ketoacidosis requires documentation of Ketones in the blood or urine (Arieff & Carroll, 1972).

12. Dilutional metabolic acidosis

It is due to a fall in the serum bicarbonate concentration secondary to extracellular volume expansion by non bicarbonate fluid. Massive amounts of normal saline infusion may produce dilutional acidosis. It is not a clinically significant entity and only of academic interest

13. Salicylate poisoning

Aspirin (acetyl salicylic acid) poisoning results in mixed respiratory alkalosis and metabolic acidosis. Metabolic acidosis is due to accumulation of salicylic acid as well as lactic acid and ketoacids. Liver plays an important role in the detoxification of salicylate. In case of overdose, this system of detoxification saturates and results in deposition of salicylates in the tissues including brain.

14. Renal Tubular Acidosis (RTA)

There are 3 types of RTA:

Distal RTA (type 1)

Proximal RTA (type 2)

Hyporenin hypoaldosteronism (RTA type 4)

There is a Type 3 RTA also which is a rare autosomal recessive disorder due to carbonic anhydrase II deficiency and has features of both distal and proximal RTA (Table 5).

	Type I Distal RTA	Type II Proximal RTA	Type IV RTA
Primary defect	Decreased distal acidification	Decreased proximal HCO_3^- reabsorption	Aldosterone deficiency Renin deficiency
Urine pH	> 5.3	Variable	Usually < 5.3
Plasma HCO_3^- meq/L	Usually < 10	Usually 15-20	Usually > 15
Fractional excretion of HCO_3^-	< 3%	15 to 20 %	< 3 %
Other abnormalities	Nephrocalcinosis, nephrolithiasis	Osteomalacia	Common in diabetics
Plasma Potassium	Usually low	Usually low	High

Table 5. Comparison of Renal Tubular Acidosis

14.1 Distal RTA (type 1)

In distal RTA, the main problem is impaired secretion of acid (H^+) from the intercalated cells of the collecting tubules. Collecting tubules has two types of cells (1) principal cells, which are responsible for sodium and potassium balance, and (2) intercalated cells which are responsible for (H^+) secretion and maintenance of acid base balance.

As a result of decreased H^+ secretion, there is decreased ammonium (NH_4^+) and decreased titratable acid excretion. Titratable acid means the acid removed by phosphate buffer system of urine. Anion Gap is normal because of retention of chloride along with H^+ ions.

Nephrocalcinosis and nephrolithiasis are known complication of RTA type 1. High urine pH facilitates calcium phosphate precipitation and stone formation in the renal tubules and urinary collecting system (Batlle et al., 2006; Karet, 2009; Rodríguez, 2002).

14.2 Proximal RTA (type 2)

In RTA type 2, the proximal bicarbonate (HCO_3^-) reabsorption threshold is reduced and this results in the loss of filtered HCO_3^- . Once a new steady state is achieved with low serum HCO_3^- the loss of bicarbonates ceases. Urine pH is initially high due to bicarbonaturia and later may drop to less than 5.3 in untreated persons.

14.3 Type 4 RTA

In type 4 RTA, the primary defect is decreased potassium (K) secretion from the distal nephron, mainly collecting tubules due to aldosterone deficiency or resistance. The decreased H^+ secretion and subsequent metabolic acidosis is secondary to defective K secretion. Most common cause of Type 4 RTA is hyporenin hypoaldosteronism syndrome. A decreased K secretion results in hyperkalemia and its treatment improves metabolic acidosis (Rodríguez, 2002).

15. Metabolic alkalosis

There are two stages of metabolic alkalosis:

(1) Generation of alkalosis, and (2) Maintenance of alkalosis

The kidneys are very efficient in correcting the metabolic alkalosis by excreting out the extra bicarbonate. Only generation of alkalosis is not sufficient to produce alkalemia. There must be some other factors present to maintain the alkalosis. Hypovolemia and hypochloremia are the most important etiologies responsible for maintenance of alkalosis (Table 6 and 7) (Khanna & Kurtzman, 2006).

15.1 Urine chloride

Measurement of urine chloride concentration is a key test used in solving the differential diagnosis of metabolic alkalosis. It differentiates between hypovolemic and euvolemic states. In metabolic alkalosis, urine chloride is more reliable indicator of volume status as compared to urine sodium. Urine sodium may be high in spite of hypovolemia in metabolic alkalosis. It is due to the obligatory loss of sodium along with bicarbonate spill over.

Based upon urine chloride concentration, the causes of metabolic alkalosis may be divided in two groups (Table 8).

