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Biochemical Approach of Acid-Base Disturbances

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Abstract

Introduction: The current paradigms in arterial blood gas analysis are based on mathematical or physicochemical models that require complex algorithms for interpretation. This leads to avoidance or dislike from health care professionals.

Objectives: To formulate a new approach to the analysis and classification of acid base disturbances.

Methodology: We conducted a systematic review of the related literature and a paradigm shift for data interpretation.

Results: Acid-base disorders can be grouped and managed according to the underlying biochemical processes.

Discussion and Conclusions: This proposal represents a new classification, which groups acid base disorders according to the underlying causal biochemical process. Disorders with an elevated anion gap relate to alterations in cellular respiration (energy/ATP production)-All disturbances with normal anion gap relate to transmembrane ion exchange.

Keywords: Acid-base equilibrium, metabolic acidosis, metabolic alkalosis, respiratory acidosis, respiratory alkalosis, alkalemia, acidemia, alkalosis, acidosis, critical care, blood gas analysis, cellular respiration.

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Abordaje bioquímico de alteraciones ácido-base

Resumen

Introducción: los paradigmas actuales del análisis de gasometrías sanguíneas están basados en modelos matemáticos o físico químicos que requieren algoritmos complejos de interpretación. Esto conduce a que los profesionales de salud eviten y/o rechacen el tema.
Objetivo: formular un nuevo abordaje para el análisis y clasificación de los trastornos ácido-base.
Métodología: revisión sistemática de la literatura sobre el tema y cambio en el paradigma de interpretación de los datos.
Resultados: los trastornos ácido-base pueden agruparse y manejarse de acuerdo con los procesos bioquímicos subyacentes.
Discusión y conclusiones: la nueva clasificación propuesta agrupa los trastornos ácido base según el proceso bioquímico subyacente. Los trastornos que elevan la brecha aniónica corresponden a alteraciones en la respiración celular (producción de energía/ATP). Los trastornos con brecha aniónica normal corresponden a alteraciones en el intercambio transmembrana de iones.

Palabras clave: equilibrio ácido-base, acidosis metabólica, alcalosis metabólica, acidosis respiratoria, alcalosis respiratoria, alcalemia, acidemia, alcalosis, acidosis, cuidados críticos, gasometría sanguínea, respiración celular.

Introduction

The three current approaches to acid-base disturbances are the physiological (kidney-lung interaction), physicochemical (Stewart method, anion gap), and the base-excess approach (CO_2 and bicarbonate levels) [1]. Since the current classification is complex and its clinical application is confusing, most clinicians avoid and fear this subject [2].

To simplify the theoretical understanding, and to facilitate its clinical application in health-care practice, we present a new classification that relates the cellular biochemical processes to the clinical presentation and its management.

Methodology

Theoretical research with systematic examination of past and current knowledge of acid-base disturbances and reorganization according to corresponding biochemical processes.

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Biochemical Approach of Acid-base Disorders

In this new system, "respiratory processes" are related to cellular respiration and energy production, rather than pulmonary (ventilatory) problems. Cellular respiration includes glycolysis, the citric acid (Krebs) cycle, and the mitochondrial respiratory chain. End products are ATP (glycolysis and respiratory chain), carbon derivates (glycolysis and Krebs) and hydrogen derivates (all steps). Disturbances depend and reflect on the substrate and the biochemical step involved [3].

Carbon dioxide is traditionally considered a volatile acid because it is excreted by the lung [4], however, CO_2 is a chemically and electrically neutral compound [5]. Hydrogen ions produced by cellular respiration are the real source of acid load in the body. All cations are acids, and all anions are bases.

Likewise, "metabolic processes" will refer to gradient-dependent or energy-dependent processes, such as enzymatic activity, ion and electrolyte transport and membrane potential mechanisms, rather than to renal causes [6]. Cells utilize gradients (whether electrochemical or osmotic) to move ions through membranes and conduct other enzymatic activity such as the Na/K ATPase pump.

