

## The Serum Anion Gap in the Evaluation of Acid-Base Disorders: What Are Its Limitations and Can Its Effectiveness Be Improved?

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### Summary

The serum anion gap has been utilized to identify errors in the measurement of electrolytes, to detect paraproteins, and, most relevant to the nephrologist, to evaluate patients with suspected acid-base disorders. In regard to the latter purpose, traditionally an increased anion gap is identified when it exceeds the upper limit of normal for a particular clinical laboratory measurement. However, because there is a wide range of normal values (often 8–10 mEq/L), an increase in anion concentration can be present in the absence of an increased anion gap. In addition, the type of retained anion can affect the magnitude of the increase in anion gap relative to change in serum  $[\text{HCO}_3^-]$  being greater with lactic acidosis compared with ketoacidosis. This review examines the methods of calculation of the serum anion gap in textbooks and published literature, the effect of perturbations other than changes in acid-base balance, and its effectiveness in identifying mild and more severe disturbances in acid-base balance. Limitations of the present methods of determining the normal anion gap and change in the anion gap are highlighted. The possibility of identifying the baseline value for individuals to optimize the use of the calculation in the detection of metabolic acidosis is suggested.

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### Introduction

Calculation of the serum anion gap has been used to detect errors in the measurement of serum electrolytes in the clinical laboratory (1), to detect paraproteins in blood (2), and, most relevant for the nephrologist, to detect and evaluate metabolic acidosis (3–6). However, the value of the serum anion gap as a tool for these purposes is undermined by the fashion in which it is presently defined and utilized.

To further explore the use of the anion gap in evaluating metabolic acidosis, we examined the criteria utilized in textbooks, review articles, and case reports of acid-base disorders for the normal level of serum anion gap, for documentation of an increased anion gap, and for the detection of mixed metabolic acid-base disturbances. We then examined the literature concerning the sensitivity of the serum anion gap in detecting mild cases of metabolic acidosis and the effect of the nature of the retained acid on the change in the serum anion gap.

We conclude that the common definition of an abnormal gap as one that exceeds the upper limit of the normal anion gap or exceeds 2 SD above a specific mean value can lead to a failure to identify some cases of metabolic acidosis, to underestimate the severity of the acid load, and to misidentify complex acid-base disorders. In addition, the nature of the putative retained acid can have an important effect on the magnitude of the increase in the anion gap, and therefore should always be considered in the interpretation of acid-base data.

We suggest that identifying the baseline anion gap specific to a patient while incorporating adjustments for changes in the serum albumin concentration and serum potassium could improve the sensitivity of this calculation in the analysis of acid-base disorders. This task might require relatively frequent determinations of the anion gap even when the patient is healthy. Frequent sampling of electrolytes might be most cost-effective in those at increased risk for developing metabolic acidosis, such as patients in the intensive care unit (ICU), individuals with diabetes, or individuals with CKD. Given its present status as a critical element in the analysis of acid-base disorders, a realistic appraisal of its limitations and the value of methods to improve its effectiveness seem warranted.

### Materials and Methods

Information concerning the definition of serum anion gap, correction factor for serum albumin concentration, and most common methods of denoting an increase or decrease in its concentration were gleaned from examination of several data sources shown below.

### Data Sources

Textbooks of medicine, nephrology, and critical care and databases including PubMed and Cochrane Database of Systematic Reviews were examined. In addition, other major sources such as UpToDate and MD Consult were examined. For textbooks, chapters

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concerning acid-base balance and disorders of acid-base balance were examined. For databases, we performed a systematic search using the following search terms: serum anion gap, delta anion gap, high anion gap metabolic acidosis, normal anion gap metabolic acidosis, mixed acid-base disturbances metabolic acidosis, metabolic alkalosis, mixed metabolic acid-base disturbances, lactic acidosis, ketoacidosis, toxic alcohols, and acetaminophen intoxication. Only articles in English published between 1970 and 2012 were examined. References of the retrieved literature were also manually reviewed to obtain additional relevant literature.

