

An Introduction to Acid Base Disorders

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Acid base homeostasis is very important for maintaining life. Extreme changes in acid base status can change protein structure, have effect on enzyme activities and ion transport and will alter almost every metabolic pathway. You can have a clue to the presence of some unsuspected but an important medical condition from identification of mild to moderate acid base disorder. The hydrogen concentration (H^+) in the body is maintained within a narrow range for the normal protein structure and optimum metabolic and enzymatic functions. Kidneys, lungs and the buffering systems maintain this H^+ through a series of interactions.

There are three different approaches currently used in assessing acid–base disorders, These are

1. Traditional or physiological approach, introduced by by Van Slyke and coworkers. This approach uses concentrations of blood carbon dioxide [CO_2] and bicarbonate [HCO_3^-].
2. The base-excess approach, evolved by Astrup and co-workers; this approach uses base excess or base deficit to assess metabolic acidosis or alkalosis.
3. The physicochemical approach, developed by Stewart. This approach measures strong ion difference and $Atot$, the total content of albumin, phosphate, and circulating nonvolatile weak acids and their dissociated anions.

In this review I will discuss the traditional or physiological approach.

Acid base terminology

Acid: An acid is a compound which donates proton or H^+ to another substance. Strength of the acid is its tendency to give H^+ . A strong acid has a high tendency to donate H^+

Base: The compound which accepts proton or H^+ is called as base. Strength of the base is its tendency to accept H^+

Types of Acids

Body produces acids in large amount by metabolic processes. These acids are of two types. Volatile or respiratory acids and fixed acids.

Volatile acids: Carbon dioxide (CO_2) which in itself is not an acid, is produced as end product of complete oxidation of carbohydrates and fats, When dissolved in water gives rise to carbonic acid (H_2CO_3) which is an acid. Solubility coefficient of CO_2 is 0.03 called as αCO_2 . Therefore normal $H_2CO_3 = pCO_2 \times 0.03 = 40 \times 0.03 = 1.2$ meq/l. Every day about 12000 to 15000 mmoles of volatile acid are produced. Since this acid is excreted by lungs therefore it is also called as respiratory acid.

Fixed acid: These acids are produced in the body by incomplete metabolism of carbohydrates (eg lactate), fats (ketones) and protein (sulphate, phosphate). Daily production of fixed acids is about 1 to 1.5 meq/Kg in adults. In infants and children fixed acids production is about 2 meq/kg. All the acids other than H_2CO_3 are fixed. These acids (30-40 meq) are excreted by kidneys as titrable acid (H_3PO_3 , H_2PO_4 , H_2SO_4) and as NH_4 (40-50 meq/day). Excretion as NH_4 can increase to 200 to 300 meq/day in case of increased H^+ in the body due to increase production or addition of acids to the body

Acid base balance: In order to maintain acid base balance, daily acid or base production must be equal to daily excretion of acid or base from the body.

Daily acid or base production = Daily acid or base excretion from the body
 The routes of excretion are the lungs for CO₂ and the kidneys for the fixed acids.
 pCO₂ is determined by amount of CO₂ produced and the alveolar ventilation

$$pCO_2 = V_{CO_2} / V_A$$

Where V_{CO₂} is CO₂ production and V_A is alveolar ventilation

Fixed acids added to extracellular fluid due to metabolism, react with bicarbonate (HCO₃⁻) present in the extracellular fluid.

HX + NaHCO₃ = NaX + H₂CO₃ ↔ H₂O + CO₂ HX is fixed acid like sulphuric acid, phosphoric acid. For every one mEq addition of fixed acid there is loss of one meq of HCO₃⁻. Bicarbonate is filtered by the kidney. Daily filtered amount of HCO₃⁻ = Serum HCO₃⁻ × GFR = 25 × 180 lit = 4500 mEq per 24 hours. Most of this filtered HCO₃⁻ is reabsorbed by the proximal tubule and remaining small amount in the distal tubule of kidneys. Kidneys also regenerate this HCO₃⁻ in the distal tubule to replace HCO₃⁻ lost during neutralization of acids. Kidneys regulate the bicarbonate (base) by regeneration of bicarbonate and by varying the amount of bicarbonate reabsorbed (reclamation). During this process kidneys excrete H⁺ as titrable acids and as NH₄. Net acid excretion = Titrable acid + NH₄ – HCO₃⁻ in urine.

Measurement of acidity.

