Short Communication

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Approaching a phenomenal contradiction in acid–base physiology

https://doi.org/10.1515/jbcpp-2025-0016
Received January 19, 2025; accepted March 7, 2025;
published online March 31, 2025

Abstract

Objectives: The study focuses exclusively on the results of an arterial blood gas report, which reveal a phenomenal contradiction if one follows the physiological and physicochemical approaches as well as the standard base excess determination to interpret an acid–base disturbance. The aim of this article is not to fully describe a clinical case and make a differential diagnosis but to analyze the blood gas report data in detail and present the conclusions that result from the application of the different approaches that exist for the interpretation of acid–base disorders.

Methods: The results of an arterial blood gas report of a patient with severe lactic acidosis were cross-examined using the standard base excess method and the physiologic and physiochemical approaches. The causes of the contradiction are discussed with a commentary on the underlying pathophysiology.

Results: The study revealed the presence of a normal anion gap (even after correction for albumin levels), a slightly increased strong ion gap and a moderately decreased standard base excess in a patient with severe lactic acidosis.

Conclusions: This real-life case provides an opportunity to give a brief overview of the current methods for investigating acid–base disturbances in a practical way, emphasizing both the common background and the conceptual differences and similarities.

Keywords: acid–base disorders; base excess; physiological approach; physicochemical approach

Text

Not long ago, we were asked to help a resident interpret an arterial blood gas report of a patient: pH=7.324, pCO_2=37.1 mmHg, pO_2=113 mmHg, [HCO_3^-]=19.3 mEq/l, Hb=8.4 g/dl, [Na^+]=147 mEq/l, [K^+]=4.3 mEq/l, [Cl^-]=116 mEq/l, [Ca^{2+}]=0.9 mmol/l (=1.8 mEq/l), Glu=85 mg/dl, [Lac^-]=11.3 mEq/l, SBE=−6.2 mmol/l; also, [Alb]=3.7 g/dl, [Pi]=4.2 mg/dl (=1.36 mmol/l) and [Mg^{2+}]=1.97 mg/dl (=0.81 mmol/l=1.62 mEq/l).

Our explanatory pathophysiological remarks follow:

First, a quick look at the results of the arterial blood gas report shows a metabolic acidosis (low pH and low –near normal– pCO_2) of the hyperchloremic type ($\frac{[Cl^-]}{[Na^+]} \approx 0.79$, or low strong ion difference ([SID]) acidosis, [Na^+]–[Cl^-]=31 mEq/l) [1]. If we apply the respiratory compensation formula "pCO_2=1.28 × [HCO_3^-]+11.55" [2], we see that the measured pCO_2 is close to the expected value that compensates for metabolic acidosis: expected pCO_2=1.28 × [HCO_3^-]+11.55=36.25 mmHg. Still, a discrepancy between the calculated anion gap ([AG]) value ($[AG]_c$=[AG]+2.5 × (4–[Alb, g/dl])=12.45 mEq/l, corrected for albumin) [3], which is considered 'normal', and the significantly elevated [Lac^-] is also readily apparent: hypothetically, the increase in negative charges in plasma should correspond to the [Lac^-] increase.[1] The only possibility that the increase in

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1 In fact, the anion gap may be a relatively insensitive indicator of lactic acidosis. For example, in about half of the patients with a serum lactate concentration between 3.0 and 5.0 mEq/L, the [AG] is within the normal range [20, 21]. Though, other studies show that in cases of lactic acidosis,

[Lac^-] (pKa=3.85, aprote anion at pH=7.4) does not lead to a quantitatively comparable increase in negative charges in plasma is if the plasma pH is very acidic (e.g. lactate at pH=3.6 behaves chemically like a weak anion). However, such conditions are not compatible with life! Nevertheless, the contradiction can be resolved if we assume that the patient's initial, normal [AG] was very low (i.e. close to 0 mEq/l) and increased to the value we calculated after the significant increase in [Lac^-].

Causes of a low anion gap

To explain a low [AG] value we apply the principle of electrical neutrality:[2]

$$[Na^+] - \left([Cl^-] + [HCO_3^-]\right) = [AG] \equiv [X^-] - [X^+]$$

where [X^-] are the unknown anions and [X^+] are the unknown cations in plasma (i.e. ions that are not included in the [AG] calculation formula).