### Definition and Characterization of the Normal Serum Anion Gap

The derivation of the serum anion gap has been described previously (3–7). It is most frequently calculated from the sum of  $\text{Cl}^- + \text{HCO}_3^-$  subtracted from the serum  $\text{Na}^+$  concentration. The major textbooks utilize this definition as do the majority of published papers. As originally conceived, serum  $\text{K}^+$  was also included in the calculation, but serum  $\text{K}^+$  is included in none of the major textbooks published in the United States and only in a minority of manuscripts. The rationale for omission is that the absolute change in its concentration observed clinically is small. However, including serum  $\text{K}^+$  in the calculation could be useful when its concentration is substantially increased or decreased. For example, if serum  $\text{K}^+$  increases from 3.5 mEq/L to 6.5 mEq/L, this would translate into an apparent 3 mEq/L change in the anion gap if it were calculated without  $\text{K}^+$ .

Table 1 summarizes the definition for the normal anion gap obtained from major textbooks or clinical medical websites including UpToDate and MD Consult (8–15). In these sources, an approximate value, or mean  $\pm$  SD, and/or range of normal values as perceived by the author(s) are listed.

Table 2 shows the mean and range of values for the serum anion gap based on data obtained from different clinical laboratories and reported in the literature. Variation in the mean and range of values among the studies reflect different methods of measuring the constituents: the values determined using either a continuous flow analyzer or ion-selective electrode (4,16–20). Two facts stand out, particularly in the studies from the literature. First, whatever the methodology utilized, the range of the normal anion gap in a population can span as much as 8–10 mEq/L. Second, the mean value for the serum anion gap is less when ion-selective electrodes are utilized, primarily due to higher reported chloride concentrations. Therefore, to utilize the serum anion gap properly, it is essential that the clinician know the mean value and range of normal for his or her clinical laboratory.

Because serum albumin constitutes a large proportion of the unmeasured anions, a reduction or increment in serum albumin concentration can alter the serum anion gap. Surprisingly, it is only within the last 13 years that a correction factor has been developed that can be introduced into clinical practice. These studies revealed that the anion gap is reduced by 2.3–2.5 mEq/L per gram of fall in serum albumin concentration, whereas it is increased to a similar

**Table 1. Definition of serum anion gap in major textbooks and web resources**

Source	Reference	Definition (mEq/L)	Comments
<i>Fluid, Electrolyte and Acid-Base Physiology</i> , 4th Ed.	Halperin <i>et al.</i> (9)	Mean $12 \pm 2$ ; presumed range, 8–16	Values to be adjusted for prevailing serum albumin concentration
<i>Clinical Physiology of Acid-Base and Electrolyte Disorders</i> , 5th Ed.	Rose (10)	Range 7–13; 3–11 with ion-selective electrodes	Values to be adjusted for prevailing serum albumin concentration; different values reflect different laboratory methods for measurement
<i>Goldman's Cecil Medicine</i> , 24th Ed.	Seifter (11)	Approximate value 10–12	No comment about correction for serum albumin
<i>Textbook of Nephrology</i> , 3rd Ed. <sup>a</sup>	Salem and Batlle (8)	10–12; 6–10 with ion-selective electrodes	Values to be adjusted for prevailing serum albumin concentration
<i>Brenner and Rector's The Kidney</i> , 8th Ed.	Dubose (12)	Mean $9 \pm 3$ ; presumed range, 3–15	Values to be adjusted for prevailing serum albumin concentration;
<i>Murray and Nadel's Textbook of Respiratory Medicine</i> , 5th Ed.	Effros and Swenson (13)	Range, 8–16	Values to be adjusted for prevailing serum albumin concentration
UpToDate 2013	Emmett (14)	Range, 7–13; 3–9 with ion-selective electrodes	Values to be adjusted for prevailing serum albumin concentration
<i>Henry's Clinical Diagnosis and Management by Laboratory Methods</i> , 22th Ed.	Oh (15)	Approximate 12; range, 8–16	Values to be adjusted for prevailing serum albumin concentration

<sup>a</sup>Discussion from third edition chosen because discussant in fourth edition, T.D. Dubose, wrote on the topic in other books and is cited.