Anion Gap (Stewart, SID) and Base Excess (Base Excess approach) are mirror reciprocal assessments of severity of disturbances in cellular respiration.

Advantages of the Biochemical Approach over Traditional Systems (Stewart/SID, Base Excess, Physiological)

1. Mathematical coherency with
    a. The true nature of carbon dioxide as a neutral compound, not as a volatile acid
    b. The isoelectric principle (all cations are acids, all anions are bases)
    c. The biochemical origin and interactions of acids and anions
2. Systematic approach to high anion gap disorders, where anions (measured or unmeasured) are a product of disturbances in cellular respiratory pathways.
    a. The elevated anion points toward the altered step
        i. Anaerobic glycolysis yields lactate
        ii. Krebs cycle

1. Fatty acids instead of glucose yields ketone bodies (diabetes, starvation, and alcohol ketoacidosis)
2. Aminoacids instead of glucose yield organic anions (organic acidemias i.e methylmalonic, isovaleric and propionic acidemias). These are usually "unmeasured". However, high AG in absence of lactate and ketone bodies points directly to OA.
3. CO_2 buildup in plasma points toward a functioning Krebs cycle in absence of proper water production in mitochondrial respiratory chain.
4. Pathway of CO production from odd-chain fatty acids in Krebs cycle.

iii. Mitochondrial respiratory chain

1. Lactate in presence of hypercapnia
2. Low bicarbonate levels with high AG / low BE

3. Prioritizes and facilitates diagnosis and treatment of high anion-gap disturbances, as they are the most life-threatening of all acid-base disturbances. This is of vital importance for health personnel in emergency, operating room, and critical care/intensive care units.

   a. High Anion Gap / Low Base Excess disturbances are commonly just managed with IV fluid therapy. However, a clear understanding of the underlying biochemical disturbance leads to a faster diagnosis and precise management.

4. Proposes a differentiation between two important and often confused terms: respiration and ventilation.

   a. Respiration refers exclusively to cellular ATP production.
   b. Ventilation refers to pulmonary gas exchange processes.

5. Facilitates insight on biochemical pathophysiology, clinical manifestations, and therapeutical approach of diseases such as Urea Cycle Disorders and Organic Acidemias; which are often lethal and common in areas like Neonatal Intensive Care Units.

   a. UCD and salicylate poisoning usually present alkaline pH with high anion gap. This tends to baffle clinicians, because there is no apparent relationship of alkaline pH with the severe clinical presentation. However, when pH of urea and salicylate are considered, the explanation is clear:

      i. Urea pH is 9.8, salicylate pH is 13.
      ii. Both can block cellular respiration by either blocking Krebs cycle (Urea) or mitochondrial respiratory chain (salicylates), which leads to cellular respiration disturbances and anion production.

iii. Buildup of both substances in plasma alkalinizes plasma pH, while anions build up.

6. Provides insight into more effective ways to treat and solve electrolyte imbalance such as hyperkalemia, based on principles of transmembrane electrochemical gradients. This is important for nephrologists, cardiologists, and intensive care unit doctors.

   a. Hyperkalemia responds to sodium intake. Given that K^+ is more abundant intracellularly, when Na^+ levels are being depleted (inadequate intake, excess loss due to diuretics etc), K^+ moves towards the interstitial and plasma compartments to compensate electrical charges and maintain cellular function. All clinical manifestations of hyperkalemia are related to altered electrical properties such as depolarization. Restoring Na^+ levels and preventing further loss will stabilize membrane functions.

   b. Opens a pathway to further explore other ion / electrolyte imbalances such as hyperphosphatemia seen commonly in persons with CKD.