The [AG] therefore decreases if: **1.** *the concentration of the unknown ions changes* or **2.** *the concentration of Na^+ and/or Cl^- is incorrectly estimated.*

In the **first case**, i.e. when: **a** [X^-] decreases [e.g. in hypoalbuminemia [4] –albumin makes up the majority of unknown anions present under physiological conditions]. or **b.** [X^+] increases, e.g. with increased K^+, Ca^{2+}, Mg^{2+} concentrations. The same occurs with lithium intoxication [5] (lithium carbonate is the active substance –the carbonate anion is a weak anion and has no effect on pH) and monoclonal IgG paraproteinemia (IgGs are positively charged/ behave like cations at normal plasma pH; the isoelectric point of IgG immunoglobulins/paraproteins is between 7.6 and 9.0, i.e. well above the normal plasma pH –whereas for IgA, for example, it is 6.9–7.2) [6]. In both parts of the first case, [AG] decreases because plasma anions, mainly Cl^-, increase to compensate for the relatively higher concentration of positive charges and a misdiagnosis of non-AG acidosis may occur. Pathophysiologically, when the difference between the concentration of positive charges and negative charges in body fluids increases (as is the case in IgG paraproteinemia, for example), an increase in [HCO_3^-] is generally expected (analogous to increased [SID] metabolic alkalosis); then HCO_3^- can predictably be replaced by an increase in Cl^-, through physiological mechanisms, e.g. HCO_3^-/Cl^- exchangers [3] [7]. The same occurs in hypoalbuminemia: when albumin decreases, as long as PCO_2 and [SID] remain unchanged, [HCO_3^-] (and [OH^-]) increase and metabolic alkalosis occurs: with increasing [OH^-], since the ionic product of water ([H^+] × [OH^-]) remains constant, [H^+] changes accordingly, i.e. it decreases, leading to alkalosis. Finally, chloride anions increase to compensate for the loss of albumin anions and restore pH; i.e. the compensatory response to hypoproteinemia is a decrease in [SID], which is due to an increase in [Cl^-] rather than a decrease in [Na^+] [8]. Therefore, hypoproteinemic alkalosis may be considered a mixed acid–base disorder. The primary disorder is the alkalizing influence of hypoproteinemia, while the second disorder prevents the compensatory increase in [Cl^-] and decrease in [SID] that could limit the pH deviation [9].

In the **second case**, a 'falsely' low [AG] value may result **a'.** from pseudohyponatremia [10] (i.e. when lipids and/or proteins are greatly elevated in plasma –in these circumstances the electrolyte measurement method used is important, e.g. flame photometry may underestimate [Na^+]) –however, the measurement of [Na^+] with blood gas analyzers avoids this 'pseudo' estimate– or **b'.** when the concentration of [Cl^-] is overestimated. For example, in the case of halide poisoning (e.g. bromide ingestion [11]), the analyzer will give elevated [Cl^-] values by measuring the bromide anions as Cl^- anions. In this situation, the [Cl^-] value is falsely elevated. Note that the increase in anion concentration (which is mistaken for hyperchloremia) does not affect the ionic balance in the serum (and pH), so no compensatory changes are required as e.g. bromide is taken up in the form of its salts (e.g. with K^+ or lithium) and [SID] remains approximately constant.

Here we should note that, in the **first case**, hyperchloremia may represent a separate electrolyte/acid–base disturbance rather than being a compensatory response. Possible causes include the administration of normal saline, e.g. during fluid resuscitation, or the presence of a septic

the increase in [AG] is disproportionately large compared to the increase in [Lac^-], i.e., a significant percentage of the [AG] increase, e.g., 70 % in one study [22], cannot be explained by the increase in [Lac^-] or, in other words, there may be other causes for the [AG] increase in lactic acidosis (unknown organic anions have been considered, e.g., Krebs cycle intermediates [23]).

2 We should emphasize the different notation used to express the relationship between [AG] and the equation with which it is calculated, i.e. [Na^+]– ([Cl^-]+[HCO_3^-]) (equality) and with the difference [X^-]–[X^+], i.e. the excess of the unknown anions (identity).

3 Since the H_2CO_3/HCO_3^- buffer system is ubiquitous in the body, it can rapidly compensate for changes in ionic balance and pH (within certain limits). This system is considered an important buffer for the body's pH deviations. It should be noted that the buffering capacity of the bicarbonate system is due partly to the fact that carbonic acid is a weak acid, and partly to the fact that CO_2 (dehydrated form of carbonic acid) is volatile and is removed from the body by exhalation (its 'concentration' is regulated by its excretion from the lungs) [24]. The final 'regulation' concerns the change of [Cl^-] in the different compartments of the body (and in the plasma), for which the role of the HCO_3^-/Cl^- exchangers seems to be particularly important.

syndrome, in which the chloride concentration may increase due to differential movement of Na^+ and Cl^- from the intracellular to the extracellular space or from the extravascular to the intravascular space; extravasation of albumin due to endothelial injury may be partly responsible for this Cl^- movement [12].