**Table 2. Mean and range of normal serum anion gap in selected studies**

Population (n)	Anion Gap Mean and Range of Values (mEq/L)	Laboratory Method	Reference
488 patients with normal electrolytes	15±2.5 (10–20)	Technicon SMA 6/60 continuous flow analyzer	Buckley-Sharp and Miller (16)
100 patients with normal electrolytes	11±2.5 (6–16)	Technicon SMA 6/60 continuous flow analyzer	Frohlich <i>et al.</i> (17)
1200 patients with normal electrolytes: Summary of three studies	12±2.0	Technicon SMA 6/60 continuous flow analyzer	Emmett and Narins (3)
29 healthy volunteers	6.4±1.4	Astra ion electrode	Winter <i>et al.</i> (18)
124 healthy volunteers	(5–12)	Beckman ion electrode	Lolekha <i>et al.</i> (19)
18,987 patients who received care between 1997 and 2007	10–18	?	Lipnick <i>et al.</i> (20)

degree with a rise in serum albumin concentration (21,22). Although not routinely included in the correction, the multiplication factor will be affected by changes in blood pH, which alters the charge on circulating albumin (23). The corrected anion gap can be calculated using the so-called Figge equation as follows (24):

$$\begin{aligned} \text{cAG} &= \text{anion gap} + 0.25 \\ &\times (\text{normal albumin} - \text{measured albumin (g/L)}) \text{ or} \\ &\text{anion gap} + 2.5 \\ &\times (\text{normal albumin} - \text{measured albumin (g/dl)}) \end{aligned}$$

The use of this equation has improved the sensitivity of the anion gap in detecting hyperlactatemia (see below). Although clinicians must make the correction for changes in serum albumin concentration, routine incorporation of the correction factor into the reporting of the anion gap by the clinical laboratory would ensure that the corrected value is always utilized by the clinician.

### Recognition of an Increase in the Serum Anion Gap

Once the range of the serum anion gap for a specific clinical laboratory has been identified and corrected for serum albumin, the clinician must determine if the anion gap is elevated. Most commonly, this is done by showing that the particular anion gap exceeds the upper range of normal for the clinical laboratory. On the other hand, some clinicians arbitrarily use the mean value for the anion gap from the clinical laboratory as the putative baseline. Assuming that the SDs of the data are not listed, any anion gap above the mean value is considered an elevated anion gap. However, if the SD is listed, then only values that exceed the mean by 2 SD would be considered abnormal.

Table 3 summarizes five studies representing >1200 patients in which the sensitivity of the anion gap and/or corrected anion gap in detecting hyperlactatemia was examined. In all studies, an increased anion gap was denoted when it exceeded the upper range of normal, either 12 or 16 mEq/L. In the first study, 43% of 56 patients with a serum lactate between 2.5 and 4.9 mmol/L and 50% of

them with serum lactate between 5 and 9.9 mmol/L had a normal serum anion gap (<12 mEq/L) (25). Similarly, in 272 consecutive patients seen in the emergency department in whom serum lactate and anion gaps were obtained simultaneously, only 58% of those with a serum lactate >2.5 mmol/L had an anion gap outside the normal range (26). These findings were confirmed in another study of 47 patients in a single ICU. Only 44% of 47 patients with serum lactate >2.5 mmol/L had an elevated anion gap (27). Correction of the anion gap for serum albumin improved the sensitivity of the anion gap in detecting mild hyperlactatemia to 75% (28) in one and 94% in the other (29).

The failure of the uncorrected or corrected serum anion gap to identify all patients with lactic acidosis, particularly when mild, is not surprising given the wide range of normal values, (a span of 8–10 mEq/L from lowest to highest values). Patients with an anion gap at the lower limit of the normal range will require an increment  $\geq 8$  mEq/L to exceed the normal range. As a result, a mild high anion gap metabolic acidosis might not be apparent to the clinician. Although not studied to the same extent, the same considerations would logically apply to other types of high anion metabolic acidosis such as ketoacidosis, toxic alcohols, salicylate intoxication, and uremic acidosis.

Two hypothetical patients illustrating the effect of the baseline anion gap on recognition of a high anion gap acidosis are shown in Table 4. In the first patient, the baseline anion gap of 3 mEq/L was at the lower limit of the normal range. The patient developed sepsis and serum lactate rose from 1 mmol/L to 2.5 mmol/L, a value abnormal for the laboratory. However, the serum anion gap rose from 3 to only 6 mEq/L, and thus remained within the normal range. With worsening of lactic acidosis, the serum lactate concentration rose to 6 mmol/L; however, the subsequent serum anion gap of 9 mEq/L still remained within the normal range for the laboratory. It is only when the lactate concentration rose to >8 mmol/L that the serum anion gap was outside the normal range. Therefore, a clinically significant lactic acidosis that was not heralded by an increased serum anion gap was present during hospitalization. Clearly, recognition of the lactic acidosis early in

