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# Acidosis and Anion Gap

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## Abstract

The journey of exploring acid and base starts long before, but much advancement was seen in the last century. In 1890, Wilhelm Ostwald electronically measured hydrogen. Svante Arrhenius won the Noble prize in 1903 for the theory of ionization. In 1908, Henderson and Black showed that bicarbonate and phosphate equilibrate with  $\text{CO}_2$  at normal body temperature. In 1923, Bronsted first put forward the idea of acid that ionizes in solution and donate hydrogen and the base accepts the hydrogen from the solution. Handerson invented the important bicarbonate buffer system and Hasselbalch First measured the actual blood pH. In 1909, S. P. S. Sorensen developed the pH scale. Later Hasselbalch-Henderson developed an equation that helped in relating pH to the blood bicarbonate and  $\text{PCO}_2$ . Acidosis has fatal consequences like CNS damage and death. Acidosis is rapidly stabilized by the body buffer systems. There are equal amounts of cations and anions in blood, but some of them are unmeasured. These unmeasured ions are mostly anions that produce an anion gap. Increased anion gap usually represents metabolic acidosis. Albumin and many other confounding factors influence the anion gap derangements. Accuracy in measuring anion gap is critically important for the evaluation of acidosis.

**Keywords:** anion gap, acidosis

## 1. Introduction

The journey of exploring acid and base starts long before, but in the last century the advancement was remarkable. In 1890, Wilhelm Ostwald electronically measured hydrogen [1]. Svante Arrhenius won the Noble prize in 1903 for the theory of ionization [2]. In 1908, Henderson and Black showed that bicarbonate and phosphate equilibrated with  $\text{CO}_2$  at normal body temperature in different solution [3]. In 1923, Bronsted first put forward the idea of acid as a substance that ionizes in solution and donate hydrogen and the base accepts the hydrogen from the solution [4]. Bronsted, Henderson and Van Slyke described acid-base balance in the early part of nineteenth century [5]. Handerson invented bicarbonate as the most important buffer system of the body, and Hasselbalch first measured the real blood pH in the early part of nineteenth century [6–8]. In 1909, S. P. S. Sorensen developed the pH scale [8]. Later Hasselbalch-Henderson developed an equation that helped in relating pH to the blood bicarbonate and  $\text{PCO}_2$  [7, 9, 10]. In the early 1980s, scientists introduced electrodes specific for each ion. Thereafter, serum electrolyte and the anion gap measurement become routine tools for assessing acidosis.

Acidosis has fatal consequences like CNS damage. Even death is not uncommon. Acidosis is characterized by a decrease in pH, and this change is rapidly

corrected by the body buffer systems. Many clinical conditions develop acidosis, as well as ionic derangements and the only correction of the underlying cause can resolve it. There are equal numbers of cations and anions in the blood and among them there are some unmeasured anions. These unmeasured anions can contribute in the clinically important anion gap. In a healthy individual, there is an acceptable range of normal anion gap. But some conditions can increase or decrease this gap. Increased anion gap usually represents metabolic acidosis. Albumin and many other confounding factors influence the anion gap derangements. Accuracy in measuring anion gap is critically important for the evaluation of acidosis.

## **2. Normal acid-base balance**

The body maintains its normal physiology by the strict balance of acid and base. The body maintains its normal arterial pH close to 7.4 at a range between 7.36–7.44, and the intracellular pH of the human body is 7.2 [11]. Normal acid-base balance is the balance between each hydrogen increase by the intake or production, and that is decreased by elimination. Acid-base balance is measured by measuring pH,  $\text{CO}_2$  and  $\text{HCO}_3^-$ . In general, consuming animal protein add acid in the body, and consuming cereals and vegetables add alkali in the body. In oxidative metabolism,  $\text{CO}_2$  is produced in the tissue, and at a similar rate, that is eliminated by the lungs. So,  $\text{pCO}_2$  persists at about 5.33 kPa (40 mm of Hg). Different buffer systems of the body play a crucial role in removing excess  $\text{H}^+$ . Metabolism of carbohydrate and fat uses  $\text{O}_2$  and produce  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . Normal lungs efficiently remove most of the  $\text{CO}_2$ . In oxidation of amino acids, carbon dioxide and water are produced along with the liberation of nitrogen as ammonia, a toxic material in the body. In the liver, the urea cycle utilizes the ammonia, where this toxic  $\text{NH}_3$  combines with  $\text{CO}_2$ , and produce urea. In the proximal tubule and other renal epithelial cells, ammonia and bicarbonate are also produced from glutamine metabolism. Some of it returns to the body fluid through the renal veins and is metabolized in the liver. And the rest of the  $\text{NH}_3$  excreted in the lumen. So,  $\text{NH}_3$  does not exist in the body fluid. Most of the  $\text{NH}_3$  is excreted in the urine, and it plays an important role in removing  $\text{H}^+$  to maintain normal acid-base balance. In the urine,  $\text{NH}_3$  binds hydrogen ion to produce  $\text{NH}_4^+$ , and it prevents excessive acidification of urine.

