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ON

A STUDY OF ACID BASE CHANGES IN ACUTE DIARRHEAL DISEASE

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BIBILIOGRAPHY

CERTIFICATE

This is to certify that this dissertation entitled ``***A STUDY OF ACID-BASE CHANGES IN ACUTE DIARRHEAL DISEASE***`` is a bonafide record of work done by **Dr.SP.S. SUBRAHMANIAN**, submitted as partial fulfillment for the requirements of M.D., Degree Examinations, (Branch I) General Medicine, March 2007.

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CONTENTS

INTRODUCTION

Disorders of acid-base homeostasis complicate a variety of disease conditions and contribute to morbidity and mortality. Unless promptly recognized, these disorders disrupt normal functioning of various organ systems and ultimately prove fatal.

The clinical settings in which such acid-base disorders occur are numerous, that attempting to list out all the causes of acid-base disturbances will be exhaustive and unwarranted. Nevertheless, to make some generalisation, it can be said, diseases of the lungs and kidneys (the two important organs involved in acid-base homeostasis), contribute to an important proportion of such acid base disturbances.

Acute Diarrheal Disease (A.D.D) is yet another cause of acid-base disturbance and the present study aims to explore the various changes that take place in the acid base mileu of patients who suffer an acute diarrheal disease.

The study tries to validate a prognostic role for such acid-base changes in acute diarrheal disease and calls for an early recognition and prompt correction of acid-base changes.

AIMS OF THE STUDY

1. To find out the acid-base disturbances resulting from acute diarrheal disease.

2. To analyse the changes in acid-base status in patients with acute renal failure due to acute diarrheal disease.

3. To find out the incidence of severe metabolic acidosis ($pH \leq 7.2$) in acute diarrheal disease.

4. To find out whether metabolic acidosis has prognostic significance in acute diarrheal disease and whether early detection and correction of metabolic acidosis can improve the outcome.

REVIEW OF LITERATURE

Diarrhea is defined as the passage of 3 or more loose, liquid or watery stools. However it is the recent change in consistency and character of the stools, rather than the number of stools that is more important (1).

The division between acute and chronic diarrhea is arbitrary. WHO/UNICEF define acute diarrheal diseases (ADD) as an attack of sudden onset which usually lasts 3-7 days, but may last upto 10-14 days.

Dysentery is defined as the passage of blood and mucus in stools.

PROBLEM STATEMENT

Diarrhea is a major public health problem in the developing world. Acute diarrhea is rivalled in importance only by respiratory infection as a cause of morbidity on a world wide scale.

An estimated 1.8 billion episodes of acute diarrhea occur each year and the disease affects all ages and both sexes. It is more common in children. The mortality rate is also higher for children with acute diarrhea than adults. In the tropical belt 15-40% of all deaths among children under 5 years of age are diarrhea related.

ETIOLOGY OF ACUTE DIARRHEA

In developing countries diarrhea is almost infectious in origin. The common infectious agents causing diarrhea are listed below:

1. VIRUSES

Rota virus
Astro virus
Adeno virus
Calci virus
Corona virus
Norwalk group viruses
Entero viruses

2. BACTERIA

Escherichia coli
Shigella
Salmonella
Vibrio cholera
Campylobacter jejuni etc

3. OTHERS

Entameba histolytica

Giardia lamblia

Trichuriasis

Cryptosporidium species

Intestinal worms etc

Non infectious causes of acute diarrhea include antibiotic associated diarrhea, inflammatory bowel disease, radiation enteritis, ischemic colitis etc. (2)

It may be beyond the scope of this study to review the usual aspects of acute diarrheal disease (ADD) like etiopathogenesis, clinical features, classification, epidemiological and public health aspects, investigations and treatment in detail.

Further references quoted focus on the fundamental aspects of acid base homeostasis, the disturbances in acid-base balance produced by acute diarrheal disease, the pathogenesis of such acid-base imbalance, clinical features, diagnosis and treatment aspects of such acid base disturbances.

REVIEW OF FUNDAMENTALS

An acid is a substance that is capable of liberating a proton or hydrogen ion when dissolved in solution.

An alkali is a substance capable of accepting a proton.

The physiologic compartments (E.C.F. and I.C.F.) in humans have an admixture of such substances, some of which donate Hydrogen ion (H^+)

(i.e., acids) and some of which accept H^+ ion (i.e.alkalis). This forms the acid-base mileu of the human body.

The hydrogen ion concentration of a compartment, represented as $[H^+]$ determines the ACIDITY of the compartment.

Under physiologic conditions the $[H^+]$ or hydrogen ion concentration of Extra Cellular Fluid (ECF) is 0.00004 mEq/L and is maintained within a narrow range (3).

Since this number is very small and cumbersome to work with, for practical purposes the acidity of a compartment is represented in pH scale.

pH is defined as the negative logarithm of $[H^+]$

i.e. $pH = - \log [H^+]$ or $\log 1/[H^+]$

The normal pH ranges between 7.35 to 7.45

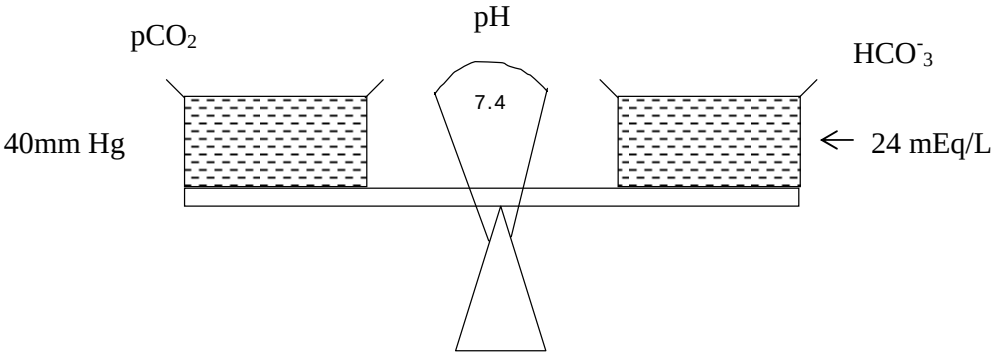
Using the above formula it can be found that pH falls as $[H^+]$ rises and vice versa.

Acid base homeostasis is essential for normal cellular functioning (as most enzyme systems require an optimal pH to work).

The term ‘ACIDEMIA` means an excess of acid in blood and the term `ALKALEMIA` means an excess of alkali in blood.