**Table 3. Sensitivity of increased anion gap in detecting hyperlactatemia**

Population (n)	Range and Anion Gap Indicating Acidosis (mEq/L)	Corrected For Serum Albumin Concentration	Sensitivity and Comments	Reference
272 patients in emergency department	>12	Yes	58% 78% with corrected anion gap	Adams <i>et al.</i> (26)
438 patients with lactate measured	5–16 >12	No	44% with elevated lactate 2.5 mmol/L had abnormal AG	Levrault <i>et al.</i> (27)
56 patients with serum lactate >2.5 mmol/L	>12 and <16  >16	No	43% with serum lactate between 2.5 and 4.9 mmol/L 50% with lactate between 5 and 9.9 mmol/L had normal AG	Iberti <i>et al.</i> (25)
143 ICU patients with serum lactate >2.5 mmol/L	10–12  >12	Yes	63% with serum lactate >2.5 mmol/L 94% with serum lactate >2.5 mmol/L with corrected AG	Chawla <i>et al.</i> (29)
Retrospective analysis of 639 values from 356 hospitalized patients	5–12 >12	Yes	39% uncorrected 75% with corrected anion gap ROC values for uncorrected and corrected AG similar	Dinh <i>et al.</i> (28)

AG, anion gap; ICU, intensive care unit; ROC, receiver operating characteristic.

**Table 4. Electrolytes in typical patients with lactic acidosis and varying baseline serum anion gaps assuming 1:1 relationship between  $\Delta\text{AG}/\Delta\text{HCO}_3^-$**

Blood Chemistries (mEq/L)	Patient 1				Patient 2		
	Baseline	Mild Lactic Acidosis	Moderate Lactic Acidosis	More Severe Lactic Acidosis	Baseline	Mild Lactic Acidosis	More Severe Lactic Acidosis
Na <sup>+</sup>	140	140	140	140	140	140	140
K <sup>+</sup>	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Cl <sup>-</sup>	113	113	113	113	106	106	106
HCO <sub>3</sub> <sup>-</sup>	24	21	18	15	24	21	18
Anion gap	3	6	9	12	10	13	16
$\Delta\text{AG}$	—	3	6	9	—	3	6
Lactate	1	2.5	6	8	1	2.5	6
Acid-base interpretation		No anion gap acidosis	Normal anion gap acidosis	High anion gap acidosis		High anion gap acidosis	High anion gap acidosis

Of course, as explained in the text, the  $\Delta\text{AG}/\Delta\text{HCO}_3^-$  often exceeds 1:1 with lactic acidosis. The hypothetical patients shown in the table are meant to emphasize the point that in some cases a relatively high serum lactate concentration will need to be present to cause the anion gap to rise outside the normal range.  $\Delta\text{AG}$ , change in anion gap

its course would provide the best conditions for its management. A similar scenario could hold for ketoacidosis or toxic alcohol exposure, two other situations in which early recognition of the disorder can improve the effectiveness of treatment.

Conversely, patient 2 had a baseline serum anion gap of 10 mEq/L, a value at the upper range of normal. An increase in the lactate level of 2.5 mEq/L immediately caused the serum anion gap to rise outside the normal range.

This situation becomes even more complicated because of the nature of the relationship between the increase in anion gap ( $\Delta AG$ ) and the fall in serum bicarbonate concentration ( $\Delta [HCO_3^-]$ ). As described below, the increase in the anion gap associated with lactic acidosis can exceed the fall in serum bicarbonate by as much as 1.8-fold. If so, a significant increase in the anion gap can be present in the absence of a perceptible fall in serum bicarbonate concentration. Were the increase in the anion gap to be a mere 2.5 mEq/L, the reduction in serum bicarbonate concentration might be close to 1 mEq/L. Because the normal range of bicarbonate can be from 24 to 29 mEq/L, a fall in bicarbonate might not even be detected.

On the other hand, the serum anion gap can be elevated to a greater degree than the rise in the measured concentration of the causative organic acid anion. Studies of patients with organic acidosis including lactic acidosis have demonstrated that the measured organic anion often can account for at most 76% of the increased anion gap (30). Similarly, in patients with documented lactic acidosis and sepsis, unmeasured anions, other than lactate, account for the bulk of the increment in the anion gap (31). Moreover, in reported cases of patients with the highest reported anion gaps  $\geq 40$  mEq/L, the cause of the increment in the anion gap was multifactorial and included contributions from changes in other moieties besides the identified organic acid anion (32).