7. Further exploration into the production and management of H^+ ions reveal that intracellular acidosis (H^+ buildup) causes cell membrane depolarization. This opens a new path to understand cellular depolarization physiology and pathology on a deeper level, providing grounds for neurologists, cardiologists, physical therapists and gastroenterologists.

   a. The current paradigm in depolarization is the influx of Na^+ ions, followed by efflux of K^+ ions and later influx of Ca^{++} ions.

   b. H^+ ions produced by cellular respiration (normally found in water molecules, but present in weak acids in high AG acidosis) exit the cell via NHE (sodium-hydrogen exchange channels).

      i. 9 main families of NHE channels, out of which 5 are involved in syndromes that include seizures or epilepsy.

      ii. H^+ ions are so small that the electrical currents they produce weren't documented in the original experiments. Now, it has been mathematically described that H^+ ions produce a current of 11 fA (fentoAmperes, $1{\cdot}10^{-14}$)

   c. Therefore, the Na^+ influx is not random but a mechanism to keep electrical balance of the exiting H^+ ions produced in mitochondria. This correlates to the higher electrical activity of cells with more mitochondria, such as nervous system and muscles.

8. Explains a different approach to Anion Gap and Base Excess, which are mirror values of cellular respiratory disturbances.

   a. Anion gap is usually overlooked or even ignored by clinicians.

b. Base excess (i.e., negative base excess) is usually understood as dehydration or corrected with bicarbonate.
   i. Bicarbonate is produced from the combination (not chemical reaction) of a dissociated water molecule and carbon dioxide.
      1. Carbon dioxide is a byproduct of Krebs cycle.
      2. Water is a byproduct of mitochondrial respiratory chain.
   ii. Carbonic anhydrase separates the Hydroxyl (OH-) ion from the Hydrogen (H^+) ion, "mounting" them on carbon dioxide (an electrochemically neutral compound with two stable double bonds).
   iii. Therefore, in the presence of low base excess, low bicarbonate always means low water production, which points toward mitochondrial respiratory chain blockage or malfunction.
   iv. Traditional theory indicates bicarbonate replacement, which, though it masks acidemia, it does not solve the root cause of the problem.

9. Alternative explanation to physiological and clinical signs of acid-base disturbances
   a. The author hypothesizes that disorders in cellular respiration would cause cells to require more oxygen to maintain minimum levels of ATP production (respiratory quotient). This can be the real cause of tachypnea and other altered breathing patterns such as Kussmaul and "metabolic alkalosis"-related tachypnea such as inborn errors of metabolism. Understanding the origin and mechanism of such clinical signs and symptoms will facilitate early diagnosis, treatment, and management.

Biochemical Classification of Acid-Base Disturbances (Fig. 1)

1. Respiratory acidosis
   Common characteristics of respiratory acidosis include:

   - pH $<$ 7.35
   - High Anion gap (st) $>$12
   - Base deficit $<$ -2.0
   - All "CAT-MUDPILES" * acidosis cause disturbances in cellular respiration [2]
   - Clinical presentation includes shock, hypovolemia, cyanosis, hypotension, tachycardia, tachypnea, cold skin and prolonged capillary refill time. May include vomiting, nausea, drowsiness, or alterations in state of alertness.

   The altered anions indicate the cellular respiratory disturbance. This allows prompt management decisions:

- Step 1: Glycolysis
  - Elevated lactate is due to anaerobic glycolysis. It indicates hypoxia and/or hypovolemia. CO_2 is low or normal due to low production (Krebs cycle). Treatment is oxygen and IV fluid or volume replacement.
- Step 2: Citric Acid (Krebs) cycle
  - Elevated ketone bodies are due to fatty acid breakdown and/or use as substrates in the Krebs cycle. They indicate intracellular glucose deficit, fasting, or decompensated diabetes, probably precipitated by infection. The treatment is restoring intracellular glucose availability, insulin, IV fluids and antibiotics if indicated.