`ACIDOSIS` means simply an excess of acid and ALKALOSIS means an excess of base, and these terminologies do not specify the physiologic compartments in which such an excess accumulates. These two terms may be used to denote the acid base disturbances occurring in any compartment Ex. intracellular acidosis, extra cellular acidosis. CSF acidosis etc.

In health the normal arterial pH of 7.40 is contributed by two components. One is pCO_2 (partial pressure of CO_2) in blood and the other is concentration of bicarbonate in blood (4).



pCO_2 represents the respiratory contribution to pH and HCO_3^- represents the metabolic contribution to pH.

Normally CO_2 is produced as a result of cellular respiration and is transported in blood in various forms, important one being carbonic acid (H_2CO_3) (5). This generation of carbonic acid as a result of CO_2 transport is one contributor to acidity of blood.

About 1mg/kg of acid is produced on an average per day by metabolism of dietary nutrients (Ex. Sulfur containing amino acids like cysteine and methionine are metabolized to sulfuric acid) and other substrates (Ex. Glucose is metabolized by anaerobic glycolysis to lactic acid in RBCs) (6). This rise in $[H^+]$ in blood will lower the pH by utilizing the blood alkali HCO_3^-. Bicarbonate level falls as a result.

Thus it is evident that a change in levels of either pCO_2 or HCO_3^- may alter the pH. Disorders of respiration effect this change in pH by altering pCO_2 and metabolic disorders effect the change in pH by altering HCO_3^- levels.

Based on the above discussion the various acid-base disturbances can be described as :

i. Metabolic Acidosis - a fall in pH due to fall in HCO_3^-

ii. Metabolic alkalosis - a rise in pH due to rise in HCO_3^-

iii. Respiratory acidosis - a fall in pH due to rise in pCO_2

iv. Respiratory alkalosis - a rise in pH due to fall in pCO_2

The influence of pCO_2 and HCO^-_3 on pH can be predicted by using the HENDERSON – HASSEL BALCH EQUATION (7)

$$pH = pK + \log \frac{\left[HCO^-_3\right]}{0.03 \times pCO_2}$$

pK is a constant (ionisation constant of bicarbonate buffer) and its value is 6.1.

Thus if normal bicarbonate level in arterial blood is 24 mEq/L and normal pCO_2 in arterial blood is 40mm Hg. It can be predicted that.

$$pH \text{ will be } 6.1. + \log\left[\frac{24}{0.03 \times 40}\right]$$

$$\therefore pH = 6.1 + \log \frac{24}{1.2}$$

$$pH = 7.4$$

In routine arterial blood gas analysis, the ABG analyser has electrodes to measure pCO_2, and $[H^+]$. Bicarbonate levels are not directly measured. Bicarbonate levels are only estimated using HENDERSON equation.

REGULATION OF ACID-BASE BALANCE

Normally the pH is kept with in a narrow range of 7.35 to 7.45.

Despite the wide fluctuation in the day to day turnover of acids, the body tries to keep the pH with in a narrow range of 7.35 to 7.45.

There are 3 primary systems that accomplish this job of regulating the acid-base balance.

They include : i. The buffers

ii. The respiratory system and

iii. The kidneys

BUFFERS

A buffer is any substance that reversibly binds hydrogen ions. The general form of buffering reaction is :

$$\text{Buffer} + H^+ \rightleftharpoons \text{Buffer} \quad (8)$$

The various buffers include bicarbonate buffer, protein buffer, phosphate buffer etc. In the following discussion the bicarbonate buffer system and its role in regulation of H^+ ion concentration is described.

The bicarbonate buffer consists of an acid - H_2CO_3 (the transport form of CO_2 in blood) and its conjugate base HCO_3^-. Under physiologic

states these two components of this buffer exist in equilibrium, which can be shown as:

$$H_2CO_3 \rightleftharpoons H^+ + HCO^-_3$$

A buffer will prevent the occurrence of sudden change in pH whenever an acid or alkali is added.

For example whenever a strong acid like hydrochloric acid is added to the above buffer, the fall in pH will be less than that expected, when there would be no buffer.

The mechanism by which bicarbonate buffer does this is shown below:

$$H_2CO_3 \rightleftharpoons H^+ + HCO^-_3$$

When HCl (hydrochloric acid) is added to this buffer the proton of HCl will combine with HCO^-_3 in the buffer and the reaction will be directed to left with formation of H_2CO_3. Even though both HCl and H_2CO_3 are acids, HCl is a strong acid with a stronger tendency to dissociate in solution while H_2CO_3 is a weaker acid, i.e. it poorly dissociates. Thus a precipitous fall in pH expected due to HCl addition is prevented. In a similar fashion addition of a strong alkali (or OH^-) will utilise the H^+ in the right hand side of the reaction and enhance the dissociation of H_2CO_3 to H^+ and HCO^-_3. Thus OH^- a strong base will be replaced by HCO^-_3 a weaker base. A similar

mechanism can be postulated for other buffer systems. Bicarbonate buffer system is the predominant extracellular buffer while the proteins constitute predominant intracellular buffer.

While the buffers come into play immediately in tackling a sudden change in pH, they cannot correct the underlying acid-base disorder and they only buy time for the other two systems-respiratory and renal systems to make the corrective measures.

ROLE OF RESPIRATORY SYSTEM IN ACID BASE HOMEOSTASIS

Whenever the ECF acidity increases it stimulates the respiratory center resulting in hyperventilation. This washes out the CO_2 in blood and lowers the pCO_2. As the pCO_2 falls pH tends to rise and compensates acidosis. This hyperventilation is evident as KUSSMAULS breathing in acute acidosis.

When the blood becomes alkalotic a compensatory hypoventilation occurs.

ROLE OF KIDNEYS IN REGULATING ACID-BASE BALANCE (9)

The kidney reclaims all the bicarbonate that is filtered at the glomerulus. Bicarbonate in plasma is freely filtered at the glomerulus. The

proximal tubule and the remaining part of nephron reabsorb bicarbonate, thus preserving the alkali resource of body.

The kidney also does the function of excreting acid and generating new bicarbonate. Substantial acid excretion takes place in the distal part of the nephron where H^+ ions will be excreted into lumen in exchange for Na^+. To prevent a precipitous fall in urinary pH, the H^+ ions will be buffered by HPO_4^{2-} (Phosphate buffer) in urine. The extent of H+ ion excretion by this way can be calculated by assessing the TITRATABLE ACIDITY of urine which is the amount of alkali required to rise the urine pH to 7.4.