The failure to detect an elevated serum anion gap in all patients with significant increments in blood lactate concentration represents an important limitation of the serum anion gap as a screening tool. Indeed, although many clinicians require a serum lactate  $\geq 5$  mmol/L for the diagnosis of lactic acidosis, others utilize values as low as 2.5–4 mmol/L because lactate concentration of this magnitude are associated with an increase in mortality (33). These observations indicate that the anion gap is a relatively insensitive indicator of the presence of lactic acidosis and has limited usefulness for monitoring its course. Thus, a direct measurement of lactate is essential for detecting suspected lactic acidosis and monitoring patients with lactic acidosis. Although it has not been studied to the same degree, similar concerns might apply to patients with other types of high anion gap acidosis.

#### Methods to Improve the Sensitivity of the Anion Gap

As shown above, correction of the serum anion gap for the prevailing serum albumin concentration improves the sensitivity of this calculation for assessing lactic acidosis, and presumably other forms of high anion gap metabolic acidosis. Utilizing the mean for the clinical laboratory as the baseline value should also reduce the magnitude of any error in estimating the change in the anion gap. However, using a baseline serum anion gap that is corrected for serum albumin concentration and specific to the individual would be the most accurate method of evaluating changes in the serum anion gap with acid-base disorders. To do this would require measurement of the anion gap when the individual is healthy and without acid-base disorders. This could be accomplished, in part, by ensuring that an anion gap panel is obtained every time chemistries are measured in patients.

In this regard, in a recent study, the value of the change in the anion gap (obtained from the difference between that obtained upon admission to a critical care unit and the prehospital value) in predicting clinical outcome was examined in  $>18,000$  patients admitted to two ICUs over a 10-year period (20). In instances in which  $>1$  pre-admission value was available, the average was utilized. A correlation between the magnitude of the increase in anion gap and clinical outcome was observed: the higher the increase in anion gap, the worse the outcome. This relationship held even when the anion gap was within the normal range for the hospital's clinical laboratory.

This approach still had limitations in identifying the magnitude of the change in lactate concentration. There were 973 individuals who had a serum lactate between 2 and 5 mmol/L. Of these, 343 individuals (35%) had no detectable increase in the anion gap. Moreover, even in the 409 individuals who had a serum lactate concentration  $>5$  mmol/L, 71 (17%) had no detectable change in the anion gap and 109 (27%) had a change in the anion gap between 0 and 5 mEq/L. Fifty-six percent of individuals with lactic levels  $>5$  had anion gaps that increased by  $>5$ .

This study raised questions about the sensitivity of even using a "personalized" anion gap to detect lactic acidosis. Nevertheless, this was a single observational study designed to determine the association between altered anion gap and prognosis, and large-scale studies whose intent would be to test the benefits of identifying the baseline anion gap in the recognition of a high anion gap metabolic acidosis are needed.

Given the emphasis on cost containment, one could argue that routine anion gap measurements to determine baseline levels would not be cost-effective in all individuals. However, one could *a priori* choose certain groups at high risk for development of high anion gap acidosis, such as patients with diabetes, history of alcoholism, kidney disease, severe cardiac disease, or hypotension, and patients admitted to the ICU or treated with metformin or various antiretroviral agents.

It should be recognized that variation from day to day in determination of the individual constituents of the anion gap could still introduce some error into the identification of a unique baseline anion gap. Averaging several baseline values to account for this variability should reduce the magnitude of any error, however.

#### The Effect of the Type of Retained Acid on the Serum Anion Gap

The accumulation of acids in the extracellular fluid can theoretically be estimated by examining the increment in the serum anion gap. The change in the serum anion gap, termed the  $\Delta$  anion gap ( $\Delta AG$ ), has been held to be matched by an equivalent reduction in serum  $[HCO_3^-]$  ( $\Delta [HCO_3^-]$ ), *i.e.*, the  $\Delta AG/(\Delta [HCO_3^-])$  is 1:1 (3). This has been based on the assumption that because protons accumulate with added anions, the serum  $[HCO_3^-]$  should decrease by a quantity exactly equal to the increase in the anion gap (*i.e.*,  $\Delta AG$ ) (6). On the basis of this perceived change, one could estimate the magnitude of the acid load and also recognize the coexistence of any additional metabolic acid-base disturbances. If the  $\Delta AG$  exceeded the  $\Delta [HCO_3^-]$ , it was concluded that a concurrent disorder