15.2 Saline responsiveness

Metabolic alkalosis may also be classified according to the response to saline administration. Urine chloride will be low in saline responsive alkalosis. Urine chloride may be high or low in saline resistant alkalosis.

Renal Loss of Acid (H⁺) Diuretics Hypermineralcoricoidosis Post Hypercapnia
Gastrointestinal Loss of Acid (H⁺) Vomiting Nasogastric Suction Chloride Loosing Diarrhea
Addition of Bicarbonate Administration of Sodium Bicarbonate Blood transfusion Milk Alkali Syndrome
Trans cellular Shift Hypokalemia
Excessive Hypotonic Fluid Loss Contraction Alkalosis

Table 6. Important Causes of Metabolic Alkalosis (According to the mechanism)

Factors Responsible for Maintenance of Metabolic Alkalosis
Volume Depletion Effective Circulatory Volume Depletion Chloride Depletion Hyperaldosteronism Hypokalemia

Table 7. Factors Responsible for Maintenance of Metabolic Alkalosis.

Causes of Metabolic Alkalosis (According to Urine Chloride Concentration)	
Urine Chloride Concentration	
Less Than 20 meq/L Hypovolemia Vomiting Nasogastric Suction Posthypercapnia	More than 40 meq/L Diuretics Hyperaldosteronism Bicarbonate Administration Bartter’s Syndrome Gitelman’s Syndrome

Table 8. Causes of Metabolic Alkalosis

15.3 Saline responsive

In these conditions, correction of hypovolemia will result in increased delivery of chloride and sodium to the distal nephron which will result in increased sodium bicarbonate excretion. Examples: Vomiting, Nasogastric Suction, Diuretics, Posthypercapnia.

15.4 Saline resistant

In these conditions, the specific treatment of underlying cause is required to correct the alkalosis. Edematous states may respond to saline but may develop pulmonary edema and worsening of peripheral edema.

Examples: Congestive heart failure, Cirrhosis, Mineralocorticoid excess, Hypokalemia and Renal Failure.

Pathophysiology of the important causes of metabolic alkalosis is discussed below.

15.5 Gastrointestinal losses

The secretion of bicarbonate from the pancreas depends upon stimuli by the acid coming from stomach to the duodenum. Vomiting or nasogastric tube drainage prevents the acid from reaching the duodenum resulting in the decreased secretion of bicarbonate. The hydrochloric acid (HCl) loss and retention of bicarbonate results in metabolic alkalosis.

15.6 Diuretics

The loop diuretics are the common cause of metabolic alkalosis. They produce alkalosis by volume contraction, increased urinary H^+ loss and hypokalemia.

15.7 Hyperaldosteronism

Primary and secondary mineralocorticoid excess results in metabolic alkalosis. It is primarily due to increased acid secretion from the distal nephron.

15.8 Post hypercapnic alkalosis

Rapid lowering of the blood carbon dioxide (CO_2) in chronic CO_2 retainers will cause post hypercapnic metabolic alkalosis. Chronic retention of CO_2 stimulates renal HCO_3^- retention to compensate for respiratory acidosis. Once CO_2 content of the blood is reduced quickly, for example, by ventilator, the compensated HCO_3^- component is unmasked resulting in metabolic alkalosis.

15.9 Milk alkali syndrome

Excessive intake of calcium salts, for example calcium carbonate, may result in metabolic alkalosis, especially in renal failure. Carbonate is converted to HCO_3^- in the body and calcium decreases HCO_3^- excretion from the kidneys. It is called milk alkali syndrome because of its association with milk intake which contains large amounts of calcium.

15.10 Hypokalemia

Decreased plasma potassium (K^+) level causes shift of K^+ from intracellular to extra cellular fluid, in an attempt to correct hypokalemia. To keep the electrical neutrality, H^+ shifts from outside to the inside of the cells. This loss of H^+ from extracellular fluid results in metabolic alkalosis.

It is interesting to note that metabolic alkalosis itself perpetuates hypokalemia. In metabolic alkalosis of any cause, transcellular shift of H^+ and K^+ takes place. H^+ ions move out of the cells to correct alkalosis and K^+ moves inside the cells producing hypokalemia.

15.11 Bicarbonate administration

As mentioned above, in euvoletic persons with normal renal function, it is impossible to produce alkalosis due to rapid renal excretion of any administered HCO_3^- . However, in

hypovolemia or in renal failure, administration of bicarbonates results in metabolic alkalosis simply due to inability of the kidneys to excrete the extra bicarbonates.