## **3. Respiratory and renal regulation of acid and base**

Excess acid is eliminated from the body by the lungs and the kidneys. In the lungs, acid is eliminated in the form of  $\text{CO}_2$ , and in the kidneys, acid is excreted as acid phosphate and ammonium.  $\text{CO}_2$  is lipid soluble, and it crosses the cell membranes in the lungs. Most of the  $\text{CO}_2$  produced in the tissue is eliminated by alveolar ventilation. Arterial and brain chemoreceptors can sense the acid and base excess, and respiratory system responds with hyper or hypo ventilation. As a result, pH is increased or decreased by increasing and decreasing  $\text{pCO}_2$  level. The regulation between  $\text{CO}_2$  and  $\text{H}_2\text{CO}_3$  level is critically maintained when the blood travels through the lung capillaries. When strong acid is added, some  $\text{HCO}_3^-$  become  $\text{H}_2\text{CO}_3$  and blood  $\text{PCO}_2$  is increased. In acidosis, carbonic acid dissociate to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . As a result, respiratory center is stimulated and it leads to hyperventilation. Hyperventilation eliminates these  $\text{CO}_2$  to maintain normal pH. In alkalosis,  $\text{CO}_2$  is retained by hypoventilation. This  $\text{CO}_2$  combines with  $\text{H}_2\text{O}$  to produce  $\text{H}_2\text{CO}_3$ , and pH is maintained.

The kidneys excrete acids, both respiratory and nonrespiratory origin and retain  $\text{HCO}_3^-$  to stabilize the pH of blood.  $\text{HCO}_3^-$  is predominantly regulated in the kidneys. The nephron reabsorbs all filtered bicarbonate in exchange for  $\text{H}^+$ . The kidneys also produce new bicarbonate to neutralize acids. Tubular cells contain carbonic anhydrase, that converts  $\text{CO}_2$  and  $\text{H}_2\text{O}$  to  $\text{HCO}_3^-$  and  $\text{H}^+$ . Newly formed  $\text{HCO}_3^-$  is shunted to peritubular capillaries and  $\text{H}^+$  is excreted in tubular lumen. Bicarbonate is also produced from glutamine metabolism along with ammonium. Some  $\text{NH}_4$  diffuses to body fluid and converts to urea in the liver. The rest of the them excreted in urine. The tubules are impermeable to bicarbonate, and it cannot be converted back to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . So, the blood  $\text{HCO}_3$  level is increased.

In the apical membrane of the kidney tubules, sodium is reabsorbed in exchange for the hydrogen ion. Salts like sulfates, phosphates, ammonia combines the hydrogen ions and excrete it. The kidneys titrate less than half of the excreted acids and the rest is excreted as ammonium [11]. For every ammonium excreted in urine, one  $\text{HCO}_3^-$  is reabsorbed.  $\text{HCl}$  and  $\text{H}_2\text{SO}_4$  are produced during dietary protein metabolism reacts with  $\text{NaHSO}_4$ , and produce  $\text{NaCl}$  and  $\text{Na}_2\text{SO}_4$ . These Na salts are excreted by the kidneys as  $\text{NH}_4\text{Cl}$ , and  $(\text{NH}_4)_2\text{SO}_4$ .