(metabolic alkalosis) was maintaining a higher  $[\text{HCO}_3^-]$  than would be expected for the elevation in anion gap (6). Conversely, if the  $\Delta [\text{HCO}_3^-]$  exceeded the  $\Delta\text{AG}$ , then a coexisting normal anion gap metabolic acidosis was perceived to be present. Indeed, in a comprehensive analysis, the  $\Delta [\text{HCO}_3^-]$  was compared with the  $\Delta\text{AG}$  in 22 randomly selected studies comprising 42 patients who had either lactic acidosis or ketoacidosis (34). The ratio of  $\Delta [\text{HCO}_3^-]/\Delta\text{AG}$  in patients with either disorder was  $0.98\% \pm 0.06\%$ , a value virtually indistinguishable from 1:1.

However, examination of the processes affecting the anion gap have suggested that this analysis is too simplistic and the stoichiometry between the  $\Delta [\text{HCO}_3^-]$  and  $\Delta\text{AG}$  might depend on the interplay of several factors, including the distribution of the anions and protons between the extracellular fluid and cellular compartments, changes in the renal generation of  $\text{HCO}_3^-$  and urinary excretion of anions, or possible changes in the valence of retained anions (35–39). Furthermore, these factors will be influenced by the nature of the retained organic acid anion, time after development of the acidosis, level of glomerular and tubular function, and volume status, to name a few (35–39).

Thus, there will be an equivalent reciprocal change in the serum  $[\text{HCO}_3^-]$  and anion gap immediately after retention of acid in the blood. However, some of the protons will enter cells as time passes. If they are accompanied by the accumulating anion, the relationship between anion gap and serum  $[\text{HCO}_3^-]$  will be unchanged. However, if there is a disparity between the rates of entry of protons and the anion (*i.e.*, the space of distribution of each), this 1:1 relationship will be altered. Indeed, in nephrectomized rats given an infusion of lactic acid or sulfuric acid the  $\Delta\text{AG}/(\Delta [\text{HCO}_3^-])$  exceeded 1:1 and was as high as 1.8:1 with lactic acid (35). This was explained by different volumes of distribution of the anion and protons, and a reduction in serum chloride resulting from its dilution by  $\text{Na}^+$  and water exiting cells during the buffering process.

Subsequently, the filtered anions are excreted accompanied by  $\text{NH}_4^+$  (resulting in  $\text{HCO}_3^-$  generation) and/or by  $\text{Na}^+$  and  $\text{K}^+$ . If urinary anion excretion exceeds the generation of  $\text{HCO}_3^-$ , the ratio of the  $\Delta\text{AG}$  to  $\Delta\text{HCO}_3^-$  will fall. In studies in humans, the  $\Delta\text{AG}/(\Delta [\text{HCO}_3^-])$  was 1:1 with ketoacidosis, but averaged 1.5 with lactic acidosis (36). The differences between the ratios with ketoacidosis compared with lactic acidosis were attributed, in part, to the large fractional excretion of ketones ( $45.8\% \pm 3.1\%$ ) with  $\text{Na}^+$  and the low fractional excretion of lactate with  $\text{Na}^+$  ( $4.7\% \pm 0.3\%$ ) (36,37). The effect on the  $\Delta\text{AG}/(\Delta [\text{HCO}_3^-])$  of the accumulation of other organic acid anions in the body fluids and their urinary excretion, such as the metabolites of methanol, has not been examined but remains of interest.

In summary, the calculation of the serum anion gap has been a useful tool in the evaluation of metabolic acidosis. It has been most useful for suspecting the presence of retained acids that could have an effect on clinical outcome and for detecting mixed metabolic acid-base disorders. Detection of an elevated anion gap, however defined, should certainly trigger an evaluation for conditions that cause its elevation. However, there are important limitations that need to be addressed to improve its effectiveness

as a tool for this purpose. Correction of the anion gap for the prevailing serum albumin concentration should be an integral component of laboratory reporting of the anion gap, rather than depending on the clinician to make the correction. Of course this might require more frequent determinations of serum albumin concentration. Inclusion of the serum  $\text{K}^+$  in the calculation of the anion gap should also be considered when serum  $\text{K}^+$  is substantially altered.