The other mode of excretion of H^+ in urine is in the form of NH_4^+. In the proximal tubules of the kidney glutamine is deaminated to form α keto glutarate and NH_3. The later combines with H^+ ions generated from H_2O and CO_2 to form NH_4^+ and excreted into the lumen. While NH_4^+ enters urine, the HCO_3^- enters blood. This also explains the generation of new bicarbonate.

Thus the important role played by kidney in acid base balance is understood. Now it is evident that renal diseases can produce metabolic acidosis by failure to reclaim bicarbonate (proximal RTA), failure of urinary acidification (distal RTA and renal failure) and reduced bicarbonate generation.

ACID-BASE DISTURBANCE KNOWN TO OCCUR IN ACUTE DIARRHEA

Metabolic Acidosis is the most characteristic acid base disorder known to occur in patients with acute diarrhea. (10)

The various factors that contribute to metabolic acidosis include:

1. loss of bicarbonate in diarrheic stools

2.Tissue hypoperfusion resulting in lactic acidosis

3.Starvation resulting in starvation keto acidosis

4.Renal failure with its attendant metabolic acidosis.

The recognition of each of these acid-base disturbances is described later in the discussion on metabolic acidosis.

Patients with acute diarrheal disease can also develop metabolic alkalosis if,

i. They have a more severe vomiting than diarrhea, because acid is lost in vomitus.

ii. Over enthusiastic correction of acidosis with alkali.

PATHOGENESIS OF METABOLIC ACIDOSIS (11)

During normal digestion many alimentary segments below the pylorus secrete bicarbonate into gut lumen. The duodenum, ileum, pancreas, gall bladder and especially the colon all secrete bicarbonate into gut lumen.

During normal digestion alkalinisation of sub-pyloric lumen takes place with equal and opposite acidification of blood.

The exactly opposite entry of bicarbonate into blood and H^+ (proton) into lumen occurs above the pylorus, i.e. in the stomach.

In diarrheal states, secretion by lower GIT increases. This increase is largely due to increase in stool volume. In addition in some diseases (ex. Cholera) the infectious or toxic agent directly stimulates the secretory activity of the gut (called SECRETORY DIARRHEA).

Thus in patients with diarrhea, large quantities of bicarbonate enter the lower gut lumen and large quantities of protons enter the body fluids. These protons are buffered by bicarbonate causing plasma bicarbonate to fall. Fall in plasma bicarbonate causes metabolic acidosis.

In severe diarrhea profound metabolic acidosis can develop with HCO_3^- below 10 mmol/L.(11)

PATHOGENESIS OF LACTIC ACIDOSIS IN ACUTE DIARRHEA (12) , (13)

Under normal conditions lactic acid is produced by RBCs, muscles etc. This lactic acid liberates a proton (H+) and an equimolar quantity of lactate.

The proton will be buffered by plasma bicarbonate pool. However under physiologic conditions HCO_3^- levels do not fall because lactate anion acts as POTENTIAL BICARBONATE, i.e., it gets converted to bicarbonate in the liver.

Lactic acidosis can develop in patients with severe diarrheal dehydration.

Lactic acidosis develops as a consequence of tissue hypoperfusion resulting from hypovolemia and shock. This type of lactic acidosis is referred to as Type A lactic acidosis. (Type B lactic acidosis occurs when there is no tissue hypoxia or hypoperfusion).

Hypoperfusion results in anaerobic metabolism. The product of anaerobic glycolysis is lactic acid. This lactic acid is produced in excess in diarrheal dehydration.

There is not only excess generation of lactic acid in anaerobic conditions, but also impaired utilisation of lactate. Normally kidneys and liver utilize lactate in aerobic condition for energy production or gluconeogenesis (Coris cycle).

PATHOGENESIS OF KETOACIDOSIS IN ACUTE DIARRHEA (14)

Ketoacidosis refers to the metabolic acidosis caused by over production of ketoacids. β-hydroxy-butyric acid and acetoacetic acid are the two important ketoacids.

Patients with diarrhea can starve and the pathogenesis of ketoacidosis in diarrhea is same as starvation ketoacidosis.

In starvation the dietary supply of glucose is reduced. This is also attended to by a reduction in insulin level and a rise in glucagon level. So the insulin/glucagan ratio falls. This reduction in substrate (glucose) along with decreased insulin/glucagon ratio promotes ketogenesis ultimately.

Normally insulin down regulates the enzyme hormone sensitive lipase. When insulin level falls as a result of starvation, lipolysis is enhanced with resultant liberation of FFA (Free Fatty Acids) into circulation. Free Fatty Aids are directed to the ketogenic pathway by glucagon.

The physiological role of kidneys in regulating acid-base balance was already discussed and it is very well understood that derangements in renal function resulting from ADD can cause metabolic acidosis.

SYSTEMIC EFFECTS OF METABOLIC ACIDOSIS (15)

Abnormalities of systemic pH may affect various organ systems and their functions.

More important than the absolute level of $[H^+]$ or pH, is the rate at which such changes in pH occur in deciding the clinical manifestations.

The systemic effects of metabolic acidosis are discussed below.

CARDIAC EFFECTS

The heart rate responds biphasically to acidemia. Tachycardia is frequently observed as the pH falls from 7.40 to 7.10. The increasing heart rate is caused by acid stimulated release of catecholamines from the adrenal medulla.

As blood pH falls below 7.10, the heart rate progressively slows. The potential mechanism behind this bradycardia is acidosis induced inhibition of chronotropic action of catecholamines.

Systemic acidosis can also predispose to the development of ventricular arrhythmias.

Severe acidemia impairs myocardial contractility when the systemic pH falls below 7.40. The direct negative inotropic effect of acidosis is

counterbalanced by the indirect positive inotropic effect mediated by catecholamines (catecholamine release is enhanced by acidosis).

When pH falls below 7.2 the negative inotropic effect of acidosis becomes more apparent.

No significant vascular effects occur when pH is above 7.20. When the pH falls below 7.2 there is a systemic vasodilatation. The hypertension complicating severe metabolic acidosis is characterized by a warm well perfused peripheries giving rise to the term `warm shock`.

Advancing acidemia causes venoconstriction (*sharpey-schafer et al.*, 1965). Peripheral venoconstriction reduces the volume normally accommodated by these capacitance vessels. So peripheral blood pool will be pushed to pulmonary circulation. This increased preload to heart increases the burden on heart resulting in heart failure and pulmonary edema.

RESPIRATORY EFFECTS

Acute severe metabolic acidosis causes hyperventilation stimulating the respiratory center which enhances the clearance of CO_2 (CO_2 is transported as H_2CO_3 and since this is exhaled through lungs H_2CO_3 is considered to be a volatile acid), thus reducing the acid content of blood.