The kidneys are largely responsible for  $\text{K}^+$  excretion and most of it is reabsorbed in the proximal tubule and in the loop of Henly. In acidosis,  $\text{K}^+$  secretion is decreased and  $\text{K}^+$  absorption is increased in the collecting duct. In alkalosis, hypokalemia develops from increased  $\text{K}^+$  secretion and reduced  $\text{K}^+$  absorption in the collecting duct.  $\text{H}^+$  and  $\text{K}^+$  exchange occur in the tubules. Serum potassium level also influences the renal acid-base balance. In hyperkalemia, potassium is available in an increased amount in the filtrate, and hydrogen will be scarce for exchange with  $\text{HCO}_3$  and there will be an imbalance. In hypokalemia, less potassium will be available for  $\text{H}^+$  and  $\text{K}^+$  exchange and hydrogen will be available to exchange with bicarbonate.

$\text{Na}^+$ ,  $\text{K}^+$  and  $\text{NH}_4^+$  are the principle urinary cations, and the principal urinary anion is chloride. Urinary anion gap helps in estimating renal  $\text{NH}_4^+$  excretion, as  $\text{NH}_4^+$  is the urinary unmeasured ion. Chloride is an important anion in neutralizing positive ions, reabsorbed in the proximal convoluted tubule and secreted in urine by the collecting duct. Secreted  $\text{H}^+$  is also buffered by urinary buffer  $\text{HPO}_4^-$  to  $\text{H}_2\text{PO}_4$ , and is excreted in urine.

#### 4. Acidosis and buffer

Acidosis results from a reduction in serum bicarbonate and cause secondary reduction of  $\text{PaCO}_2$  resulting in a low blood pH. It develops from the addition of hydrogen or removal of  $\text{HCO}_3$  from the body.  $\text{PaCO}_2$  in blood is  $38 \pm 2$  mm of Hg and  $\text{HCO}_3$  is  $24 \pm 2$  mmol/L. Metabolic acidosis is characterized by the blood pH  $<7.38$  and bicarbonate  $<22$  mmol/L [12].

Acid and base disorders are: respiratory acidosis and respiratory alkalosis, and metabolic acidosis and metabolic alkalosis [13]. In respiratory acidosis,  $\text{PaCO}_2$  is increased and it is compensated by renal  $\text{H}^+$  excretion,  $\text{HCO}_3$  retention and  $\text{HCO}_3$  generation. In respiratory alkalosis, decreased  $\text{PaCO}_2$  is compensated by renal  $\text{HCO}_3$  excretion. In metabolic acidosis,  $\text{HCO}_3$  is reduced and it is compensated by hyperventilation and  $\text{PaCO}_2$  reduction.  $\text{HCO}_3$  is increased in metabolic alkalosis, and it is compensated by increasing  $\text{PaCO}_2$  by hypoventilation [14]. Usually, respiratory disorders cause derangements of  $\text{CO}_2$  level in the blood, and change in  $\text{HCO}_3$  level is developed from metabolic disturbances.

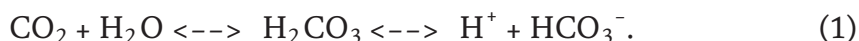
In the blood, Alkali is present mainly in the form of sodium bicarbonate, and bicarbonate is bound to other bases. Increase in  $\text{BHCO}_3$  and decrease in  $\text{H}_2\text{CO}_3$

results in alkalosis, and decrease in  $\text{BHCO}_3$  and increase in  $\text{H}_2\text{CO}_3$  results in acidosis [13]. The body contains many acids. They are hydrochloric acid, carbonic acid, citric acid, lactic acid, phosphoric acid and carboxylic acid. Acute metabolic acidosis is developed by the overproduction of organic acids, like lactic acid and keto acid. Chronic acidosis is caused by bicarbonate wasting and impaired urinary acidification.

Blood cells are more acidic than serum, which influences the distribution of electrolyte and water between them. These transports took place with the oxygenation and reduction of hemoglobin and shift of bases ( $\text{Na}^+$ ,  $\text{K}^+$ ) due to changes in pH. Under normal environment  $\text{Na}^+$  and  $\text{K}^+$  do not diffuse through the cell wall. Shifting of water and electrolyte through membrane results from the change in anion ( $\text{HCO}_3^-$  and  $\text{Cl}^-$ ) and  $\text{H}^+$  concentration, and that changes in cell volume.  $\text{CO}_2$ , relative electrolyte concentration and weak acid concentrations are three independent variables that regulate blood pH [15].

