A Commentary on Albumin in Acidosis

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is a subset of sepsis in which, despite adequate volume resuscitation, hypotension persists, and serum lactate level exceeds 2 mmol/L.\[1\]

Hypovolemia, reduced vascular tone, endothelial dysfunction, and microcirculatory alterations are the determinants of impaired tissue perfusion in these conditions.\[2\]

Under physiological conditions, most energy is generated from the metabolism of glucose, by the process of oxidative phosphorylation.\[3\] Disturbances of tissue perfusion reduce tissue oxygenation and form the basis for energy failure because energy can be produced only by the anaerobic glycolysis.

Anaerobic metabolism is a rescue measure that can be sustained only for little time because it is inefficient, requires relatively larger quantities of glucose, and produces lactic acid. When lactate production exceeds the metabolic threshold of the liver and other organs, lactate accumulation occurs, and metabolic acidosis (MA) may develop.\[3\]

MA is a clinical disturbance characterized by an increase in plasma acidity that is generally defined as an arterial pH below 7.35 and bicarbonate below 20 mmol/L in the absence of hypercapnia. It occurs when either an increase in the production of nonvolatile acids or a loss of bicarbonate from the body overwhelms the mechanisms of acid–base homeostasis.\[4\]

Anion gap (AG) is defined as the difference between the primary measured cations (sodium and potassium) and the primary measured anions (chloride and bicarbonate) in serum. Because of its low and narrow extracellular concentration, K+ is often omitted from the calculation.

The missing negative charge is made up of weak acids (A−; albumin and phosphate) and strong anions (lactate, ketones, exogenous compounds, etc.). Normal values with relatively wide ranges reported by most laboratories are 12 ± 4 mEq/L (if K+ is considered) and 8 ± 4 mEq/L (if K+ is not considered).\[3\]

The use of AG assessment to interpret and diagnose the etiology of MA was originally described by Narins and Emmett in 1977.\[6\] Nowadays, it is still worldwide used to understand MA etiology because various disorders that produce MA can affect it differently.

The MA therefore can be classified as to whether the AG is normal (6–12 mEq/L), low (<6 mEq/L), or elevated (>12 mEq/L).

Generally, a decreased AG may suggest hypoalbuminemia, IgG paraproteinemia, and bromide, lithium, or iodide intoxication; a normal AG may indicate loss of bicarbonate with compensatory increase in chloride (diarrhea, ileostomy fluid, urine), whereas an elevated AG may indicate the presence of strong anions (lactic acidosis [LA], uremia, diabetic ketoacidosis, milk-alkali syndrome, propylene glycol, isoniazid intoxication, rhabdomyolysis/renal failure, and salicylates).\[4\]

MA in sepsis is usually characterized by elevated lactate levels and subsequent high AG acidosis. Kidney impairment due to sepsis-induced hypoperfusion can further increase AG because of strong anions retention. Hypoalbuminemia, a common finding in septic patients, can cause a decrease in the measured AG and thereby mask the presence of an elevated AG.\[2\]

To better define the AG, we should separate weak acids from the strong anions. Normally, approximately 75% of the plasma AG is determined by plasma albumin concentration.

Albumin is commonly measured in g/dl; a simple way to calculate the effective ionic concentration of albumin is:

\[
\text{Alb (mEq/L) } \approx 2.5 \times \text{ measured albumin (g/dl)}.
\]

Thus, the plasma AG must be adjusted by adding or subtracting 2.5 mEq/L from the calculated value for each 1 g/dl of plasma albumin below or above the average normal value of 4.2 g/dl, respectively (ACAG = AG corrected for albumin).

\[
\text{ACAG} = \text{measured AG } + 2.5 \times (4.2 - \text{measured albumin (g/dl)})
\]

Phosphate is usually expressed in mg/dl; to calculate mmol/L, we have to use the formula:

\[
\text{P (mmol/L) } = \frac{\text{measured P (mg/dl)}}{3095}
\]
Unmeasurable strong anions (USA) are determined using this formula:

\[
\text{USA (mmol/L)} = \text{AG} - \text{Alb} - \text{P} - \text{Lac} - \text{Ketones}
\]

Applying the formulas above, we can detect the determinants of MA. In septic patients, ACAG helps us to better define the severity of MA.

In their recent IJCIIS article titled “A profile of metabolic acidosis in patients with sepsis in an Intensive Care Unit setting” Ganesh, et al.,\(^7\) presented the results of a prospective study designed to describe the determinants of MA in septic patients at Intensive Care Unit (ICU)-admission and during the first day of ICU stay.

The authors enrolled 75 patients with sepsis and found that 49% of patients had high AGMA (H-AGMA), 28% had LA, 12% had both, and 23% had normal AG acidosis. Interestingly, only 42% of LA patients had H-AGMA, whereas 58% of patients with LA had low or normal AGMA. This may be due to hypoalbuminemia. Using the approach described above could resolve this uncertainty.

The authors analyzed factors that influenced the outcome: They found lactacidemia and hypoalbuminemia as possible determinants. These findings reflect previous studies’ results and are compatible with sepsis’ pathophysiology: Lactate is a marker of energy failure; hypoalbuminemia is a marker of microcirculatory/endothelial dysfunction. Lactates are strong anions and when they accumulate, they produce MA.

Albumin is the major determinant of plasma colloid osmotic pressure; it acts as a carrier for several compounds, and it has scavenger, antioxidant, and anti-inflammatory properties and is a buffer molecule for pH homeostasis. Hypoalbuminemia therefore impairs these fundamental functions.

From above, we can understand why nonsurvivor has less albumin and more lactate.

In conclusion, the article by Ganesh, et al.,\(^7\) in the December 2016 issue of IJCIIS highlights the importance of MA and its determinants in septic patients. Using the AG approach to explore the etiology of MA is useful, but it is not enough: We have to analyze the components: Albumin, phosphate, and unmeasurable strong ions. The approach proposed above may be a simple solution.

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