Acidity in the extracellular fluid (ECF) is measured by [H]⁺. Normal H⁺ concentration is equal to 38-42 nmoles average is 40 nmole/L. That is equal to 0.00000004 mole/L. This amount is very small compared to serum sodium of 140 mmole/L. For convenient sake negative log of this value is used which is called as pH. Negative log of this value 0.00000004 is 7.4 which is normal pH. Henderson-Hasselbalch equation is used to calculate the pH.

$$pH = pK_a + \log \frac{\text{Base}}{\text{Acid}} \text{--- For bicarbonate/carbonic acid buffer system } pK_a \text{ is } 6.1.$$

$$pH = 6.1 + \log \frac{HCO_3}{H_2CO_3} \quad \text{or} \quad pH = 6.1 + \log \frac{HCO_3}{a \cdot pCO_2} \quad pH = 6.1 + \log \frac{24}{0.03 \times 40} = 7.4$$

H⁺ can also be determined by Kassirer Bleich equation

$$H^+ = 24 \times \frac{pCO_2}{HCO_3}$$

Relationship between pH and H⁺

In clinical practice acidity is measured as pH. In order to use Kssirer Bleich equation you should know the relationship between pH and H⁺. You can find out H⁺ from pH by three methods,

1. At pH 7.4 H⁺ is = 40 neq/l. If pH is decreased then to find out H⁺ you multiply 40 by 1.25 for each 0.1 unit drop in pH.

$$pH \ 7.3 \ H^+ = 40 \times 1.25 = 50$$

$$pH \ 7.2 \ H^+ = 40 \times 1.25 \times 1.25 = 62$$

$$pH \ 7.1 \ H^+ = 40 \times 1.25 \times 1.25 \times 1.25 = 78$$

If pH increases H⁺ decreases. For every 0.1 unit increase in pH you multiply 40 by 0.8.

$$\text{For } pH \ 7.5 \ H^+ = 40 \times 0.8 = 32$$

$$pH \ 7.6 \ H^+ = 40 \times 0.8 \times 0.8 = 25$$

2. Between pH of 7.25 to 7.5 for change of pH of 0.01 unit H⁺ changes by 1. For pH 7.5 H⁺ = 30. For pH 7.3 H⁺ is 50. If pH is < 7.2 then H⁺ will increase by 25 for every 0.1 unit drop in pH.

3. For every 0.3 unit change in pH H^+ doubles or halves. If pH is 7.1 H^+ doubles ie 80. If pH is 7.7, H^+ halves equal to 20.

Acid Base Disorder

An **acid base disorder** is a change in the normal value of extracellular pH that may result when renal or respiratory function is abnormal or when an acid or base load overwhelms excretory capacity.

Euphemia

If pH is normal ie.7.38 – 7.42 the condition is called as Euphemia

Alkalemia- If H^+ in ECF is decreased or pH is more than normal, condition is called alkalemia.

Acidemia.

If H^+ is increased in ECF or pH is below the normal range, condition is called academia.

Acidosis

Any process that results in acidemia is called as acidosis.

Alkalosis

Any process that causes alkalemia is called as alkalosis.

Physiological or compensatory response to acid base alteration

The body responds to any change in acid-base status by three systems to minimize the change in pH.

- First defense: Buffering
- Second defense: Respiratory : alteration in arterial pCO_2
- Third defense: Renal response: alteration in HCO_3^- or H^+ excretion

Buffers

The buffer systems in the body are the systems that defend against any alteration in pH. These systems usually consist of a weak acid mixed with its salt and a strong base. Extracellular buffers include bicarbonate/carbonic acid, hemoglobin, and plasma proteins. Intracellular buffers are phosphates and proteins. If a strong acid is added it is neutralized by the base and if strong base is added it is neutralized by the weak acid. Furthermore H^+ is also buffered by bones. Body has a huge buffering capacity, and this system is first line of defense against any attempt to alter pH and has immediate effect.

Respiratory defense.

From both Handerson Hesselback and Kasirrer Bleich equations it is evident that pH or H^+ is the function of ratio of HCO_3 and H_2CO_3 ($0.03 \times pCO_2$). If there is any alteration in HCO_3 due to metabolic problem there is physiological compensatory response by respiratory system. Patient will hyperventilate in case of decrease in HCO_3 and hypo ventilate if there is increase in HCO_3 . This minimizes the change in ratio of HCO_3 to H_2CO_3 and hence the pH or H^+ . This respiratory response to metabolic problem takes minutes to hours.

Renal response.

In case of increase or decrease in pCO_2 due to respiratory problem (respiratory acidosis or alkalosis) kidneys will alter HCO_3 or H^+ excretion. If there is respiratory acidosis kidneys will decrease HCO_3 excretion and raise serum HCO_3 level. In case of respiratory alkalosis kidneys increase HCO_3 excretion. Thus the effect on pH or H^+ is minimized. This renal response is a slow process and takes 2-5 days for full response. Thus change in serum HCO_3 in response to change in pCO_2 is different in acute and chronic respiratory problems.