15.12 Multiple blood transfusions

Massive blood transfusion occasionally results in metabolic alkalosis. Citrate which is used as an anticoagulant in blood is converted to bicarbonate in the liver resulting in metabolic alkalosis.

15.13 Contraction alkalosis

Loss of water around a fixed amount of HCO_3^- results in increased concentration of HCO_3^- and metabolic alkalosis. The increased pure water loss and hypotonic fluid loss by loop diuretics, excessive sweating and congenital chloride diarrhea are examples of conditions associated with contraction alkalosis.

15.14 Bartter's syndrome and Gitelman's syndrome

These are the autosomal recessive disorders characterized by hypokalemia and metabolic alkalosis.

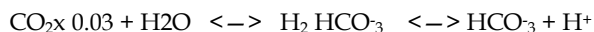
In Bartter's syndrome, there is a defect in the sodium chloride transport in the thick ascending limb of the loop of Henle at the site of action of loop diuretics. The characteristic abnormalities include hypokalemia, metabolic alkalosis and increased urinary calcium excretion.

In Gitelman's syndrome, there is a defect in the sodium chloride transport in the distal tubule which is the site of action of thiazide diuretics. The characteristic abnormalities include hypokalemia, metabolic alkalosis, decreased urinary calcium excretion, and hypomagnesaemia.

16. Respiratory acidosis and alkalosis

16.1 Respiratory acidosis

The primary event in respiratory acidosis is retention of CO_2 . Metabolism of carbohydrates and fats results in the production of CO_2 which combines with H_2O to form H_2HCO_3^- . It then dissociate into acid (H^+) and bicarbonate (HCO_3^-).



Kidneys compensate to respiratory acidosis by increasing acid (H^+) excretion.

Lungs through alveolar ventilation remove CO_2 . In the absence of ventilation, CO_2 will accumulate in the body and will result in severe acidosis (rise of free H^+ ions and drop of pH). This type of acidosis is called respiratory acidosis (Arieff & Carroll, 1972).

According to the Henderson-Hasselbalch equation, pH depends upon the ratio of bicarbonate and PCO_2 .

$$(\text{H}^+) = 24 \times \frac{\text{PCO}_2}{\text{HCO}_3^-}$$

$$\text{pH} = 6.10 + \log \frac{\text{HCO}_3^-}{0.03 \text{ P CO}_2}$$

The partial pressure of CO_2 (PCO_2) in the arterial blood is in equilibrium with that in the alveolar air. Normal arterial PCO_2 is approximately 40 mmHg. CO_2 is not an acid. It increases the acidity of the solution through the formation of H_2CO_3 . Increased PCO_2 will increase the H_2CO_3 concentration. It then dissociates into the acid (H^+) and bicarbonate (HCO_3^-).

In contrast to metabolic acidosis, bicarbonate (HCO_3^-) does not act as a buffer in respiratory acidosis. It is part of the problem, not part of the solution. Sodium bicarbonate administration in respiratory acidosis is not beneficial, rather may be harmful. Administration of bicarbonate will result in an initial transient rise in pH due to the left shift. Then, H_2CO_3 will immediately dissociate and the net result will be higher PCO_2 , higher HCO_3^- , higher H^+ , and lower pH.

Intracellular buffers mostly hemoglobin (Hgb) bind free H^+ and form $\text{H}^+\text{-Hgb}$ which is carried to lungs by the blood circulation. In the lungs, H^+ is released from Hgb and combines with available HCO_3^- to form CO_2 , which is exhaled by lungs to the atmosphere.

Increasing ventilation is the only treatment of respiratory acidosis. Renal response to increased H^+ excretion takes about 3 to 5 days to complete. At this stage, the respiratory acidosis is termed chronic. The $\text{PCO}_2/\text{HCO}_3^-$ ratio improves to settle pH at a higher level than it was in acute phase. This renal compensation is always suboptimal. If the pH is 7.4 or above, it means that there is a concomitant component of metabolic alkalosis.

The degree of compensation and expected pH after compensation are predefined (Table 2).

16.1.1 Causes of respiratory acidosis

The cause of respiratory acidosis is only one, that is, decreased ventilation. Several conditions can lead to decreased ventilation and respiratory acidosis. Causes of decreased ventilation may be divided into three groups. Important ones are listed here:

Central: Narcotics, Sedatives, Anaesthesia,

Peripheral: Neuropathies, Muscle weakness, Myopathies

Pulmonary and Airway Pathology: Pneumonia, Pneumothorax, Sleep apnea, and Emphysema.