The body has different buffer systems to maintain the normal pH of the body. Elkinton Jr. reported that multiple level of buffering linked different series of ionic exchanges which includes hydrogen, sodium, potassium, and other anions. The buffers absorb excess hydrogen and hydroxyl ions. They help in the maintenance of neutrality during redistribution of the hydrogen ion [16].

A buffer system consists of a weak acid with its conjugate base, or a weak base with its conjugate acid. Blood is a strong solution, and it has many important components that maintain the buffer systems. These include hemoglobin, bicarbonate, carbonic acid, plasma proteins, RBCs and plasma phosphate [17].  $\text{HCO}_3^-/\text{CO}_2$  buffer is the most important buffer system of the body, and plays a major role in regulating pH of the blood. But, the rest of the buffer systems have minimum contribution in pH regulation. In dissolved state, bicarbonate and carbon dioxide ion remains in equilibrium. Bicarbonate reduces strong acid to carbonic acid, whereas carbonic acid neutralizes strong base (Eq. (1)).



When  $\text{CO}_2$  and water is converted to  $\text{HCO}_3^-$  and hydrogen ions, this hydrogen ion is then buffered by hemoglobin [18].

Proteins have a buffering capacity, including hemoglobin. Protein can accept and donate  $\text{H}^+$ , if there is  $\text{H}^+$  excess or it is reduced. Hemoglobin has a distinct types of buffer action. When blood passes through the capillaries, it loses oxygen and took  $\text{CO}_2$  to raise the  $\text{PaCO}_2$  and maintain the pH. Hemoglobin plays an important role in transporting both oxygen and carbon dioxide. In 1914, Douglas, Haldane and Christiansen tried to prove that the hemoglobin binds more  $\text{CO}_2$  in the reduced form than the oxygenated form [19].

The phosphate buffer system works in the internal environment of all cells. But, in the blood  $\text{H}_2\text{PO}_4^-$  and  $\text{HPO}_4^{2-}$  are found in a very low concentration. Sodium dihydrogen phosphate neutralizes strong bases and sodium monohydrogen phosphate neutralizes strong acids. The Phosphate buffer system plays an important role in the kidneys.

## 5. Acid base physiology

Two types of variables, dependent and independent, are important in acid-base balance [20]. Bicarbonate, hydroxyl ion, hydrogen ion or pH, weak acid, anion and carbon trioxide are dependent variables and they are determined by three independent

variables  $p\text{CO}_2$ , total weak acid and net strong ion charge [21]. Lungs, kidneys, liver and gut regulated this balance. Traditional bicarbonate/carbon-di-oxide approach, base excess approach and Stewart's physicochemical methods are widely discussed for measuring the acid base disorders as well as to explore the physiology of body fluid.

## 6. Traditional physiological approach

$\text{HCO}_3/\text{CO}_2$  buffer system is the basis of this approach. Carbonic acid freely moves in the body fluid and dissociates into bicarbonate automatically when needed. Bicarbonate in the body acts as alkaline reserve.  $\text{CO}_2$ , pH and  $\text{HCO}_3$  can be calculated by Hasselbalch-Henderson Equation (2) [7, 9].

$$\text{pH} = \text{pK} + \log_{10} \left[ \frac{[\text{HCO}_3^-]}{s\text{PCO}_2} \right] \quad (2)$$

This equation states that not only  $\text{HCO}_3$  and  $\text{CO}_2$ , but also their ratio determines the pH. In this equation,  $\text{PCO}_2$  is the respiratory component and  $\text{HCO}_3^-$  is the metabolic component of the acid base imbalance. This buffer system is the largest and independent buffer system of the body and whole body acts as an open system for  $\text{CO}_2$ . In traditional approach balance is determined by the influx and efflux of  $\text{H}^+$  and  $\text{HCO}_3$ .

## 7. Base excess approach

Astrup and Siggaard-Anderson introduced base excess approach, which is close to the traditional approach [22, 23]. Base excess can be calculated from bicarbonate concentration and pH of the body [4]. It can estimate the acid base status of non-respiratory origin. If base excess is too high, then it is metabolic alkalosis. If base excess is too low, then it is metabolic acidosis. When a deviation of normal blood pH is corrected by administering base, then it is called base deficit. Which is a characteristic of metabolic acidosis. Base deficit with increase anion gap suggest the addition of acid in the body fluid. If there is a base deficit with normal anion gap, then there is bicarbonate loss from the body.