This hyperventilation may be clinically evident as KUSSMAULS BREATHING (rapid deep breathing) as in acute acidosis or it may be a subtle increase in the depth of respiration as in chronic metabolic acidosis.

Metabolic acidosis has two opposite effects on tissue oxygen delivery.

The first effect described as BOHR EFFECT is the interaction of H+ ions with hemoglobin. Increased protons with in the RBCs decrease the affinity of hemoglobin for oxygen, thus facilitating tissue oxygen delivery.

The second effect that occurs over 12-36 hours is due to the depletion of 2,3-DPG (2,3, Diphosphoglycerate) a compound which facilitates tissue oxygen delivery.

If follows that acute acidosis initially beneficially affects tissue oxygenation by eliciting Bohr effect. However the progressive depletion of 2,3-DPG in RBCs over time annuls this beneficial effect of acidosis.

In a similar way acute alkalinisation may abruptly depress tissue oxygenation. The chronically acidotic patient has a near normal tissue oxygenation resulting from the offsetting effects of low pH and RBC 2,3-DPG depletion. Excessively rapid therapy with alkali may remove the beneficial Bohr effect promoting tissue hypoxia.

GASTRO INTESTINAL EFFECTS

Abdominal pain, distention, nausea and vomiting are often prominent symptoms and occasionally severe enough to suggest acute abdomen.

RENAL MANIFESTATIONS

With acute metabolic acidosis serum bicarbonate falls and therefore the filtered load of bicarbonate decreases to lower levels. Since the filtered load of bicarbonate is diminished, its absolute reabsorption in the earliest portion of the proximal tubule falls, thereby rendering unfavorable, the generation of passive forces required for nonactive sodium chloride reabsorption. Accordingly more sodium chloride is delivered distally, a portion of which escapes into the final urine effecting the natriuresis of acute acidosis.

Other systemic effects of metabolic acidosis can be summarized as follows.

a.METABOLIC / HORMONAL

Protein wasting

Catecholamine secretion

Mobilisation of Ca^{2+} from bone

b. **HAEMATOLOGICAL** :

Leukocytosis

c. CNS :

CNS depression

INTERPRETATION OF ARTERIAL BLOOD GAS VALUES (16) (17)

ABG interpretation starts with interpreting the pH. (or H^+ ion concentration)

The normal pH ranges between 7.35 to 7.45. If the pH is below 7.35, acidosis will be diagnosed and if it is above 7.45 alkalosis will be diagnosed.

If the pH is between 7.35 and 7.45 it may be a normal ABG study or it may be produced as a result of combination of acidosis and alkalosis.

If acidosis occurs due to a rise in pCO_2 the condition is termed respiratory acidosis and if it occurs due to a fall in bicarbonate the condition is termed metabolic acidosis. In a similar fashion, alkalosis (increased pH) due to rise in H CO_3^- is termed metabolic alkalosis and that occurring due to a fall in pCO_2 is termed respiratory alkalosis.

If the pH is normal, as already discussed there are two possibilities:

1. Normal ABG
2. A combination of acidosis and alkalosis.

In the first case pCO_2, HCO^-_3 and pH will all be with in the normal range.

In the second case pH will be normal, but there will be deviation in HCO_3^- and pCO_2 levels in the same direction, i.e., if HCO^-_3 is below the normal range (metabolic acidosis) then pCO_2 will also be low (respiratory alkalosis) and if HCO_3^- levels are high, (metabolic alkalosis), then pCO_2 also will be high (respiratory acidosis).

This sort of a change in levels of both pCO_2 and HCO_3^- is a common observation and occurs as a compensatory phenomenon.

For instance if a patient develops metabolic acidosis due to loss of bicarbonate in diarrheic stools, then the respiratory system tries to compensate for this acidosis by increasing CO_2 excretion by means of hyperventilation. Similarly the kidneys try to regulate the excretion of acid and generate bicarbonate according to pCO_2 levels. If a patient develops respiratory acidosis due to a pulmonary disease process like COPD, kidneys increase acid excretion and increases bicarbonate production thus elevating serum bicarbonate levels.

Thus derangements in acid-base homeostasis resulting from a primary abnormality in one system will be compensated by an exactly opposite adjustment in the other system.

Sometimes such opposite changes in both systems occur, not simply as a compensatory response, but as a result of primary pathologies in both systems.

For example a patient who develops respiratory acidosis as a result of Guillain Barre Syndrome (with respiratory paralysis) may vomit and develop a concomitant metabolic alkalosis.

To know whether the deviation in the pCO_2 or HCO_3^- occurs as a compensatory response to the acid base change that has previously occurred or represents a primary change by itself, knowing the limits of compensation may be useful.

If the deviation in HCO_3^- or pCO_2 level falls within the compensatory limits for the previous change in pCO_2 or HCO_3^- respectively, then it is likely that the change is only compensatory and the disorder is labeled simple acid base disorder. However if pCO_2 or HCO_3^- response to a primary acid-base disorder falls outside the compensatory range, then it forms another primary disorder by itself. Combination of two primary disorders means a MIXED ACID BASE DISORDER.

The extent of compensation that is possible for any respiratory or metabolic disorder has been determined by animal and human studies. The data accumulated from these studies has been developed into 95% confidence limits. (18) (19).

SUMMARY OF EXPECTED COMPENSATION FOR ACUTE AND CHRONIC ACID-BASE DISORDERS

SL.NO	PRIMARY DISORDER	EXPECTED COMPENSATION
1.	Acute respiratory acidosis	For a 15mm Hg increase in pCO_2, HCO_3- increases ImEq/L –significant compensation takes 24-48hrs
2.	Chronic respiratory acidosis	For every 10mm. Hg rise in pCO_2 HCO_3^- increases 4mEq/L
3.	Acute respiratory alkalosis	For every 5mm. Hg decrease in pCO_2 HCO_3- decreases lmEq/L. Significant compensation requires 24-48 hrs.
4.	Chronic respiratory alkalosis	HCO_3- falls 5 mEq/L for every 10 mm. Hg. fall in pCO_2
5.	Metabolic acidosis	pCO_2 = (1.5 X HCO_3-)+8$\pm$2 or pCO_2 falls by 1.3 mm. Hg. for 1mEq/L. fall in HCO_3-
6.	Metabolic alkalosis	pCO_2 change is variable. For each lmEq/L increase in HCO_3-, pCO_2 increases by 0.6mm. Hg.

The Acid-Base nomogram can also be used to predict the compensatory response.

So far the recognition of simple and mixed acid-base disorder was discussed. Since diarrhea causes metabolic acidosis, the following discussion reviews the evaluation of metabolic acidosis.