Identification of the unique baseline for each patient might facilitate recognition of early or mild cases of metabolic acidosis. To the extent that early identification is valuable in reducing complications and mortality of these disorders, establishing approaches to recognize mild changes in the anion gap should be a high priority. Acknowledging the limitations of the current uses of the anion gap and incorporating measures to improve its effectiveness will make the anion gap a more practical tool in the evaluation of acid-base disorders.

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#### References

- Lolekha PH, Lolekha S: Value of the anion gap in clinical diagnosis and laboratory evaluation. *Clin Chem* 29: 279–283, 1983
- van Hoesen KH, Joseph RE, Gaughan WJ, McBride L, Bilotti E, McNeill A, Schmidt L, Schillen D, Siegel DS: The anion gap and routine serum protein measurements in monoclonal gammopathies. *Clin J Am Soc Nephrol* 6: 2814–2821, 2011
- Emmett M, Narins RG: Clinical use of the anion gap. *Medicine (Baltimore)* 56: 38–54, 1977
- Kraut JA, Madias NE: Serum anion gap: Its uses and limitations in clinical medicine. *Clin J Am Soc Nephrol* 2: 162–174, 2007
- Emmett M: Anion gap interpretation: The old and the new. *Nat Clin Pract Nephrol* 2: 4–5, 2006
- Goodkin DA, Krishna GG, Narins RG: The role of the anion gap in detecting and managing mixed metabolic acid-base disorders. *Clin Endocrinol Metab* 13: 333–349, 1984
- Narins RG, Emmett M: The anion gap. *Lancet* 1: 1304–1305, 1977
- Salem MM, Battle D: Metabolic acidosis. In: *Textbook of Nephrology*, edited by Massry S, Glasscock R, 3rd Ed., Philadelphia, W.B. Saunders, 1998, pp 430–468
- Halperin ML, Kamel KS, Goldstein MB: Tools to use to diagnose acid-base disorders. In: *Fluid, Electrolyte and Acid-Base Physiology*, 4th Ed., edited by Halperin ML, Goldstein MB, Kamel KS, Philadelphia, W.B. Saunders, 2010, pp 39–57
- Rose BD: Metabolic acidosis. In: *Clinical Physiology of Acid-Base and Electrolyte Disorders*, 5th Ed., edited by Rose B, Post T, Philadelphia, McGraw-Hill, 2001, pp 540–603
- Seifter JL: Acid-base disorders. In: *Goldman's Cecil Medicine*, 24th Ed., edited by Goldman L, Schafer AL, Philadelphia, Saunders Elsevier, 2011, pp 741–753
- Dubose TD: Disorders of acid-base balance. In: *Brenner and Rector's The Kidney*, 8th Ed., edited by Brenner BE, Philadelphia, Saunders Elsevier, 2011, pp 595–639