## 8. Stewart approach

Here  $\text{H}^+$ /proton is the preliminary determinant in acid base disturbances, not the  $\text{CO}_2$  [21]. The dependent variables are  $\text{H}^+$ ,  $\text{OH}^-$ ,  $\text{CO}_3^{2-}$ , HA (weak acid),  $\text{A}^-$  (weak anions),  $\text{HCO}_3^-$  and pH. The independent variables are strong ion difference (SID), total non-volatile weak acids ( $\text{A}_{\text{tot}}$ ) and  $\text{PaCO}_2$  [24]. Among them the strong ion difference has maximum effect on the hydrogen ion concentration. With that, acid base disorder can be divided into three categories: 1. respiratory (increase or decrease  $\text{PaCO}_2$ ), 2. SID changes (excess or deficit of strong ions or water) and 3. inorganic phosphate or albumin deficit or excess ( $\text{A}_{\text{tot}}$  changes). In Stewart approach, a large number of variables are needed to calculate SID. Sodium, potassium, calcium and magnesium are strong positive ions, and chloride and lactate are the negative ions [25]. Bicarbonate and albumin are the balancing ion in strong ion difference. Strong ion difference ( $\text{mEq/L}$ ) = [strong cations] – [strong anions]. Weak acid dissociates in body fluid (Eq. (3)).



$A^-$  Resembles weak anions, that vary with pH. Strong ion difference is filled with this weak  $A^-$ , and  $HCO_3^-$ ,  $H^+$ ,  $OH^-$ ,  $CO_3^{2-}$  are also present in minute amount, but are less important. There are many unmeasured anions accounts for ion difference. For electrical neutrality, strong ion difference and the total charge of weak ions must be equal [26]. Normal SID is dominated by sodium and chloride. But other negligible, but measurable ions are present there. Here narrowing of SID from an increase in  $[Na^+]$  has alkalizing effect, whereas an increase in  $[Cl^-]$  has acidifying effect. From the ionic basis metabolic acid base disturbances are about four major types [25]: (1) The water effect, and it is produced by dilutional effect on SID. Free water intake and intravenous infusion can produce it. (2) The chloride effect is caused by chloride change, and administration of normal saline is the common cause. (3) The protein effect is produced by a change in albumin concentration. (4) There are other factors, and those are influenced by unmeasured anions, that cause a wide anion gap.

## 9. Anion gap

In vivo, true ion gap cannot exist. There are many anions and cations in the blood. Blood cations and anions must be equal. Sodium, chloride and bicarbonate have the highest concentrations, and they are calculated for anion gap for their largest variability in different pathologic conditions. Anion gap is the difference between serum sodium ion and bicarbonate plus chloride. There are wide variations in the reported anion gap. Widely accepted anion gap is 8–12 mmol/L [15]. Anion gap is clinically important for assessing acidosis. Normal anion gap (hyperchloremic) acidosis and increased anion gap acidosis [27] are two important types of anion gap acidosis. Common serum cation levels are sodium  $138.8 \pm 4.56$  mmol/L, potassium  $4.05 \pm 0.21$  mmol/L, magnesium  $0.98 \pm 0.05$  mmol/L [28] and calcium  $2.2\text{--}2.7$  mmol/L [29]. And normal serum anion levels are chloride  $97.7 \pm 3.42$  mmol/L and acetate  $0.23 \pm 0.04$  mmol/L [28]. The sum of cations and anions should be equal (Eq. (4)).

$$Na^+ + K^+ + Mg^{+} + Ca^{+} + Protein^{+} = Cl^{-} + OA^{-} + HCO_3^{-} + SO_4^{-2} + HPO_4^{-2}/HPO_4^{-} + Protein^{-} \quad (4)$$