EVALUATION OF METABOLIC ACIDOSIS

The first step in the evaluation of metabolic acidosis involves estimating the ANION GAP.

CONCEPT OF ANION GAP (20)

The ECF is normally electrically neutral. In other words, the net positive electrical change in the ECF (Cations) equals the net negative electric change (anions). This can be represented in algebric language as follows.

CATIONIC CHARGES	=	ANIONIC CHARGES
$(Na^+) + (K^+)$ + Unmeasured Cations like Mg^{2+}	=	$(HCO_3^-) + (Cl^-)$ + Unmeasured anions like Phosphate, Sulphate, Lactate, albumin etc.
$(Na^+)+(K^+) – [HCO_3^+ + Cl^+]$ =		(Unmeasured anions) – (Unmeasured cations)

This difference between unmeasured anions and unmeasured cations is called ANION GAP.

$$(Na^+) + (K^+) - (HCO_3^- + Cl^-) = \text{ANION GAP}$$

The normal anion gap, when obtained by using the above formula is 14-18 mEq/L. Sometimes (K^+) is omitted from calculation of anion gap

because of its negligible concentration and if such a formula is used normal value for anion gap will be 12-14 mEq/L.

HOW DOES ANION GAP HELP EVALUATING METABOLIC ACIDOSIS? (21)

Metabolic acidosis can be produced as a result of loss of bicarbonate usually from GIT or kidney or as a result of accumulation of acids (Ex. Sulfuric acid, lactic acid, ketoacids etc.) as a result of cellular metabolism.

When the primary abnormality is a loss of bicarbonate (as in diarrhea or Renal Tubular Acidosis) the electroneutrality of ECF is maintained by a compensatory rise in chloride level, the condition being termed HYPERCHLOREMIC acidosis or NORMAL ANION GAP METABOLIC ACIDOSIS.

Accumulation of endogenous acids of cellular metabolism like lactic acid, ketoacid, sulfuric acid also decrease the bicarbonate level, but here there is an additional accumulation of acidic anions like lactate, acetoacetate and sulfate. This can be depicted as.

$$HA\ (ACID) + HCO_3 \longrightarrow H_2CO_3 + A^-\ (ACIDIC\ ANION)$$

HCO^-_3 falls as a result of buffering the H^+ ions released from HA. A^- or the acidic anion like lactate, sulfate etc accumulates. This

accumulation of unmeasured anions increases the anion gap and thus the acidosis becomes an INCREASED ANION GAP metabolic acidosis.

EVALUATION OF NORMAL ANION GAP METABOLIC ACIDOSIS (21)

Given the clinical picture of diarrhea, a normal anion gap acidosis can be taken to mean bicarbonate loss through GIT.

Like-wise presence of clinical features of Renal Tubular Acidosis (RTA) [a condition where bicarbonate is lost through kidney] like renal rickets, renal stones, failure of urinary acidification with a consistent family history suggests RTA.

However the following evaluation will be required to make a confirmatory diagnosis of these disorders if only ABG is available.

i. UAG (URINARY ANION GAP) OR URINE NET CHARGE:

UAG is the difference between the difference between the major measured cations and anions in urine.

$UAG = [Na^+]_U + [K^+]_U - [Cl^-]_U$

Since NH_4^+ is the major unmeasured urinary cation a negative UAG reflects a high NH_4^+ excretion.

Conversely a positive UAG signifies either low NH_4^+ excretion. The former occurs in diarrhea and later in RTA.

EVALUATION OF INCREASED ANION GAP METABOLIC ACIDOSIS (21)

Important causes of increased anion gap metabolic acidosis include.

i. Renal Failure with retention of endogenously produced acids like sulfuric acid etc.

ii. Lactic acidosis

iii. Keto acidosis

iv. Salicylate poisoning or other toxin ingestions.

Hence evaluation of an increased anion gap metabolic acidosis would necessitate measuring serum creatinine, as a part of renal function test, serum lactic acid level, qualitative and quantitative tests for ketoacids and a toxicology screen if circumstances dictate.

Now it is evident that diarrhea can produce a normal anion gap metabolic acidosis because of bicarbonate loss, and an increased anion gap metabolic acidosis due to ARF, lactic acidosis and ketoacidosis.

TREATMENT OF METABOLIC ACIDOSIS (22)

Treatment of metabolic acidosis with alkali must be reserved for severe acidemia except when patient has no ``Potential bicarbonate`` in plasma. Potential bicarbonate indicates presence of a metabolisable anion like lactate, acetoacetete etc., that can be converted to bicarbonate in liver. Thus it is not always necessary to give alkali in lactic acidosis and keto acidosis. Infact alkali administration may paradoxically worsen lactic acidosis and thus correction of underlying disorder must be the aim in the above two situations.

In renal failure acidosis is due to retention of acids and there is no potential bicarbonate and hence acidosis requires intervention and all efforts to reestablish a normal renal function must be undertaken.

In diarrhea bicarbonate is lost in stools and thus there is no potential bicarbonate in plasma and hence alkali replacement is necessary.

Correction of metabolic acidosis requires either oral or intravenous alkali in an amount necessary to slowly rise the plasma bicarbonate to 20 mmol/L to 22 mmol/L.

In general severe acidosis ($pH \leq 7.2$) requires intravenous bicarbonate about 50 to 100 mEq to be administered slowly over 30 to 45 minutes. Provision of such modest quantities of alkali in this situation provides an

added measure of safety, but it is essential to monitor plasma electrolytes especially K^+. The goal is to increase pH to 7.2 and not to normal.

Before the discussion on acid-base metabolism is ended the normal values are summarised

PARAMETER	NORMAL RANGE
i. pH	7.35 to 7.45
ii. PCO_2	35 to 100mm Hg
iii. PO_2	80 – 100 mm. Hg.
iv. HCO^-_3	24 – 28 mEq/ L
v. Anion gap	12 – 14 mEq/L
vi. Base Excess	- 2 to + 2 mEq/L

CONCEPT OF BASE EXCESS (23)

The normal value is –2 to + 2. Values outside this range indicate existence of a non respiratory (metabolic) contribution to the acid base disorder. If it is below – 2 it means there is metabolic acidosis and values above +2 indicate metabolic alkalosis.

Finally the assessment of hydration status in acute diarrhea is described. This system adopted from Mandell, Douglas Text Book on Principles and Practice of Infectious Diseases, 5th Edition is described below and was followed in this study.