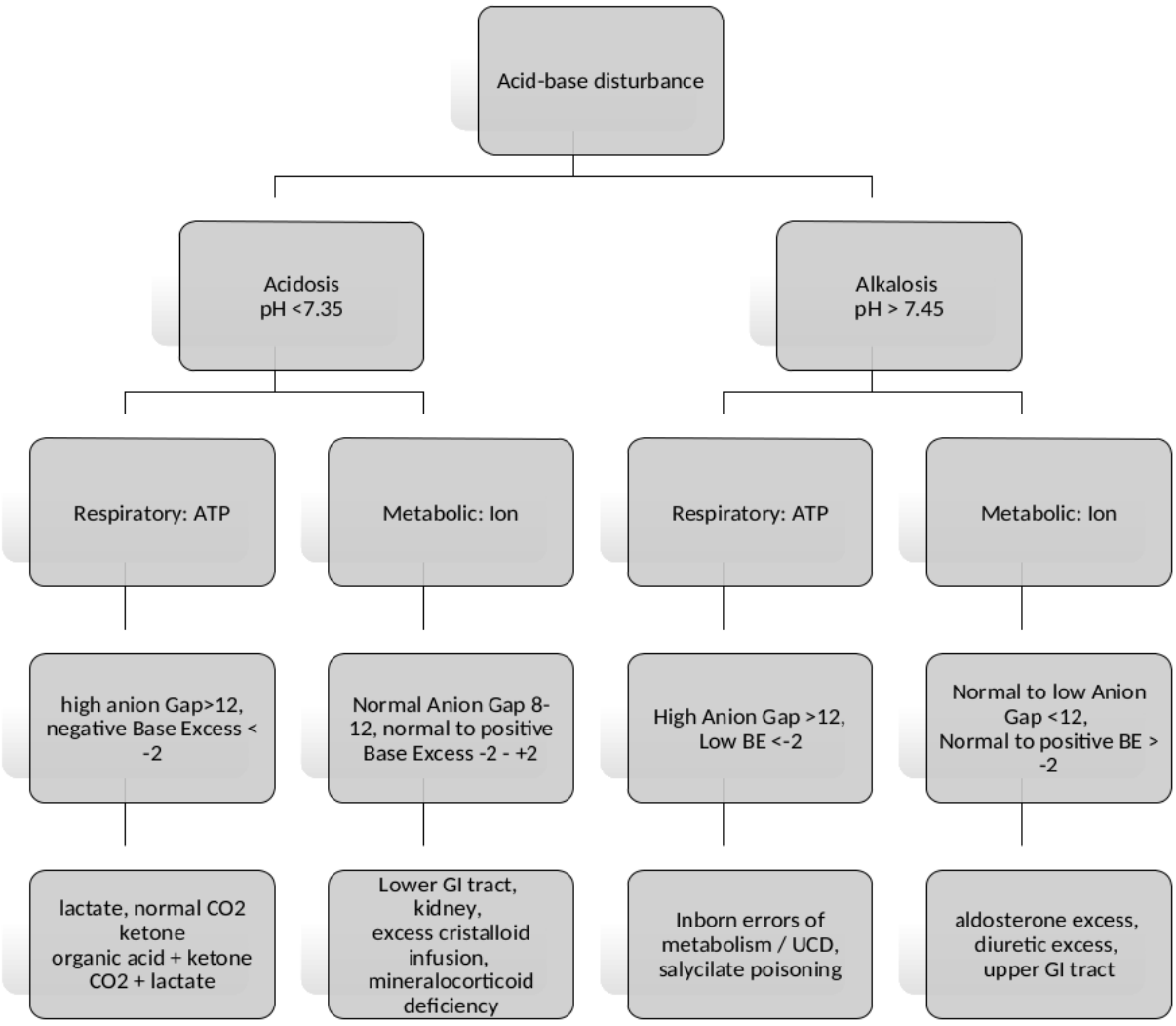

Figure 1. Biochemical classification of acid-base disturbances

Source: Author's classification with information provided in the text and references.

- Organic anions (i.e., propionic, isovaleric, methylmalonic acid) result from using amino acids as a substrate for Krebs cycle. They indicate inborn (life-threatening) errors of metabolism, prolonged fasting or malignancies. The management is nutritional approach.