There are other ions which are not commonly measured, are unmeasured anions and cations [30]. Under normal conditions, albumin and phosphate accounts for this anion gap. There are many clinical conditions, where urate, lactate, ketone bodies, sulfate, salicylates, penicillin's, citrate, pyruvate, and acetates are also responsible for increased anion gap [5]. So, anion gap [31] is Eq. (5)

$$Na - (Cl^{+} + HCO_3^{-}) = UA - UC \quad (5)$$

## 10. Unmeasured anion

Presence of unmeasured anion in blood is the anion gap and it represents metabolic acidosis [32]. When unmeasured anions like lactate and pyruvate donates proton then that proton is buffered by bicarbonate. And bicarbonate consumption increases the anion gap. The most common causes include lactic acidosis, diabetic ketoacidosis, uremia and acidosis due to drugs and toxins. Methanol, propylene glycol, ethylene glycol, salicylate, and some inborn error of metabolism are

other causes of unmeasured anions [33]. Both lactate and  $\beta$ -hydroxybutyrate are increased in both Gram-positive septicemia [34] and starvation [35]. Krebs cycle intermediate citrate, isocitrate, malate,  $\alpha$ -ketoglutarate, succinate and D-lactate are increased in different types of acidosis. Intestinal ischemia and short bowel syndrome cause increase in D-lactate [35]. Plasma proteins are mostly anionic comprising 75% of the unmeasured anion [36–38]. Treatment with Sodium thiosulfate that has no hydrogen can cause severe metabolic acidosis [39].

## 11. Increased anion gap

It usually indicates acidosis. Increase blood lactate, ketoacidosis, uremia (in advanced renal failure), drugs (salicylate and penicillin), ethylene glycol, methanol are contributor of high anion gap acidosis. But the increase anion gap can be due to laboratory error, hyperphosphatemia [30]. Massive rhabdomyolysis, hippurate, oxalate can also cause increased anion gap acidosis [31]. Diabetes, starvation and alcohol are the most common cause of ketoacidosis. In alcoholic ketoacidosis, primary keto acid is  $\beta$ -hydroxybutyrate. It can be missed in conventional assessment of ketonuria. High anion gap and normal lactate level are characteristics of alcoholic acidosis [40]. Starvation alone can cause high anion gap acidosis [41]. In the third trimester of pregnancy, short period of starvation can cause ketogenesis with a very high anion gap acidosis [42]. Septic shock, hypoxemia, hypovolemic shock, cyanide, mesenteric ischemia, CO poisoning, causes hypoxic type of L-lactic acidosis [43]. Non-hypoxic, L-lactic acidosis develops from seizure, thiamine deficiency, metformin, methanol, ethylene glycol, salicylate, propylene glycol, niacin, isoniazide, iron, propofol, toluene, paraldehyde, non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs [12]. Recurrent 5-oxoprolinuria from inborn errors of metabolism is a rare cause of high anion gap metabolic acidosis [44]. Uremia results from not only reduced ammonia secretion but also reduced filtration of sulfate and phosphate anions, and increases the anion gap [45]. Polyclonal gammopathies are also contributor of increased anion gap [46]. Serum albumin is an important contributor to the anion gap and hypoalbuminemia is a common comorbid condition. That is why, albumin correction is crucial for the anion gap calculation [36, 37]. To explore the cause of the metabolic acidosis anion gap must be corrected for albumin as well as lactate [43]. A high anion gap can be masked by a concomitant low anion gap results from hypoalbuminemia.

## 12. Reduced anion gap

In anion gap calculation, sodium is the only cation that is measured. But, hypercalcemia, hyperkalemia and hypermagnesemia can produce significant decrements in anion gap. So, clinical correlation and correction of such abnormality is important. Plasma proteins comprise two third of the unmeasured anion, and hypoalbuminemia is a common cause for the low anion gap [31, 36, 37]. The reduced anion gap is usually seen in delusional states, hypernatremia, hypoalbuminemia, hypermagnesemia, hypercalcemia, bromide intoxication, hyperviscosity associated diseases etc. [47]. Sometimes it can be due to laboratory error, paraproteinemia [48, 49], or iodide [30, 50], gastrointestinal bicarbonate loss and diarrhea [31]. It has been reported that Lithium carbonate intoxication can also produce low or absent anion gap [51]. Non-sodium containing paraprotein IgG in multiple myeloma increase the unmeasured cations and reduce the anion gap [48, 52, 53]. Hypercalcemia and hypoalbuminemia in paraproteinemia also contribute to low anion gap [52].