PARAMETER	MILD DEHYDRATION	MODERATE DEHYDRATION	SEVERE DEHYDRATION
Mentation	Alert	Restless	Drowsy, confused or comatose
Radial Pulse Rate	Normal	Increased	Very Increased
Volume	Normal	Weak	Feeble or impalpable
Respiration	Normal	Deep	Deep and Rapid
Systolic BP	Normal	Low	Not recordable
Skin elasticity	Retracts Fastly	Retracts Slowly	Very Slow Retraction
Eyes	Normal	Sunken	Very Sunken
Urine output	Normal	oliguria	Oliguria

MATERIALS AND METHODS

STUDY DESIGN

This study is a prospective study conducted in Thanjavur Medical College, Department of General Medicine and Department of Nephrology.

In this study patients admitted for acute diarrheal disease in medical ward and infectious disease ward were included.

INCLUSION CRITERIA

Patients older than 12 years of age, who presented with acute diarrheal were included.

Acute diarrhea was defined as passage of 3 or more loose stools per day for a duration of less than 14 days.

Both sexes were included in the study.

EXCLUSION CRITERIA

Since this study aims at identifying the acid-base changes occurring as a result of acute diarrhea, the following patients were excluded.

1. Patients who had coexisting diseases like COPD, or other lung diseases likely to produce respiratory acidosis in ABG,

Diabetes Mellitus patients (who might have Type IV RTA – hyporeninemic hypoaldosteronism), liver disease and chronic kidney diseases were excluded, because these pathologies might themselves produce abnormalities in ABG.

2. Patients who were on drugs likely to produce Acid-Base disturbances were also excluded.

Ex. Metformin (for PCOD)

Cholestyramine

Calcium or Magnesium chloride

Lysine or Arginine hydrochloride

Acetazolamide

Drugs causing RTA (Renal Tubular Acidosis)

Ex. Cotrimoxazole

Spironolactone

Triamterene

STUDY PERIOD

This study was conducted between SEPTEMBER 2004 and AUGUST 2006.

STUDY POPULATION

The study included 52 patients, 28 males and 24 females. The youngest patient in the study was 17 years of age and the oldest patient was 78 years of age. All satisfied the inclusion and exclusion criteria.

STUDY PROTOCOL AND LABORATORY INVESTIGATIONS

In all patients preliminary history regarding duration of diarrhea, presence of vomiting and oliguria was recorded.

Clinical examination was focussed on identifying the degree of dehydration, acidotic breathing if any, vital signs and systemic examination to rule out coexisting diseases that might confound the acid-base picture.

In all patients routine urinalysis for albumin, sugar, deposits was done. Also urine was analysed for acetone, since patients with diarrhea could starve resulting in starvation keto acidosis.

In all patients haemoglobin estimation was routinely done. It is mandatory to know the hemoglobin level for determining oxygen content of blood in ABG analysis.

If any patient was found to have renal failure (defined as serum creatinine > 2mg%), serial measurements were made as appropriate and after treatment.

OBTAINING THE ARTERIAL BLOOD SAMPLE (24)

About 1cc. of arterial blood sample is required for Arterial Blood Gas analysis (ABG).

Arterial blood was drawn from any one of radial artery, brachial artery or femoral artery. Before radial puncture was done, the patency of ulnar artery was ensured by doing Allens test.

Arterial blood was drawn in heparinised syringe (containing about 0.1 ml. Of heparin which was used to rinse the syringe), by inserting the needle at an angle of about 30^0 to the skin surface while puncturing the radial artery. All strict aseptic precautions were undertaken.

It was ensured that no air got admixed with the blood sample in the syringe, by using a robber cork to close the bevel edge of the needle.

TRANSPORTING THE ARTERIAL BLOOD SAMPLE (24)

All arterial blood samples were transported to the lab immediately or with in 15 to 20 minutes. If a delay of 15 to 20mts. was anticipated, samples were transported in closed containers having ice packs. However no sample was allowed to freeze. If a delay of more than 20 minutes occurred due to unavoidable reasons, such samples were excluded.

INTERPRETING ABG RESULTS AND FURTHER ACTIONS

The various parameters obtained like pH, pO_2, pCO_2, HCO_3^-, Base Excess (BE) were analyzed and ABG values interpreted in a systematic way as previously described.

Anion gap was to be calculated separately using the formula, AG (Anion Gap) = $Na^+ - [Cl^- + HCO_3^-]$. Value used, as reference was 12-14 mEq/L. An anion gap of more than 14 was interpreted as high anion gap.

In case a high anion gap acidosis was encountered serum albumin was measured, since perturbation in albumin level might itself alter anion gap.

Further evaluation of increased anion gap acidosis mandated test for ketones which was routinely done in the study and measurement of serum lactate levels which could not be done.

All patients were under continuos observation and repeat investigations like renal parameters and ABG were done (even if not mentioned) as the clinical condition would dictate. For instance administration of bicarbonate intravenously was carefully monitored with serum electrolytes and ABG. Other investigations like stool analysis for evaluating diarrhea were routinely done.

TREATMENT PROTOCOL FOLLOWED

All patients were rehydrated with oral fluids, ORS and with IV Fluids (2:1 saline, lactate cycle) as required. (34)

If any patient had severe acidosis (pH $\leq$ 7.2) bicarbonate was administered intravenously. About 50-75 ml. of 7.5% sodium bicarbonate was infused IV slowly over a period of one hour.

If the patient presented with elevated renal parameters fluid challenge with 1.0 to 1.5 litres of IVF was given. If the patient showed improvement in urine output and clinical picture, rehydration therapy was continued. If the patient had persistent oliguria despite rehydration and other uremic manifestations mandating dialysis, peritoneal or haemodialysis was undertaken. Periodic monitoring of renal functions was also undertaken. Antibiotics were given as appropriate. Patients were discharged once diarrhea stopped and renal functions returned to normal if they initially had renal failure.

OBSERVATIONS AND RESULTS

Fifty two patients with acute diarrhea were included in the study.

The following observations were made.

I.ACID-BASE DISTURBANCES OBSERVED

In descending order of frequency

i. Normal anion gap metabolic acidosis

ii. Increased anion gap metabolic acidosis

iii. Normal ABG study.

Total No of Patients Studied	No of Patients with Normal Anion Gap Acidosis	No.of Patients With Increased Anion Gap Acidosis	No. of Patients with Normal ABG
52	32	14	6

The relative contribution of each type of ABG study can be pictorially represented as shown in the pie chart in the next page.

I.ACID BASE DISTURBANCES IN PATIENTS WITH ARF DUE TO ACUTE DIARRHEA

14 out of 52 patients with acute diarrhea had ARF.