Figure 1 illustrates the above pathophysiological remarks. The Gamblegrams show no $[H^+]$. This is because $[H^+]$ in serum is about 40 nEq/l, which is much lower than the concentration of the main electrolytes in plasma, whose concentration is measured in mEq/l (which is of the order of 1×10^6 times). In addition, a change of hundreds of thousands of equivalents of strong ions (e.g. K^+) is required to cause a change of 1 Eq/l of $[H^+]$ (the buffer value –related to the change of [SID]– for plasma is -6.9×10^5) [13].

Strong ion gap vs. anion gap

At this point, it would be useful to investigate whether the physicochemical analysis (Stewart's approach), would lead to different results. A problem for the clinical application of Stewart's original, detailed approach is its mathematical complexity. For this reason, simplified methods have been proposed for use by clinicians [14]. The Strong Ion Gap ([SIG]), which is calculated from the difference between the effective [SID] ($[SID_{eff}]$) and the apparent [SID] ($[SID_{app}]$), corresponds to the unknown anion excess (including that of lactate). Therefore, using the relevant equations [4] [14], [SIG]=7 mEq/l. Thus, despite the detailed calculations, even this approach cannot quantitatively account for the observed increase in $[Lac^-]$. To note, [SIG] corrected for water excess or deficit, by multiplying the observed value by the correction factor $[Na^+]_{normal}/[Na^+]_{observed}$, corresponds to 6.67 mEq/l, i.e. it is only slightly higher than the value used in studies to detect acidosis due to the presence of unknown anions (>6 mEq/l) [14] or the upper limit in the suggested normal reference range (<5 mEq/l) [15].[5] Moreover, if we include $[Lac^-]$ in the calculation of $[SID_{app}]$, the value of [SIG], corresponding to the concentration of unknown (an) ions other than lactate, becomes negative (–4.3 mEq/l). In fact, as with [AG], [SIG] quantifies $[X^-]–[X^+]$ ($[SIG] \equiv [X^-]–[X^+]$); thus, an increased unmeasured cation concentration reduces [SIG] [15]. Assuming that the measurements of the other electrolytes are correct, the negative [SIG] value means that there is at least a similar amount of unknown cations in the plasma that were not included in the ion balance equations, e.g. IgG paraproteins or lithium, leading to a subsequent compensatory increase in $[Cl^-]$ which, as mentioned above, may be mistaken for hyperchloremic acidosis ($[Cl^-]$ corrected for water excess or deficit equals 110.5 mEq/l) [14]. However, there could also simply be an independent, simultaneous increase in positive and negative charges in the plasma; although this seems less likely, it still needs to be clarified. Figure 2 illustrates the acid–base variables of the physicochemical approach mentioned above. Concerning hypoalbuminemia, it has no impact on the diagnostic accuracy of [SIG] as it is included in the equation used to calculate it (albumin is not part of the unknown anions but is used to determine them). Thus, when calculating [SIG], low $[Alb^-]$ is compensated by an equivalent increase in $[Cl^-]$ (and/or $[HCO_3^-]$) and [SIG] is not affected. In contrast, the increase in $[Cl^-]$ (and/or $[HCO_3^-]$) caused by the decrease in $[Alb^-]$ reduces [AG]. As mentioned earlier, albumin is the main component of normal [AG], the most important, physiologically present 'unknown anion'. Accordingly, we need to know either *what the normal [AG] is*, i.e. the [AG] when there is no metabolic acidosis with an increase in the unknown

4 The calculations of the acid–base variables were carried out on the basis of the following formulas [14]:

$$[SIG] = [SID_{app}] - [SID_{eff}], [A^-] = [Alb^-] + [Pi^-]$$

$$[\text{SIG}] : \text{Strong Ion Gap}, [\text{SID}_{\text{app}}] : \text{apparent SID}, [\text{SID}_{\text{eff}}] : \text{effective [SID]}$$

