# How to interpret the anion gap

WILLIAM D. PAULSON, M.D.

- **Do you know the anion gap reference value of your clinical laboratory?**
- **Why do changes in unmeasured anion and unmeasured cation levels alter the anion gap?**
- **What are the major causes of an altered anion gap in critically ill patients?**
- **Why are $\Delta AG$ and $\Delta HCO_3$ equal in diabetic ketoacidosis?**
- **What are the limitations in using the anion gap to diagnose acid-base disorders?**

Because the serum anion gap ($Na - [Cl + HCO_3]$) is readily obtained from the electrolyte measurements of an analyzer, it is usually one of the first determinations made in the evaluation of acid-base disorders.[1] For this reason, anion gap measurements are widely used in hospitalized patients, particularly the critically ill.

This is the first article in an ongoing series about acid-base diagnosis. My focus here is on the interpretation of the anion gap, especially in patients with metabolic acidoses or mixed acid-base disorders. In future articles, I will discuss the interpretation of arterial blood gas measurements as well as provide case studies on the diagnosis of acid-base disorders.

### Understanding the anion gap

To fully understand the anion gap, it is useful to recall that body fluids are electroneutral. That is, the total concentration of cations equals the total concentration of anions, in milliequivalents per liter (Figure 1):

$$Na + K + Ca + Mg = Cl + HCO_3 + \text{albumin} + \text{organic anions} + PO_4 + SO_4$$

*Dr. Paulson is an associate professor of medicine (designee) at the Louisiana State University School of Medicine in Shreveport.*

The anion gap is found by rearranging the above equation[2]:

$$\begin{aligned}\text{Anion gap} &= Na - (Cl + HCO_3)\\ &= (\text{albumin} + \text{organic anions} + PO_4 + SO_4) - (K + Ca + Mg)\\ &= (\text{unmeasured anions}) - (\text{unmeasured cations})\end{aligned}$$

The anion gap equation shows that the measured ions ($Na$, $Cl$, $HCO_3$) can be used to yield information about the unmeasured anions and unmeasured cations. For example, an increase in unmeasured anions or a decrease in unmeasured cations will increase the anion gap. (Note: Analyzers actually measure the total $CO_2$ content, not $HCO_3$ itself, but total $CO_2$ content is usually a good approximation of $HCO_3$.)

### Anion gap reference value

The traditional reference value given for the anion gap has been 12 mEq/L, but many of the analyzers currently used produce different values.[3,4] Thus, clinicians should know the reference value of their clinical laboratory when measuring the anion gap or assessing a change in its value. At Louisiana State University Medical Center, for instance, the Kodak Ektachem analyzer recently gave a value of $12.1 \pm 4.0$ ($\pm$ 2 SD) mEq/L in 58 healthy subjects. In the discussion below, the reference value for the anion gap is assumed to be 12 mEq/L (interval, 8 to 16 mEq/L).

### Causes of change

The major causes of a change in the anion gap are summarized in Table 1.

- *Low anion gap:* The most common cause of a low anion gap probably is hypoalbuminemia, which frequently occurs in critically ill patients. A decrease in the albumin level of 1 g/dL should reduce the anion gap by roughly 2.5 mEq/L.[5]
- *High anion gap:* The most common causes of a high anion gap are metabolic acidoses in which $HCO_3$ is titrated by organic acids such as lactic acid and keto acids. When the anion gap is at least 25 to 30 mEq/L, an organic acidosis is almost always present, regard-

less of whether the $HCO_3$ level is reduced.[6]

Metabolic alkalosis with fluid-volume depletion raises the anion gap roughly 5 mEq/L for each 0.1 increase in pH.[7] The cause of this increase is not fully understood, although an increase in the albumin concentration and a pH-induced increase in the negative charge of albumin are contributory.[8]

I will use diabetic ketoacidosis as the model of an anion gap acidosis in this paper because it is common and because electrolyte patterns in this disorder have been thoroughly studied. During ketoacidosis, keto acids release hydrogen ions and thereby titrate $HCO_3$ in the following reaction:

$$\text{Ket-H} + NaHCO_3 = \text{NaKet} + H_2O + CO_2$$

In this model, each milliequivalent of $HCO_3$ that is consumed is replaced by 1 mEq of ketone anion. As the anion gap equation demonstrates, an increase in organic anions raises the anion gap.

### Diagnosing high anion gap acidosis

The first step in using the anion gap to diagnose acid-base disorders is to compute the difference between the measured value and the reference value:

$$\Delta AG = \text{measured value} - \text{reference value}$$

As discussed earlier, the reference value depends on the analyzer, but is assumed to be 12 mEq/L in the examples below.