Compensatory responses to various primary acid base disturbances are given in table 1.

Initial or primary acid base disorder	Compensatory response
Metabolic Acidosis	$\Delta\text{PCO}_2 = 1.25 \times \Delta \text{HCO}_3$ $\text{PCO}_2 = 40 - (1.25 \times \Delta\text{HCO}_3)$ $\text{pCO}_2 = 1.5 (\text{HCO}_3) + 8 \pm 2$ Winter's formula
Metabolic Alkalosis	$\Delta\text{PCO}_2 = 0.6 \times \Delta \text{HCO}_3$ $\text{pCO}_2 = 40 + (0.6 \times \Delta \text{HCO}_3)$ $\text{pCO}_2 = 0.9 (\text{HCO}_3) + 9 \pm 2$
Respiratory Acidosis	HCO_3 increases by 1 mEq/L for every 10 mmHg increase in pCO_2 for acute respiratory acidosis. $\text{HCO}_3 = 24 + (0.1 \times \Delta\text{pCO}_2)$ HCO_3 increases by 3.5 mEq/L for every 10 mmHg increase in pCO_2 $\text{HCO}_3 = 24 + (0.35 \times \Delta\text{pCO}_2)$
Respiratory Alkalosis	HCO_3 drops 2 mEq/L for every 10 mmHg acute drop in PCO_2 . $\text{HCO}_3 = 24 - (0.2 \times \Delta\text{PCO}_2)$ HCO_3 drops 5 mEq/L for every 10 mmHg chronic drop in PCO_2 . $\text{HCO}_3 = 24 - (0.5 \times \Delta\text{PCO}_2)$.

Table 1: Formulas and relationship between different acid-base disturbances

Remember that this physiological compensatory response tend to minimize the change in pH in ECF. In intracellular fluid the effect can be different. If patient has metabolic acidosis, decrease in HCO_3 , pCO_2 will decrease. If you correct serum bicarbonate level patient will stop hyperventilating resulting in increase in pCO_2 . This CO_2 diffuses into the cells more rapidly as compared to HCO_3 . This results in temporary increase in pCO_2 and intracellular acidosis. If the patient has circulatory failure CO_2 will be removed from the cells slowly leading to accumulation of intracellular CO_2 and intracellular acidosis.

Full versus complete compensation

Full compensation is that which is within predicted physiological range and brings pH close to normal but not normalize the pH. Complete compensation brings the pH to normal. Chronic respiratory alkalosis is the only acid base disorder in which compensation is almost complete ie. pH may be normalized.

Classification of Acid base disorders

Simple acid base disorders

Mixed acid base disorders

Double

Triple

Quadruple

Simple acid base disorder.

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

Respiratory \nearrow pCO_2 increases = Respiratory acidosis
 \searrow pCO_2 decreases = Respiratory alkalosis
 Metabolic \rightarrow HCO_3 increases = metabolic alkalosis
 \searrow HCO_3 decreases = metabolic acidosis

Whenever there is primary change in one of the components of acid base system plus physiological compensatory response in the opposite component to minimize effect on H^+ or pH the disorder is called as simple disorder. For example simple respiratory acidosis is increase in

pCO₂ with appropriate increase in HCO₃ as per table 1. Simple metabolic alkalosis is a process in which there is increase HCO₃ with appropriate increase in pCO₂. Thus there are four simple acid base disorders.

Metabolic acidosis

Metabolic acidosis is a process that results in increase in H⁺ concentration or decrease in pH due to addition of acids in the body or loss of base from the body. Arterial blood gases analysis usually carried out to determine acid base status, does not tell you about the type of metabolic acidosis present. To determine the type of metabolic acidosis you need serum electrolytes and calculation of anion gap.

Anion gap (AG) = Serum sodium - (serum chloride + serum bicarbonate). Normal anion gap is 8-12 mEq with average 10 mEq/L. AG represents unmeasured cations. Serum albumin is main unmeasured cation that affects AG. When there is change in serum albumin SG should be corrected for albumin as per formula.