13. Effros R, Swenson E: Acid-base balance. In: Murray and Nadel's Textbook of Respiratory Medicine, 5th Ed., edited by Mason RJ, Broaddus VC, Martin T, King T Jr, Schraufnagel D, Murray JF, Nadel JA, Philadelphia, W.B. Saunders, 2010, pp 135–156
14. Emmett M: The anion gap/HCO<sub>3</sub> ratio in patients with a high anion gap metabolic acidosis. In: *UpToDate*, edited by Bassow DS, UpToDate, Waltham, MA, 2012
15. Oh MS: Evaluation of renal function, water, electrolyte and acid-base balance. In: *Henry's Clinical Diagnosis and Management by Laboratory Methods*, 22 Ed., edited by McPherson RA, Pincus MR, Philadelphia, W.B. Saunders, 2011, pp 169–192
16. Buckley-Sharp MD, Miller AL: The anion gap. *Lancet* 2: 206, passim, 1973
17. Frohlich J, Adam W, Golbey MJ, Bernstein M: Decreased anion gap associated with monoclonal and pseudomonoclonal gammopathy. *Can Med Assoc J* 114: 231–232, 1976
18. Winter SD, Pearson JR, Gabow PA, Schultz AL, Lepoff RB: The fall of the serum anion gap. *Arch Intern Med* 150: 311–313, 1990
19. Lolekha PH, Vanavanan S, Lolekha S: Update on value of the anion gap in clinical diagnosis and laboratory evaluation. *Clin Chim Acta* 307: 33–36, 2001
20. Lipnick MS, Braun AB, Cheung JT, Gibbons FK, Christopher KB: The difference between critical care initiation anion gap and prehospital admission anion gap is predictive of mortality in critical illness. *Crit Care Med* 41: 49–59, 2013
21. Carvounis CP, Feinfeld DA: A simple estimate of the effect of the serum albumin level on the anion gap. *Am J Nephrol* 20: 369–372, 2000
22. Feldman M, Soni N, Dickson B: Influence of hypoalbuminemia or hyperalbuminemia on the serum anion gap. *J Lab Clin Med* 146: 317–320, 2005
23. Madias NE, Ayus JC, Adrogue HJ: Increased anion gap in metabolic alkalosis: The role of plasma-protein equivalency. *N Engl J Med* 300: 1421–1423, 1979
24. Figge J, Jabor A, Kazda A, Fencl V: Anion gap and hypoalbuminemia. *Crit Care Med* 26: 1807–1810, 1998
25. Iberti TJ, Leibowitz AB, Papadakos PJ, Fischer EP: Low sensitivity of the anion gap as a screen to detect hyperlactatemia in critically ill patients. *Crit Care Med* 18: 275–277, 1990
26. Adams BD, Bonzani TA, Hunter CJ: The anion gap does not accurately screen for lactic acidosis in emergency department patients. *Emerg Med J* 23: 179–182, 2006
27. Levraut J, Bounatirou T, Ichai C, Ciais JF, Jambou P, Hechemia R, Grimaud D: Reliability of anion gap as an indicator of blood lactate in critically ill patients. *Intensive Care Med* 23: 417–422, 1997
28. Dinh CH, Ng R, Grandinetti A, Joffe A, Chow DC: Correcting the anion gap for hypoalbuminaemia does not improve detection of hyperlactataemia. *Emerg Med J* 23: 627–629, 2006
29. Chawla LS, Jagasia D, Abell LM, Seneff MG, Egan M, Danino N, Nguyen A, Ally M, Kimmel PL, Junker C: Anion gap, anion gap corrected for albumin, and base deficit fail to accurately diagnose clinically significant hyperlactatemia in critically ill patients. *J Intensive Care Med* 23: 122–127, 2008
30. Gabow PA, Kaehny WD, Fennessey PV, Goodman SI, Gross PA, Schrier RW: Diagnostic importance of an increased serum anion gap. *N Engl J Med* 303: 854–858, 1980
31. Maciel AT, Park M: Unmeasured anions account for most of the metabolic acidosis in patients with hyperlactatemia. *Clinics (Sao Paulo)* 62: 55–62, 2007
32. Oster JR, Singer I, Contreras GN, Ahmad HI, Vieira CF: Metabolic acidosis with extreme elevation of anion gap: Case report and literature review. *Am J Med Sci* 317: 38–49, 1999
33. Mikkelsen ME, Miltiades AN, Gaijeski DF, Goyal M, Fuchs BD, Shah CV, Bellamy SL, Christie JD: Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med* 37: 1670–1677, 2009
34. Narins RG, Bastl CP, Rudnick MR, Javaheri S, Stom MC, Jones ER: Acid-base metabolism. In: *Current Nephrology*, edited by Gonick H, New York, Wiley and Sons, 1982, pp 79–130
35. Madias NE, Homer SM, Johns CA, Cohen JJ: Hypochloremia as a consequence of anion gap metabolic acidosis. *J Lab Clin Med* 104: 15–23, 1984
36. Kim HY, Han JS, Jeon US, Joo KW, Earm JH, Ahn C, Kim S, Lee JS, Kim GH: Clinical significance of the fractional excretion of anions in metabolic acidosis. *Clin Nephrol* 55: 448–452, 2001
37. DiNubile MJ: The increment in the anion gap: Overextension of a concept? *Lancet* 2: 951–953, 1988
38. Adrogue HJ, Eknoyan G, Suki WK: Diabetic ketoacidosis: Role of the kidney in the acid-base homeostasis re-evaluated. *Kidney Int* 25: 591–598, 1984
39. Kamel KS, Cheema-Dhadli S, Halperin FA, Vasudevan S, Halperin ML: Anion gap: May the anions restricted to the intravascular space undergo modification in their valence? *Nephron* 73: 382–389, 1996

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