An example of the serum electrolyte profile in a patient with diabetic ketoacidosis is shown in Table 2. In this example, $HCO_3$ has decreased from 26 to 11 mEq/L and the anion gap has increased from 12 to 27 mEq/L, so that:

$$\Delta AG = \Delta HCO_3 = 15 \text{ mEq/L}$$

In reality, titration of body fluids by organic acids is more complicated than simple titration of $HCO_3$.[9] For example, in diabetic ketoacidosis, keto acids also titrate non-$HCO_3$ extracellular buffers (such as albumin) and intracellular buffers. In addition, if glomerular filtration is preserved, a portion of the ke-

## Table 1 – Major causes of change in the anion gap

| |
|---|
| **Low anion gap** |
| Decreased unmeasured anions |
| Hypoalbuminemia |
| Increased unmeasured cations |
| Multiple myeloma (cationic paraproteins) |
| Laboratory error |
| **High anion gap** |
| Increased unmeasured anions |
| Lactic acidosis |
| Ketoacidosis |
| Renal failure |
| Toxic ingestions |
| Massive rhabdomyolysis |
| Metabolic alkalosis with volume depletion and hyperalbuminemia |
| Decreased unmeasured cations |
| Laboratory error |

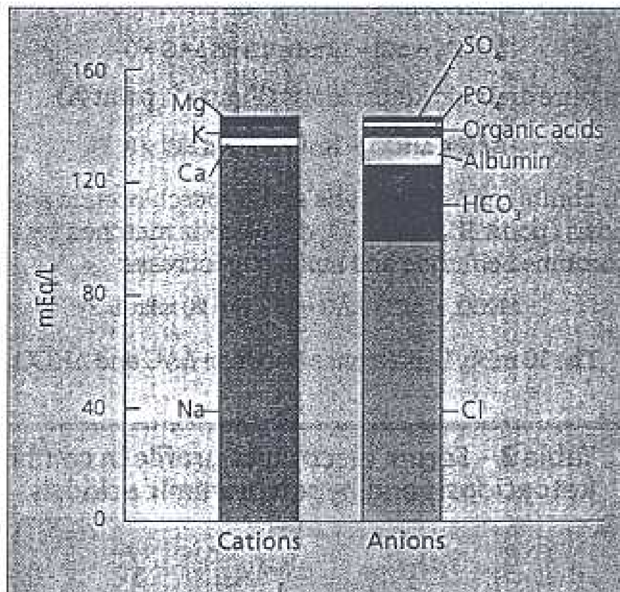


*Figure 1 – The electroneutrality of body fluids is illustrated by this profile of normal serum electrolyte values. The total concentration of cations equals that of anions.*

**Glossary of terms**

| | | | | | |
|---|---|---|---|---|---|
| AG | Anion gap | $HCO_3$ | Bicarbonate | Na | Sodium |
| Ca | Calcium | K | Potassium | $PO_4$ | Phosphate |
| Cl | Chloride | Ket | Ketone anion | $SO_4$ | Sulphate |
| H | Hydrogen | Mg | Magnesium | Δ | Change |

tone anions may be excreted in the urine. Nevertheless, $\Delta AG$ and $\Delta HCO_3$ are roughly equal in diabetic ketoacidosis (Figure 2), which suggests that these additional factors offset each other.[10]

### Diagnosing mixed acid-base disorders

Once an anion gap acidosis is diagnosed, the relationship between the anion gap, $HCO_3$, and chloride concentrations can help determine whether a mixed acid-base disorder is present. For example, consider a patient with diabetic ketoacidosis in whom hyperchloremic metabolic acidosis has been induced by diarrhea (Table 3).

In this example, $NaHCO_3$ is lost in the stool and replaced by dietary NaCl. This is equivalent to titration of $NaHCO_3$ by hydrochloric acid:

$$HCl + NaHCO_3 = NaCl + H_2O + CO_2$$

Thus, in pure hyperchloremic acidosis, the $HCO_3$ decrease is matched by an equal chloride increase, without significantly altering the anion gap:

$$\Delta HCO_3 = \Delta Cl = 10 \text{ mEq/L and } \Delta AG = 0$$

In pure diabetic ketoacidosis (Figure 3, point A):

$$\Delta AG = \Delta HCO_3 = 10 \text{ mEq/L and } \Delta Cl = 0$$

In combined ketoacidosis and hyperchloremic acidosis (point B), the $HCO_3$ decrease is matched by a combined chloride and anion gap increase:

$$\Delta HCO_3 = \Delta Cl + \Delta AG = 10 + 10 = 20 \text{ mEq/L}$$

The 10 mEq/L difference between $\Delta AG$ and $\Delta HCO_3$ in this mixed disorder seems large. It would be useful to know the likelihood that such a difference is due to random laboratory variation rather than to the presence of a mixed disorder. Regression analysis has recently shown that in 95% of patients with pure diabetic ketoacidosis, $\Delta AG$ and $\Delta HCO_3$ differ at most by 8 mEq/L (Figure 3).[10] Thus, a difference of 10 mEq/L suggests either hyperchloremic acidosis or respiratory alkalosis (since both can lower $HCO_3$ and raise chloride). In this example, the history of diarrhea supports the possibility of hyperchloremic acidosis. An arterial blood gas measurement would help confirm this diagnosis.

### Limitations of the anion gap

The comparison between $\Delta AG$ and $\Delta HCO_3$ in Figure 3 assumes anion gap acidoses are the only acid-base

**Table 2 – Serum electrolyte profile in diabetic ketoacidosis**

| Electrolyte | Normal (mEq/L) | Ketoacidosis (mEq/L) |
|---|---|---|
| Na | 141 | 141 |
| Cl | 103 | 103 |
| $HCO_3$ | 26 | 11 |
| Anion gap | 12 | 27 |
| $\Delta HCO_3$ | 0 | 15 |
| $\Delta AG$ | 0 | 15 |

**Table 3 – Serum electrolyte profile in combined diabetic ketoacidosis and hyperchloremic acidosis**

| Electrolyte | Hyperchloremic acidosis (mEq/L) | Keto-acidosis | Ketoacidosis + hyperchloremic acidosis (mEq/L) |
|---|---|---|---|
| Na | 141 | 141 | 141 |
| Cl | 113 | 103 | 113 |
| $HCO_3$ | 16 | 16 | 6 |
| Anion gap | 12 | 22 | 22 |
| $\Delta HCO_3$ | 10 | 10 | 20 |
| $\Delta AG$ | 0 | 10 | 10 |
| $\Delta Cl$ | 10 | 0 | 10 |

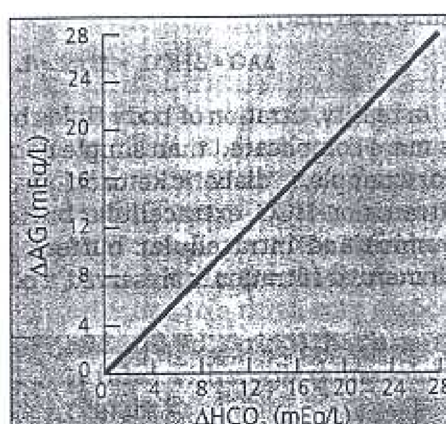


*Figure 2 – In diabetic ketoacidosis, the anion gap increase ($\Delta AG$) is predicted to equal the $HCO_3$ decrease ($\Delta HCO_3$), as this regression line shows.*

disorders that alter the anion gap. With the notable exception of metabolic alkalosis, this is a reasonable approximation in clinical practice. Respiratory acid-base disorders have a minimal effect on the anion gap.[8] For unknown reasons, hyperchloremic acidosis may lower the anion gap[7,8]; however, in disorders—such as diarrhea—that are accompanied by fluid-volume depletion, this effect may be offset by an increase in unmeasured anions (for example, albumin). In clinical practice, it is generally assumed that the anion gap is unchanged in hyperchloremic acidosis. In comparing $\Delta AG$ and $\Delta HCO_3$, clinicians should also recall that a number of conditions that are not acid-base disorders can alter the anion gap (Table 1).

This discussion has used diabetic ketoacidosis as the model of an anion gap acidosis. The relationship between $\Delta AG$ and $\Delta HCO_3$ is less well defined in other anion gap acidoses, however, and in some cases may be somewhat different from diabetic ketoacidosis. In addition, detailed criteria for diagnosing mixed disorders in other anion gap acidoses have not yet been determined.

For example, the ratio of $\Delta AG$ to $\Delta HCO_3$ is roughly 1.4 in lactic acidosis.[11,12] The ratio may be higher than 1.0 because the urinary excretion of lactate, unlike ketone anions, is ordinarily negligible.[11] Thus, if $\Delta HCO_3$ is 10 mEq/L, then $\Delta AG$ is predicted to be roughly 14 mEq/L. A mixed disorder might be suspected if $\Delta AG$ is substantially different from 14 mEq/L, but how large that difference should be has not been determined.