All 14 patients had increased anion gap metabolic acidosis.

III. INCIDENCE OF SEVERE METABOLIC ACIDOSIS

(PH $\leq$ 7.2)

7 out of 52 patients with acute diarrhea had severe metabolic acidosis (pH $\leq$ 7.2).

Out of these 7 patients, 5 had renal failure and 2 patients had normal renal parameters.

RENAL FUNCTION IN PATIENTS WITH SEVERE ACIDOSIS

Total No. of Patients With Severe Metabolic Acidosis	No. of Patients with renal failure	No. of Patients with normal renal function
7	5	2

INCIDENCE OF SEVERE METABOLIC ACIDOSIS

Category	Total No. of Patients	No. of Patients with severe Acidosis	Incidence of Severe Metabolic Acidosis
Patients with Acute Diarrhea	52	7	13.46%
Patients with Acute Renal Failure Due to Acute Diarrhea	14	5	35.71%
Patients with Normal Renal Function	38	2	5.26%

IV.MORTALITY RATE

Two out of 52 patients with acute diarrhea died.

Both patients had renal failure and severe acidosis

MORTALITY IN METABOLIC ACIDOSIS ACCORDING TO pH

pH	Total No. of Patients	No. of Patients Deaths	Mortality Rate
pH $\leq$ 7.2	7	2	28.57%
pH > 7.2	45	0	0%

MORTALITY IN POST DIARRHEAL ARF

Total No. of Patients	No. of Patients Who Died	Mortality Rate
14	2	14.2%

DISCUSSION

This study aims at identifying the various acid-base disturbances that occur in patients with acute diarrhea, the acid-base abnormalities that occur in post diarrheal ARF, and to findout if there is a prognostic significance for metabolic acidosis.

To accomplish the above tasks, 52 patients with acute diarrhea were included in the study. Among the 52 patients 28 were males and 24 were females. The mean duration of diarrhea at presentation was 2.01 days

Among the 52 patients studied 14 patients (9 Men & 5 Women) had renal failure (serum creatinine more than 2mg%) at initial presentation to hospital(25). The mean duration of diarrhea on admission, in this population was 2.85 days. None of the patients developed renal failure after admission to hospital.

The ABG values of all 52 patients were interpreted in a systematic way as previously described.

I.ACID BASE CHANGES OCCURRING IN ACUTE DIARRHEA

The following 3 types of Acid-Base changes were observed on analysing the ABG values of all 52 patients: .

1. Normal anion gap metabolic acidosis
2. Increased anion gap metabolic acidosis
3. Normal ABG study.

Out of the 52 patients studied, 32 patients had a normal anion gap metabolic acidosis, 14 patients had an increased anion gap metabolic acidosis, 6 patients had normal ABG values.

Hence it is inferred that **NORMAL ANION GAP METABOLIC ACIDOSIS IS THE MOST COMMON ACID-BASE ABNORMALITY** in acute diarrheal illness.

The reason for a normal anion gap metabolic acidosis, as described previously is loss of bicarbonate in diarrheic stools.

The other findings noted in this population of patients included

i. Hyperchloremia findings (Sr. Chloride > 105 mEq/L)

ii. Normal Na^+ and K^+ values

iii. A less severe acidosis (ie. pH > 7.20) in most (30 out of 32) patients

iv. Expected range of respiratory compensation.

Hyperchloremia occurring in this population was a compensatory response to loss of bicarbonate in stools, so as to maintain the electro neutrality of Extra Cellular Fluid (ECF) (Hence referred to as HYPERCHLOREMIC ACIOSIS)

Even though serum sodium and potassium levels were normal hypokalemia can also be anticipated, because patients with acute diarrheal disease lose potassium through GIT. Like wise dysnatremia can also be anticipated.

30 out 32 patients had a pH above 7.20 and all had respiratory compensation in the expected range.

The next common acid-base-disturbance observed was an increased anion gap metabolic acidosis (14 patients).

A patient with acute diarrheal illness can develop increased anion gap metabolic acidosis for the following reasons.

i. Development of renal failure with retention of acidic anions like sulfate, phosphate etc.
ii. Lactic acidosis occurring as a result of tissue hypoperfusion.
iii. Keto acidosis due to starvation.

All patients in this group were evaluated with the above possibilities in mind.

It was observed that all 14 patients had renal failure (Sr. creatinine > 2.0 mg%) and their urine tested negative for ketones. Serum albumin was measured in this population of patients. (because albumin is a normal anionic constituent of plasma and perturbations in albumin level may alter AG) and found to be with in the normal reference range. Serum lactate could not be measured.

Hence one explanation that could be offered for the increased anion gap metabolic acidosis in this setting was renal failure.

Serum chloride level was found to be normal in all patients (an expected finding in increased anion gap acidosis). Na^+ and K^+ levels were found to be normal.

The least common acid-base status in acute diarrheal illness was normal ABG study (6 patients).

The following 3 possibilities must be considered when one encounters a normal ABG analysis in acute diarrhea :

i. A patient might have a mild diarrheal illness, so that there is only a minimal bicarbonate loss, which is of no biochemical significance.

ii. A combination of metabolic acidosis (due to bicarbonate loss in stools) and metabolic alkalosis (due to loss of acid in vomits) may occur in patients with acute diarrheal diseases. So a normal ABG study in the clinical context of severe vomiting and diarrhea should suggest a combination of metabolic acidosis and metabolic alkalosis. In this clinical situation pH, pCO_2, HCO^-_3, AG all will be normal.

iii. A combination of high anion gap acidosis (ex. renal failure, lactic acidosis) and metabolic alkalosis (due to vomiting) may coexist. Here pH, pO_2, pCO_2 and HCO^-_3 will be normal, but anion gap will be high.

All 6 patients who had normal ABG study were clinically suffering from a milder degree of diarrhea and dehydration and vomiting was not a prominent manifestation.

So a milder diarrheal illness may be postulated as the reason behind the normal ABG study, than a mixed acid base disorder. No significant difference in the clinical presentation of each of the 3 groups of patients could be noted.

These 3 patterns of acid-base disturbances are well recognized manifestation of acute diarrhea described in text books in Internal Medicine and Arterial Blood Gas analysis. But this study gives the relative proportion of each of the 3 patterns observed in acute diarrhea (61.5%, 27% and 11.5%).

A similar study conducted in children with gastroenteritis in Feb.1993 in Soroka Medical Centre, Beer sheva, Israel (*Weizman-Z, Houri S et al*.,) inferred that 70% of children with acute gastroenteritis had a normal anion gap metabolic acidosis and the remaining 30% had increased anion gap metabolic acidosis.