### 13. Normal anion gap

Measuring anion gap is a routine for evaluating acidosis, and normal anion gap is sometimes misleading. As we know, the increase in anion gap is usual in metabolic acidosis. And acidosis is due to acid retention or ingestion. Normal anion gap acidosis is due to loss of  $\text{HCO}_3^-$  from the body. Hyperchloremic normal anion gap acidosis is characterized by acidosis with excess chloride ions [54]. Here, the low  $\text{HCO}_3^-$  level is a characteristic feature. Reduced negatively charged bicarbonate is compensated by the negatively charged chloride movement into the extracellular space, and normal anion gap is maintained. The causes of gastrointestinal and renal loss of bicarbonate are diarrhea, ureteral diversions, pancreatic and biliary fistulas, toluene ingestion, acetazolamide, ifosfamide, topiramite, tenofovir, renal tubular acidosis. These are the causes of normal anion gap acidosis. Rapid infusion of 0.9% normal saline can also cause hyperchloremic metabolic acidosis [55]. If the blood anion gap is normal, but there is acidosis, then the urinary anion gap Eq. (6) is calculated [12].

$$[\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] \quad (6)$$

The urinary anion gap is negative in diarrhea, sodium infusion and proximal renal tubular acidosis. Whereas, positive urinary anion gap is found in both type 1 and type 4 renal tubular acidosis. Renal tubular acidosis is sometimes the only presenting feature of many chronic diseases and conditions associated with polyclonal gammopathies.

### 14. Metabolic acidosis and anion gap

Metabolic acidosis results from gain of anions and loss of cations. Potassium chloride, hydrogen chloride, sodium chloride, arginine hydrochloride, calcium chloride, ammonium chloride, lysine hydrochloride can cause hyperchloremia and increase anion gap. Hyperphosphatemia increases the anion gap. But renal tubular acidosis [33], amiloride and triamterene cause a non anion gap hyperchloraemic acidosis and hyperkalemia due to impaired bicarbonate production.

Anion gap should be measured for all types of metabolic acidosis. High anion gap metabolic acidosis is a subtype of non-respiratory acidosis. Mnemonics were used for remembering the causes of high gap metabolic acidosis such as KUSMALE (Ketoacidosis, Uraemia, Salicylate poisoning, Methanol, Paraldehyde, Lactate, Ethylene glycol) and MUD PILES (Methanol, Metformin uremia, Diabetic ketoacidosis, Paraldehydes, iron, isoniazid, Lactate, ethylene glycol, Salicylates and starvation). As paraldehyde induced acidosis is extremely rare and recently three anion gap generating organic acid has been recognized. They are Short bowel syndrome producing D-lactic acid, chronic paracetamol use induced 5-oxoproline (or pyroglutamic acid) especially in malnourished woman and high dose propylene glycol (used in lorazepam, phenobarbital) infusions generate acidosis. Also, Iron and Isoniazid can cause lactic acidosis. So, GOLD MARK is a new acronym for metabolic acidosis [Glycols (ethylene and propylene), Oxyproline, L-lactate, D-lactate, Methanol, Aspirin, Renal failure, Ketoacidosis] [56]. Metabolic acidosis also caused by renal bicarbonate loss in type 2 renal tubular acidosis, renal dysfunction in type 4 renal tubular acidosis, type 1 renal tubular acidosis and ingestion of ammonium chloride [31]. Acute rheumatism causes lactate induced acidosis also [57]. Symptomatic correction of acidosis will not eliminate the problem. If the clinical features suggest acidosis, then it should be assessed for anion gap as well.

Following anion gap measurement accordingly history of drug, toxins and diseases need to be evaluated for managing the exact pathology thus acidosis will be properly treated.

## 15. Albumin, phosphate, lactate and corrected anion gap

At normal blood pH 7.4 plasma proteins are mostly anionic. It has been estimated that anion gap decreases by 2.5 mEq/L for every 10 gm/L drop of serum albumin [36, 37]. Several studies had observed that 2–2.5 times changes in albumin influences in anion gap changes [58]. Albumin contributes a greater part of the normal anion gap [46]. Phosphate and lactate contribute some anion gap as well [59]. Consideration of all of these contributors are important in explaining changes in anion gap. Calculation of anion gap is crucial in critically ill patients. Anion gap should be adjusted for Eq. (7) albumin, phosphate and lactate with the following equation [59].

$$\text{Anion gap} = \{(\text{Na}) + (\text{K}) - (\text{Cl}) - (\text{HCO}_3)\} - \{2 \times \text{albumin g/dl} + 0.5 \times \text{phosphate mg/dl}\} - \{\text{lactate mmol/L}\} \quad (7)$$

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