- Step 3: Mitochondrial respiratory chain
  - Hypercapnic respiratory acidosis is due to mitochondrial respiratory chain blockage, probably caused by organophosphates, use of remdesivir [7] or antiretroviral agents, metformin [8], and other toxic agents [2]. Since there is no water formation, there is no carbonic acid production and carbon dioxide accumulates in blood. Concomitant hyperlactatemia indicates that active glycolysis is taking place to produce ATP.
  - High CO_2 (hypercapnia)
  - Mild to severe hyperlactatemia (rescue mechanism for minimum ATP production)
  - In absence of contact with any chain uncoupler such as the aforementioned, mitochondrial inborn errors of metabolism should be considered and screened for.

"CAT MUDPILES": Carbon dioxide/Cyanide poisoning, congenital heart failure, Aminoglucosides, Toluene/Teophyline, Methanol, Uremia, Diabetic/Alcoholic/Starvation ketoacidosis, Paracetamol/Phenphormin/Paraldehyde, Iron/Isoniazid/Inborn Errors of Metabolism, Lactic acidosis, Ethanol/Ethyleneglycol, Salycilate intoxication

2. Respiratory alkalosis
   Common characteristics of most cases of respiratory alkalosis are:

   - pH >7.45
   - High Anion gap, >12
   - Base deficit < -2
   - Low CO_2 (<35 mm Hg arterial or < 40 mm Hg in venous blood sample) (hypocapnia – low production due to Krebs blockage)

   Clinical characteristics include tachycardia, tachypnea, dizziness, shock, lethargy, altered state of mind, cerebral edema, liver failure, coma and/or death. Acidosis due to alterations in cellular energy production is masked by a potent alkali, which shifts plasma pH up. The main respiratory alkalosis are:

   - Urea cycle disorders, including congenital or acquired variants, which can be lethal. Altered nitrogen metabolism allows an alkalinizing urea (pH 9.8) effect. Alpha ke-

toglutarate production blocks the Krebs cycle. The treatment is dialysis, and if the patient survives, a nutritional approach is granted.

- Salicylate poisoning. Salicylate blocks the Krebs cycle and respiratory chain, causing organ failure and death. Respiratory acidosis or alkalosis will depend on the number of salicylates (pH 13) present in blood. The treatment includes hemodialysis, stopping the medication, gastric lavage, using activated charcoal, and IV fluids [9].

3. Metabolic acidosis
   Common characteristics of metabolic acidosis include:

   - pH $<$7.35
   - Anion gap: normal. No other anions found.
   - Base excess − 2 to +2
   - CO_2 normal.
   - Low bicarbonate with normal to high potassium.
   - Clinical presentation may include tachycardia, dehydration, vomiting and /or diarrhea. Renal causes may present with growth retardation and varying degrees of bone mineral disease.

   If the biochemical presentation consists of low bicarbonate, high chloride, and normal to low potassium level, the most probable causes are:

   - Lower gastrointestinal losses (diarrhea, pancreatic or small bowel drainage). Management: replace IV fluids with bicarbonate.
   - Type 1 or type 2 Renal Tubular acidosis. Management: replace bicarbonate.
   - Other mechanisms (acid loads, dilution acidosis caused by excess of saline solution, cation excess resins, Hippurate). Management: remove the acid load.

   If the biochemical presentation consists of low bicarbonate, high chloride, and high potassium levels (hyperkalemic metabolic acidosis with normal anion gap):

   - Type 4 renal tubular acidosis (primary or secondary mineralocorticoid deficiency, resistance, or renal tubular dysfunction) [10]. The treatment is mineralocorticoid replacement if indicated. Hyperkalemia is corrected by normalizing sodium concentration in plasma.

4. Metabolic alkalosis
   Common characteristics include:

- pH >7.45
- Anion gap normal to low (8-12 or lower)
- Base excess: normal to high (-2 - +2 or higher)
- CO_2 normal.

Clinical presentations include:

- Upper gastrointestinal tract – vomiting (hypertrophic pyloric stenosis), ingestion of sodium bicarbonate, milk-alkali syndrome. The disturbance is loss of fixed acid or gain of bicarbonate buffer. To treat, stop vomiting, or stop ingestion of causative agent.
- Volume contraction due to renal causes and acid losses, especially hyperaldosteronism or loop or thiazide diuretics (volume contraction). Management includes stopping diuretics. Study aldosterone function, discard/manage secondary causes of hyperaldosteronism (e.g., hypertension medications, heart failure) [10].