Corrected AG = Calculated AG + 2.5 * (4 - serum albumin)

If there is addition of acid other than HCl you get anion gap metabolic acidosis (AGMA). When there is loss of HCO₃, which is usually replaced by Cl, you get normal anion gap metabolic acidosis (NAGMA). Addition of acid could be from endogenous (lactic acidosis, uremic acidosis, ketoacidosis) or exogenous sources (methanol, Ethylene glycol, toluene). HCO₃ loss could be from kidneys or GI tract

Metabolic alkalosis

Metabolic alkalosis is a process that results in alkalemia due to loss of acid or addition of base in the body. This results in high HCO₃, high pH and high pCO₂. Metabolic alkalosis may be due to increased proximal tubular reabsorption and increased H⁺ secretion or increased H⁺ secretion by distal tubule. ECF volume depletion and secondary hyperaldosteronism is associated with low urinary chloride – chloride responsive metabolic alkalosis. ECF volume expansion due to primary aldosterone excess is associated with high urinary chloride – chloride resistant metabolic acidosis

Respiratory Acidosis

Respiratory acidosis is a process that results in acidemia due to increase in pCO₂ with physiological response that is metabolic alkalosis (increase in HCO₃). Respiratory acidosis results from intrinsic lung disease or ventilation perfusion mismatch. This is associated with high alveolar arterial O₂ (A-aO₂) gradient. Respiratory acidosis can also occur due to hypoventilation due to CNS depression or abnormality of chest wall. In this type A-aO₂ gradient is within normal range.

Respiratory Alkalosis

Respiratory alkalosis is a process that results in alkalemia due to decrease in pCO₂ with physiological response that is metabolic acidosis (decrease in HCO₃). Respiratory alkalosis like acidosis can be associated with high or normal A-aO₂ gradient.

Acute Vs Chronic

Respiratory processes alkalosis or acidosis can be acute or chronic depending upon the renal compensation as shown in table 1.

Mixed Disorders:

Mixed disorders are when more than one primary acid base disorder is present. If there is no physiological response to primary disorder or the response is less than expected or more than expected then mixed acid base disorder is present.

You need to remember that physiologically there is never complete compensation except for chronic respiratory alkalosis. pH does not become normal due to physiological compensation. It points to the direction of primary disorder. For example if a patient has metabolic alkalosis with compensatory respiratory acidosis, pH will remain on alkalemic side. If pH is normalized then it is mixed metabolic alkalosis and respiratory acidosis. Mixed disorder is present if there is change in one component and the other component is normal or both components abnormal but pH is normal or both components are in the same direction.

Types of mixed disorders

These can be double, triple or quadruple.

Double disorders

Metabolic acidosis + respiratory alkalosis, metabolic acidosis + respiratory acidosis. metabolic alkalosis + respiratory alkalosis, metabolic acidosis + respiratory alkalosis. Mixed metabolic acidosis AGMA+ NAGMA, metabolic alkalosis and metabolic acidosis

Triple disorders

Metabolic alkalosis+ Metabolic acidosis and one of the respiratory disorder respiratory alkalosis or acidosis. A patient with uremia has vomiting and gets aspiration pneumonia.

Quadruple disorder

AGMA+ NAGMA, Metabolic alkalosis, plus respiratory acidosis or alkalosis. Example. A patient with advanced renal failure gets diarrhea, vomiting and develops respiratory alkalosis due to pulmonary edema or a patient with severe pneumonia, treated with aminoglycosides gets renal failure and develops vomiting and diarrhea

Further reading.

Adrogué HJ, Gennari FJ, Galla JH, Madias NE. Assessing acid-base disorders. *Kidney Int* 2009;76:1239–1247.

Seifter JL. Integration of acid-base and electrolyte disorders. *N Engl J Med* 2014;371:1821–1831

Herber RJ, A practical approach to acid-base disorders. *West J Med*, 1991; 2 :146-51

Hamm LL, Nikhoul N, Hering-Smith K. Acid-base homeostasis. *Clin J Am Soc ;* 10(12): 2232–2242.

Alshehri AA, Alyahya MA, Alsolamy SJ (2015) Acid-Base Disturbance: A Comprehensive flowchart-based diagnostic approach. *Emergency Med* 2015, 5:3

<http://dx.doi.org/10.4172/2165-7548.1000245>

Seifter JL, Chang HY, Disorders of Acid-Base Balance: New Perspectives *Kidney Dis* 2016; 2: 170–186

Narins RG, Emmett M. Simple and mixed acid-base disorders: a practical approach. *Medicine (Baltimore)* 1980; 59: 161-187.

Berend K, de Vries AP, Gans RO. Physiological approach to assessment of acid-base disturbances. *N Engl J Med* 2014;371:1434–1445..

Hsu BS, Lakhani SA, Wilhelm M, Acid-Base Disorders. *Pediatrics in Review* 2016, 37 361-37

Herd AM, An approach to complex acid-base problems, Keeping it simple. *Can Fam Physician.* 2005; 51(2): 226–232.