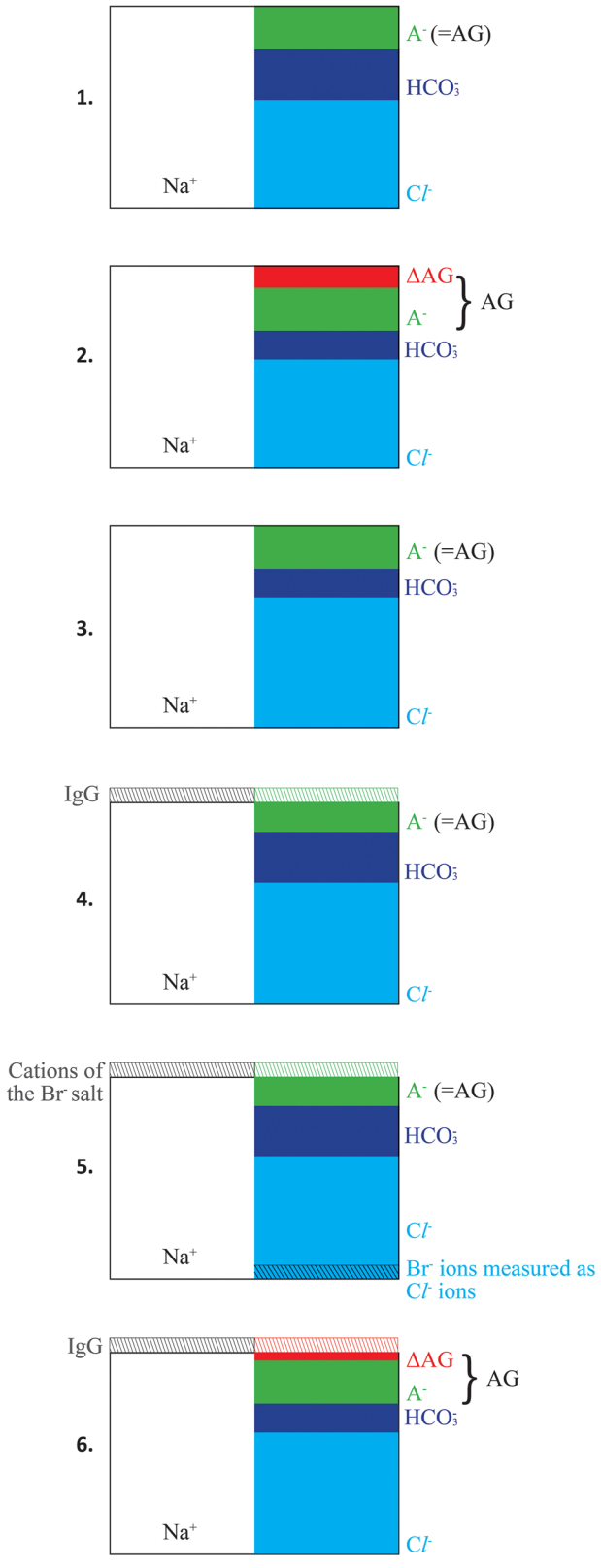
$$[\text{SID}_{\text{app}}] = [\text{Na}^+] + [\text{K}^+] + [\text{Ca}^{2+}] + [\text{Mg}^{2+}] - [\text{Cl}^-] - [\text{Lac}^-] \ (\text{in mEq/l})$$

$$[\text{SID}_{\text{eff}}] = [\text{HCO}_3^-] + [\text{Alb}^-] + [\text{Pi}^-] \ (\text{in mEq/l})$$

$$[\text{Alb}^-] = [\text{albumin}] \times (0.123 \times \text{pH} - 0.631), [\text{Pi}^-] = [\text{phosphate}] \times (0.309 \times \text{pH} - 0.469)$$

[albumin] in g/l, [phosphate] in mmol/l

5 The physicochemical approach involves the calculation of $[SID_{app}]$, $[SID_{eff}]$ and [SIG] to investigate the acid–base status of a patient. However, the assessment of these acid–base parameters requires the measurement of many variables and the calculated values may vary depending on the analyzer used. The resulting differences may have important clinical and research implications [25]. Thus, according to the electroneutrality principle, $[SID_{app}]$ and $[SID_{eff}]$ must be equal, i.e. $[SIG] \approx 0$ mEq/l. A numerical difference, i.e. $[SID_{app}] - [SID_{eff}] > 0$, represents the net electrical charge in the plasma required to fulfil the electroneutrality constraint due to the possible presence of unknown endogenous anions (e.g. organic anions), exogenous anions (anions derived e.g. from the use of gelatin-based resuscitation fluids which, nevertheless, are no longer used today) [26] as well as an unknown quantity that depends on inaccuracies in ion measurements; the above imply that [SIG] can also be elevated even in cases where there is no obvious acid–base disturbance.



anions or *what the [AG] would be if [Alb] were normal*, i.e. the corrected [AG]), in order to draw the correct conclusions about the X^- excess [evidenced by the increase in [AG] above the normal value, i.e. the value corresponding to the concentration of albumin (plus phosphate)].