Discussion

The author proposes a new classification of Acid-Base disturbances based on underlying biochemical processes. This approach utilizes the standards of patient care and current blood gas analysis equipment and results, while having several advantages over the three current approaches (Base Excess, Physiological and Physicochemical/SID). Understanding acid-base disturbances from a biochemical perspective will enhance and optimize diagnosis and management of several pathologies.

Conclusions

• High Anion Gap (or Low Base Excess) disturbances should always indicate a disturbance in cellular respiration hence, respiratory disturbance. This compromises ATP production and ultimately, all energy-dependent processes.

• Clinical presentation of cellular respiratory disturbances is usually acute and severe, including shock, coma, lethargy, and death. They constitute real urgencies and should be approached as such.

• Clinical presentation of metabolic disturbances (ion transport) is usually chronic and mild to moderate. Metabolic disturbances are less prone to present acute decompensation unless something compromises cellular respiration.

• Mixed clinical presentations may occur (i.e. gastroenteritis + chronic kidney disease, etc.). In this case, respiratory disturbances (high anion gap) should be solved first, because they indicate a disruption in the ATP production process, which compromises cell energetics. Then, correct any electrolyte imbalances, if any.

• This classification can be learned, understood, and applied easily in every clinical context, facilitating therapeutical approach and decision-making when a health professional faces a critical case.

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Conflicts of Interest

The author declares no conflicts of interest regarding this publication.

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References

[1] Berend K. Diagnostic Use of Base Excess in Acid-Base Disorders. NEJM. 2018 ;378(15):1419-1428. https://doi.org/10.1056/NEJMra1711860 ↑See page 2

[2] Dzierba AL, Abraham P. A Practical Approach to Understanding Acid-Base Abnormalities in Critical illness. J Pharm Practice. 2011;24(1):17-26. https://doi.org/10.1177/0897190010388153 ↑See page 2, 6, 8

[3] Ahmad M, Wolberg A, Kahwaji C. Biochemistry, Electron Transport Chain.. [Online]. StatPearls; 2021 [cited 2022]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526105/#_NBK526105_pubdet_ ↑See page 3

[4] Anesthesia Education Website. Acid-base physiology. [Online]. [cited 2022] Available from: https://www.anaesthesiamcq.com/AcidBaseBook/ab2_1.php ↑See page 3

[5] United states environmental Protection Agency. Technical Overview of Volatile Organic Compounds. [Online].; 2021. Available from: https://www.epa.gov/indoor-air-quality-iaq/technical-overview-volatile-organic-compounds#conclusion ↑See page 3

[6] Kaufman DA. Interpretation of ABgs. [Online]. American Thoracic Asociation. [cited 2022] Available from: https://www.thoracic.org/professionals/clinical-resources/critical-care/clinical-education/abgs.php ↑See page 3

[7] Saha A, Bhattacharya M, Sharma G, Lee SS, Chakraborty C. Probable Molecular Mechanism of Remdesivir for the Treatment of COVID-19: Need to Know More. J. ARCMED. 2020;51(6):585-586. https://doi.org/10.1016/j.arcmed.2020.05.001 ↑See page 8

[8] Blough B, Moreland A, Mora A. Metformin-induced lactic acidosis with emphasis on the anion gap. Proc (Bayl Univ Md Cent). 2015;28(1):31-33. https://doi.org/10.1080/08998280.2015.11929178 ↑See page 8

[9] Palmer BF, Clegg DJ. Salicylate Toxicity. NEJM. 2020;382:2544-2555. https://doi.org/10.1056/NEJMra2010852 ↑See page 9

[10] DuBose TD. Metabolic and respiratory acidosis. In Wilcox CS. Therapy in Nephrology and Hypertension.: Saunders Elsevier. 2008:368-380. https://doi.org/10.1016/B978-141605484-9.50033-2 ↑See page 9, 10