16.2 Respiratory alkalosis

The primary event in respiratory alkalosis is decreased PCO_2 . According to the Henderson-Hasselbalch equation, pH depends upon the ratio of bicarbonate and PCO_2 as mentioned above. Lower the PCO_2 , the higher the pH and vice versa.

Extracellular buffers are not efficient in respiratory alkalosis. Intracellular buffers e.g. protein, phosphate and Hgb act to release intracellular H^+ in an attempt to correct the alkalosis. This response also is not very efficient. Renal response of decreasing H^+ secretion takes 3 to 5 days to complete. At this stage, it is called chronic respiratory alkalosis.

16.2.1 Causes of respiratory alkalosis

Like respiratory acidosis, the cause of respiratory alkalosis is only one, that is, increased ventilation. Important causes of increased ventilation are listed here:

Hypoxemia, Sepsis, Salicylate intoxication, Pregnancy, stroke, Liver Failure, Psychological Causes, Artificial by ventilator (Kaplan & Frangos, 2005).

17. Conclusion

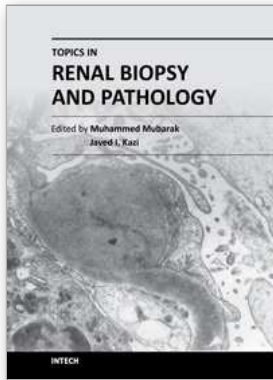
Primary acid base disorders are metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis. In practice, patients often present with mixed and complex acid

base problems. Understanding the underlying pathophysiology is the best way of reaching at the correct diagnosis. The various formulae are helpful but are not substitute to the clear concepts.

18. References

- Arieff AI, & Carroll HJ. (1972). Nonketotic hyperosmolar coma with hyperglycemia: clinical features, pathophysiology, renal function, acid-base balance, plasma-cerebrospinal fluid equilibria and the effects of therapy in 37 cases. *Medicine (Baltimore)*, Vol. 51, No. 2, pp.73-94.
- Adroge HJ, & Madias NE. (1998). Medical progress: Management of life threatening acid base disorders. *N Eng J Med*, Vol. 338, No. 1, pp. 26-34.
- Absar Ali. Nephrology on Fingertips. Florida: PIP Printers, 1994.
- Battle DC, Hizon M, Cohen E, Gutterman C, & Gupta R. (1988). The use of the urinary anion gap in the diagnosis of hyperchloremic metabolic acidosis. *N Engl J Med*, Vol. 318, No.10, pp. 594-9.
- Battle D, Moorthi KM, Schlueter W, & Kurtzman N. (2006). Distal renal tubular acidosis and the potassium enigma. *Semin Nephrol*, Vol. 26, No. 6, pp. 471-8.
- Boron WF. (2006). Acid base transport by the renal proximal tubule. *J Am Soc Nephrol*, Vol. 17, No. 9, pp. 2368-82.
- Corey HE. (2005). Fundamental principles of acid-base physiology. *Crit Care*, Vol. 9, No. 2, pp. 184-92.
- Corey HE. (2003). Stewart and beyond: New models of acid base balance. *Kidney Int*, Vol. 64, No. 3, pp. 777-87.
- Fidkowski C, & Helstrom J. (2009). Diagnosing metabolic acidosis in the critically ill: bridging the anion gap, Stewart, and base excess methods. *Can J Anaesth*, Vol. 56, No. 3, pp. 247-56.
- DuBose T, Hamm L. Acid base and electrolyte disorders: A companion to Brenner and Rector, The kidney. Philadelphia: WB Saunders; 1999
- DeFronzo RA. (1980). Hyperkalemia and hyporeninemic hypoaldosteronism. *Kidney Int*, Vol. 17, No. 1, pp. 118-34.
- DuBose TD Jr, Good DW, Hamm LL, & Wall SM. (1991). Ammonium transport in the kidney: new physiological concepts and their clinical implications. *J Am Soc Nephrol*, Vol. 1, No. 11, pp.1193-203.
- Emmett M, & Narins RG. (1997). Clinical use of the anion gap. *Medicine (Baltimore)*, Vol. 56, No. 1, pp. 38-54.
- Halperin M and Goldstein M. Fluid electrolyte and acid base physiology: Aproblem based approach. 3rd edition. Philadelphia,WB Saunders;2002
- Kellum JA. (2007). Disorders of acid base balance. *Crit Care Med*, Vol. 35, No. 11, pp. 2630-6.
- Kellum JA, Kramer DJ, & Pinsky MR. (1995). Strong ion gap: a methodology for exploring unexplained anions. *J Crit Care*, Vol. 10, No. 2, pp. 51-5.
- Khanna A, & Kurtzman NA. (2006). Metabolic alkalosis. *J Nephrol*, Vol. 19, Suppl. 9, pp. S86-96.
- Kraut JA, & Madias NE. (2010). Metabolic acidosis: pathophysiology, diagnosis and management. *Nat Rev Nephrol*, Vol. 6, No. 5, pp. 274-85.
- Kellum JA. (2005). Clinical Review: Reunification of acid base physiology. *Crit Care*, Vol. 9, No. 5, pp. 500-7.