Studies on `Acidosis in Cholera` – *Zalunardo et al.,* October 2004, `The Acidosis of Cholera – contributing factors` – *Wang F Butler et al*., NEJM DEC 1986 are comparible studies.

II.ACID BASE CHANGES IN ARF DUE TO ACUTE DIARRHEA

The next aim of this study is to analyse the acid-base changes that occur in patients developing renal failure due to acute diarrhea.

Among the 52 patients studied 14 patients had renal failure at presentation to hospital. All 14 patients demonstrated a HIGH ANION GAP METABOLIC ACIDOSIS. 5 out of 14 patients had severe metabolic acidosis ($pH \leq 7.2$). In all 14 patients urine tested negative for acetone and

serum albumin was normal. All 14 patients had normal Na^+ and K^+ levels. This observation is comparable with preexisting literature. (26)

III.INCIDENCE OF SEVERE METABOLIC ACIDOSIS

It was found that 7 out of 52 patients with acute diarrhea had a severe metabolic acidosis i.e., pH $\leq$ 7.2 in ABG study. Hence the incidence of severe metabolic acidosis in patients with acute diarrhea was 13.46%.

Among these 7 patients, 5 patients had renal failure and 2 patients had normal renal function. So the incidence of severe acidosis in patients with renal failure due to diarrhea was 5 out of 14 patients, i.e. 35.71% and the incidence of severe acidosis in patients with normal renal function was 2 out of 38 patients i.e. 5.26%.

So severe metabolic acidosis occurred in both groups of patients with acute diarrhea (i.e., patients with renal failure and patients with normal renal function).

The higher incidence of severe acidosis in patients with renal failure than in those with out renal failure only exemplifies the pivotal role of kidneys in maintaining a normal acid-base mileu.

IS METABOLIC ACIDOSIS A PROGNOSTIC MARKER?

To find out the prognostic significance of metabolic acidosis patients were stratified into 2 groups, one having a pH $\leq$ 7.2 (severe metabolic acidosis) and the other having a pH > 7.2.

pH of 7.2 is used as the demarcation between the two groups for the following reasons:

a. Patients with severe metabolic acidosis are at a higher risk of developing adverse manifestations like CNS depression, cardiovascular dysfunction and pulmonary edema.

b. Because of the threat posed by severe metabolic acidosis on various organ systems, patients with pH < 7.2 must be promptly recognised and treated with bicarbonate infusion.

c. Previous studies could identify a poor prognosis for patients with pH $\leq$ 7.2 (M.A – Muthusethupathi et al., 1990 MMC, Chennai).

When such a pH demarcation was used it was observed that 7 out of 52 patients with acute diarrhea had severe acidosis and the remaining 45 patients had a pH > 7.2. All patients with pH $\leq$ 7.2 were treated with IV bicarbonate (7.5%) in a way described previously.

The prognosis in each group was assessed by calculating the mortality rate.

It was found that two out of seven patients with severe acidosis died while no death occurred in the remaining 45 patients. So the incidence of mortality in those with severe acidosis was 28.57% while no death occurred in those with a pH > 7.2.

Hence it is evident that prognosis interms of mortality is worse in those with severe acidosis.

This calls for early recognition and prompt correction of metabolic acidosis.

Among the 7 patients with severe acidosis both deaths occurred in those with ARF. So it can be inferred that the mortality rate is still high (2 out of 5) i.e. 40% if both renal failure and severe acidosis operate in the same patient.

A study conducted on post diarrheal ARF by M.A. Muthusethupathi, S. Sivakumar et al., in MMC, Chennai in 1990 aimed at assessing the prognostic significance of metabolic acidosis in post diarrheal ARF.

The study concluded that early identification and prompt correction of metabolic acidosis with bicarbonate could reduce the mortality from the

previous figures of 53% in post diarrheal ARF (before the wide spread availability of ABG) to 26%.

In the current study of 52 patients with acute diarrhea, 14 had renal failure and 2 patients died due to ARF and its consequences (including acidosis). So the mortality rate for post diarrheal ARF in this study is 2 out of 14 or 14.2%.

So this reduction in mortality can be attributed to early identification and prompt correction of metabolic acidosis.

Thus metabolic acidosis has prognostic significance and early correction of acidosis improves outcome.

CONCLUSION

The most common acid-base disturbance observed in patients with acute diarrheal disease is NORMAL ANION GAP METABOLIC ACIDOSIS.

Other acid-base patterns observed include increased anion gap metabolic acidosis and a normal ABG study.

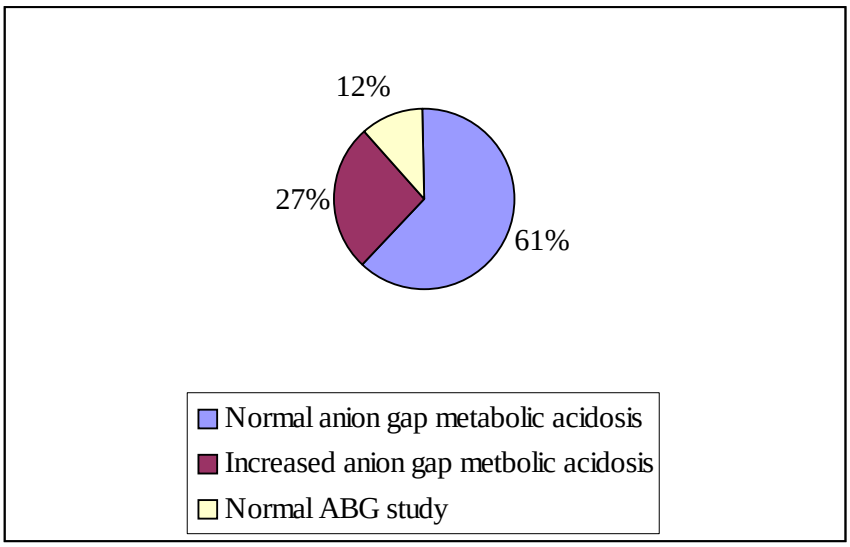
A normal ABG must be interpreted in the clinical context because mixed acid base disorders may produce normal values in ABG analysis.

The acid-base abnormality observed in post diarrheal ARF is increased anion gap metabolic acidosis.

Metabolic acidosis is a prognostic factor and early recognition and prompt correction of metabolic acidosis improves the outcome in acute diarrheal disease and post diarrheal ARF.

ACID-BASE DISTURBANCES OBSERVER IN

ACUTE DIARRHEAL DISEASE



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