## SELECTED REFERENCES

1. Emmett M, Narins RG: Clinical use of the anion gap. *Medicine* 1977;56:38-54.
2. Oh MS, Carroll HJ: Current concepts: The anion gap. *N Engl J Med* 1977;297:814-817.
3. Winter SD, Pearson JR, Gabow PA, et al: The fall of the serum anion gap. *Arch Intern Med* 1990;150:311-313.
4. Paulson WD, Lurie AA: Comparison of the serum anion gap measurements of analyzers, abstracted. *J Am Soc Nephrol* 1995;6:442.
5. Figge J, Mydosh T, Fencl V: Serum proteins and acid-base equilibria: A follow-up. *J Lab Clin Med* 1992;120:713-719.
6. Gabow PA, Kaehny WD, Fennesey PV, et al: Diagnostic importance of an increased serum anion gap. *N Engl J Med* 1980;303:854-858.
7. Adrogué HJ, Brensilver J, Madias NE: Changes in the plasma anion gap during chronic metabolic acid-base disturbances. *Am J Physiol* 1978;235:F291-F297.
8. Paulson WD: Effect of acute pH change on serum anion gap. *J Am Soc Nephrol* 1996;7:357-363.
9. Adrogué HJ, Eknoyan G, Suki WK: Diabetic ketoacidosis: Role of the kidney in the acid-base homeostasis reevaluated. *Kidney Int* 1984;25:591-598.
10. Paulson WD, Gadallah M: Diagnosis of mixed acid-base disorders in diabetic ketoacidosis. *Am J Med Sci* 1993;306:295-300.
11. Orringer CE, Eustace JC, Wunsch CD, et al: Natural history of lactic acidosis after grand-mal seizures: A model for the study of an anion-gap acidosis not associated with hyperkalemia. *N Engl J Med* 1977;297:796-799.
12. Oh MS, Carroll HJ, Goldstein DA, et al: Hyperchloremic acidosis during the recovery phase of diabetic ketosis. *Ann Intern Med* 1978;89:925-927.


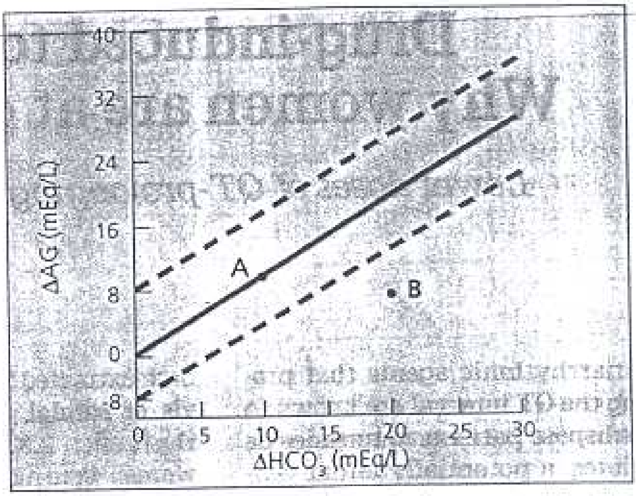


*Figure 3 – A mixed acid-base disorder is suggested by this graph depicting findings from a hypothetical patient with diabetic ketoacidosis (point A), in whom hyperchloremic acidosis develops (point B). The fact that the $HCO_3$ decrease ($\Delta HCO_3$) is more than 8 mEq/L larger than the anion gap increase ($\Delta AG$) points to a mixed disorder. Pure anion gap acidoses should produce values within the dashed lines. The solid line denotes $\Delta AG = \Delta HCO_3$.*

## How to interpret the anion gap: Clinical conclusions

**1.** You must know your clinical laboratory's reference value for the serum anion gap to accurately compute a change in the anion gap. The reference value may not be the traditional 12 mEq/L.

**2.** The higher the anion gap, the greater the likelihood that an organic acidosis is present, regardless of whether the $HCO_3$ level is reduced.

**3.** In diabetic ketoacidosis, the anion gap increase roughly equals the $HCO_3$ decrease:

$$\Delta AG = \Delta HCO_3$$

The relationship between $\Delta AG$ and $\Delta HCO_3$ may not be exactly one-to-one in other anion gap acidoses (such as lactic acidosis).

**4.** If $\Delta AG$ differs from $\Delta HCO_3$ by more than 8 mEq/L in a patient with diabetic ketoacidosis, a mixed acid-base disorder is suggested.

**5.** Acid-base disorders are not the only cause of an altered anion gap. For example, hypoalbuminemia may obscure an actual anion gap increase by lowering the anion gap.

**6.** The history, physical examination, and other laboratory data (such as an arterial blood gas measurement) are usually needed to complete the evaluation of an acid-base disorder.