

[Test Your Knowledge: Anion Gap in Metabolic Acidosis](#)

The serum anion gap is a common tool used in clinical practice. Recent advances have led to a new mnemonic [GOLD MARK](#) to differentiate the various causes of anion gap metabolic acidosis. A recent article in *AJKD* by [Vichot and Rastegar](#) discusses the use of anion gap in metabolic acidosis. The following questions will test your knowledge on this very important topic in nephrology.

1. The serum anion gap can be calculated by which of the following?
 - A. Concentration of measured anions minus concentration of measured cations
 - B. Concentration of unmeasured anions minus concentration of unmeasured cations
 - C. Concentration of serum albumin plus concentration of serum phosphate
 - D. Concentration of serum albumin plus concentration of serum organic acids
2. What reference values should be used when deciding whether a patient has an abnormal serum anion gap?
 - A. Serum anion gap between 3 and 9 mEq/L
 - B. Lowest patient's serum anion gap found in the medical records
 - C. Serum anion gap between 8 and 16 mEq/L
 - D. Baseline patient's serum anion gap
3. Which of the following is most likely associated with a low serum anion gap?
 - A. IgA multiple myeloma
 - B. Treatment of myasthenia gravis
 - C. Severe hypomagnesemia
 - D. Metabolic alkalosis
4. The concept of "delta AG/delta HCO₃⁻" is used to diagnose mixed metabolic disorders by assuming that the changes in AG and bicarbonate are numerically equal. This does not apply to type A lactic acidosis where the ratio is usually around 1.6. Which one of the following contributes to this higher observed delta/delta ratio in type A lactic acidosis?
 - A. The volume of distribution of hydrogen ions is restricted to the extracellular fluid, which decreases the ratio below 1:1
 - B. Many acid anions contributing to the serum anion gap are eliminated with sodium and potassium in the urine, which increases the ratio above 1:1
 - C. Systemic hypoperfusion associated with lactic acidosis causes kidney dysfunction, which can decrease renal lactate elimination increasing the ratio above 1:1
 - D. Unmeasured anions that can increase in the plasma are not usually due to acids
5. Which one of the following is *not* a risk factor for pyroglutamic acidosis?
 - A. Female sex
 - B. Malnutrition
 - C. Reduced GFR
 - D. Warfarin use

Post prepared by Dr. Helbert Rondon, eAJKD Contributor.

Solutions to eAJKD's [Test Your Knowledge: Anion Gap in Metabolic Acidosis](#)**1. B. Concentration of unmeasured anions minus concentration of unmeasured cations**

[The serum anion gap](#) can be calculated by the difference between the concentration of measured cations (Na^+) and measured anions (Cl^- and HCO_3^-). Potassium is usually not considered as one of the measured cations because of its small and relatively fixed contribution. However, the serum anion gap can also be expressed as the concentration of unmeasured anions minus the concentration of unmeasured cations. The unmeasured anions are composed mainly of proteins (e.g., albumin) with minor additions from organic (e.g., lactate) and inorganic (e.g., sulfate and phosphate) acids. The unmeasured cations are largely represented by potassium, calcium, and magnesium.

2. D. Baseline patient's serum anion gap

The reference range for serum anion gap was classically established by the technique of flame atomic emission spectrometry (FAES) in the 1970s. This range was set at 12 ± 4 mEq/L ever since. With the development of ion selective electrodes (ISE) technology in 1982, the new reference range was reset at 6 ± 3 mEq/L. It seems that the ISE technique causes a lower estimation of serum sodium and a higher estimation of serum chloride. However, given the wide range of the normal anion gap and the variation in different laboratories, the serum anion gap should be compared to the baseline serum anion gap for the individual patient when deciding if a patient has an abnormal serum anion gap.

3. B. Treatment of myasthenia gravis

Serum anion gap is usually calculated by the formula: $\text{Na} - (\text{Cl} + \text{HCO}_3)$. Therefore, [a low serum anion gap](#) can result from the following:

- Underestimation of serum Na^+
 - Hyperviscosity, historically when measured by FAES (e.g., multiple myeloma, Waldenstrom's macroglobulinemia)
 - Severe hyponatremia (serum $\text{Na}^+ < 120$), historically when measured by FAES
- Overestimation of serum Cl^-
 - Bromide (e.g. pyridostigmine bromide for myasthenia gravis)
 - Iodide
 - Hypertriglyceridemia, historically when measured by FAES

If we also conceptualize the serum anion gap as the difference between unmeasured anions and unmeasured cations, then we also can find other causes:

- Decreased unmeasured anions:

- Hypoalbuminemia
- Increased unmeasured cations:
 - Severe hyperkalemia
 - Severe hypercalcemia
 - Severe hypermagnesemia
 - IgG multiple myeloma (IgG is cationic. On the other hand, IgA multiple myeloma actually increases serum anion gap since IgA is anionic.)
 - Lithium
 - Polymixin B

4. C. Systemic hypoperfusion associated with lactic acidosis causes kidney dysfunction, which can decrease renal lactate elimination increasing the ratio above 1:1

[The 2 most important limitations for the use of the delta/delta ratio](#) are: (1) Hydrogen ion volume of distribution is not limited to the ECF with more than 50% of hydrogen buffered intracellularly. This will decrease the drop in serum HCO_3^- , and increase the delta/delta ratio above 1:1; (2) Many acid anions contributing to the serum anion gap are eliminated along with sodium or potassium in the urine. This will limit the increase in serum anion gap, and decrease the delta/delta ratio below 1:1.

In ketoacidosis, the above 2 conditions occur simultaneously, and the delta/delta ratio is close to 1. However, in type A lactic acidosis only the first condition is met. Systemic hypoperfusion causes renal underperfusion and limits the elimination of lactate by the kidneys, causing an increase in the delta/delta ratio approximately to 1.6. In other types of high anion gap metabolic acidosis it is possible to encounter other unmeasured anions that can significantly increase the serum anion gap, such as phosphate or hyperalbuminemia from hemoconcentration.

5. D. Warfarin use

A review of the literature on cases of [pyroglutamic acidosis](#) shows that most patients are women, malnourished which predispose to glutathione deficiency, and have various degrees of reduced GFR. Other factors found in case series include sepsis, chronic alcohol abuse, and liver disease. Warfarin use is not a known contributor to this disorder.