- Karet FE. (2009). Mechanisms in hyperkalemic renal tubular acidosis. *J Am Soc Nephrol*, Vol. 20, No. 2, pp.251-4.
- Kamel KS, Ethier JH, Richardson RM, Bear RA, Halperin ML. (1990). Urine electrolytes and osmolality: when and how to use them. *Am J Nephrol*, Vol. 10, No. 2, pp. 89-102.
- Kellum JA. (2005). Determinants of plasma acid-base balance. *Crit Care Clin*, Vol. 21, No. 2, pp. 329-46.
- Kraut JA, Madias NE. (2007). Serum anion gap: Its uses and limitations in clinical medicine. *Clin J Am Soc Nephrol*, Vol. 2, No. 1, pp.162-74.
- Kraut JA, & Kurtz I. (2005). Metabolic acidosis of CKD: diagnosis, clinical characteristics, and treatment. *Am J Kidney Dis*, Vol. 45, No. 6, pp.978-93.
- Kraut JA, & Kurtz I. (2008). Toxic alcohol ingestions: clinical features, diagnosis, and management. *Clin J Am Soc Nephrol*, Vol. 3, No. 1, pp. 208-25.
- Lowenstein. Acids and Basics. New York University, 1993
- Kaplan LJ, & Frangos S. (2005). Clinical review: Acid-base abnormalities in the intensive care unit. *Crit Care*, Vol. 9, No. 2, pp. 198-203.
- Lynd LD, Richardson KJ, Pursell RA, Abu-Laban RB, Brubacher JR, Lepik KJ, & Sivilotti ML. (2008). An evaluation of the osmole gap as a screening test for toxic alcohol poisoning. *BMC Emerg Med*, Vol. 8, No. 5.
- Narins RG, & Emmett M. (1980). Simple and mixed acid-base disorders: a practical approach. *Medicine (Baltimore)*, Vol. 59, No. 3, pp.161-87.
- Rose B, Narins R, Post T. Clinical Physiology of Acid base and Electrolyte Disorders. New York. McGraw Hill, Medical Publishing Division; 2001
- Oh M, & Carroll HJ. (2002). Value and determinants of urine anion gap. *Nephron*, Vol. 90, No. 3, pp. 252-5.
- Rastegar A. (2007). Use of the DeltaAG/DeltaHCO₃ ratio in the diagnosis of mixed acid-base disorders. *J Am Soc Nephrol*, Vol. 18, No. 9, pp. 2429-31.
- Rastegar A. (2009). Clinical utility of Stewart's method in diagnosis and management of acid-base disorders. *Clin J Am Soc Nephrol*, Vol. 4, No. 7, pp.1267-74.
- Rodríguez Soriano J. (2002). Renal tubular acidosis: the clinical entity. *J Am Soc Nephrol*, Vol. 13, No. 8, pp. 2160-70.
- Rose B, & Post TW. Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th ed, McGraw-Hill, New York, 2001
- Schrier R, Renal and Electrolyte Disorders. 6th edition. Philadelphia: Lippincott Williams and Wilkins, 2003
- Schoolwerth AC. (1991). Regulation of renal ammoniogenesis in metabolic acidosis. *Kidney Int*, Vol. 40, No. 5, pp. 961-73.



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There is no dearth of high-quality books on renal biopsy and pathology in the market. These are either single author or multi-author books, written by world authorities in their respective areas, mostly from the developed world. The vast scholarly potential of authors in the developing countries remains underutilized. Most of the books share the classical monotony of the topics or subjects covered in the book. The current book is a unique adventure in that it bears a truly international outlook and incorporates a variety of topics, which make the book a very interesting project. The authors of the present book hail not only from the developed world, but also many developing countries. The authors belong not only to US but also to Europe as well as to Pakistan and Japan. The scientific content of the book is equally varied, spanning the spectrum of technical issues of biopsy procurement, to pathological examination, to individual disease entities, renal graft pathology, pathophysiology of renal disorders, to practice guidelines.

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