Figure 1: Gamblegrams of the *presumed ionic composition of the serum*, i.e. created taking into account measurements of specific serum electrolyte concentrations (Na^+, Cl^-, HCO_3^-) to calculate the anion gap (AG), in the normal state, where AG=[A^-]†, (Gamblegram 1) and in the case of: high anion gap metabolic acidosis (HAGMA), where AG=[A^-]+ΔAG (Gamblegram 2), hyperchloremic acidosis (non-AG metabolic acidosis) (Gamblegram 3), increase of unknown cations in serum (e.g. IgG) (Gamblegram 4), spurious hyperchloremia (overestimated [Cl^-] due to bromide ingestion) (Gamblegram 5), HAGMA in a patient with IgG paraproteinemia (Gamblegram 6). A similar reduction in HCO_3^- 'space' is observed in **Gamblegrams 2 and 3**, with the remaining space (making up the difference with cations) being filled by unknown anions (which generate the ΔAG)‡ in Gamblegram 2, i.e., in HAGMA, and by Cl^- in Gamblegram 3, i.e., in non-AG metabolic acidosis.In **Gamblegrams 4**, **5** and **6**, the upward expansions in the anion columns (shown with stripes) represent the additional amount of the unknown anions in the serum [i.e., those that form AG, either in a healthy state (only A^-) or in HAGMA (A^-+ΔAG)], that are not detected due to the incorrect calculation of AG from the concentrations of Na^+, Cl^- and HCO_3^-. In **Gamblegram 4**, the cation column contains Na^+ as well as the positive charges of the IgG paraproteins, which, however, are not perceptible –they are not included in the ion balance equations used to calculate AG in serum (they are displayed as an extension at the top of the cation column). For reasons of electrical neutrality, the excess positive charge is 'balanced' by an equal increase in the [Cl^-] value, resulting in a lower than normal calculated AG (spurious A^- decrease); the 'space' of HCO_3^- does not change as the difference between positively and negatively charged strong ions remains constant. In **Gamblegram 5**, the negative charge of the bromide ions is erroneously perceived as an increase in [Cl^-] (for this reason it is represented as an additional quantity of anions in the 'space' occupied by Cl^-). Since bromide is taken up in its salt form, i.e. with positively charged ions (e.g. with potassium or lithium, shown as an extension at the top of the cation column), [SID] in serum does not change and the pH remains normal –a single increase in bromide ions would theoretically lead to HAGMA. The 'space' of HCO_3^- thus remains constant, while the calculated AG ([A^-]) decreases and can even assume a negative value (depending on the increase in measured [Cl^-], which is related to the amount of bromide consumed). Finally, in **Gamblegram 6**, HAGMA occurs in addition to IgG paraproteinemia. The increased concentration of the unknown anions (e.g. lactate) lowers [HCO_3^-] and increases the (previously low, see Gamblegram 4) normal AG; however, the calculated AG value could be erroneously regarded as almost normal and the slight increase in ΔAG as insignificant. In this way, acidosis of the hyperchloremic type may be misdiagnosed. †A^-: non-volatile weak acids, mostly albumin. ‡ΔAG=-calculated AG ([Na^+] – ([Cl^-] + [HCO_3^-]) – Normal AG.

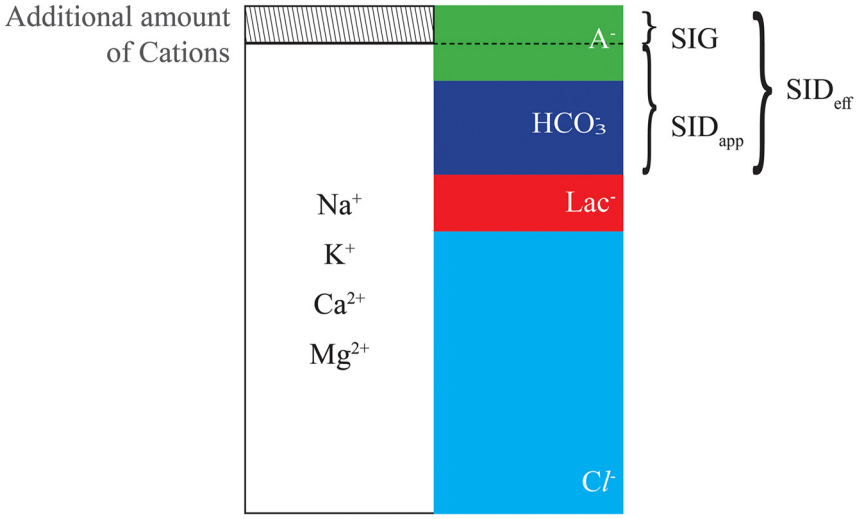


Figure 2: The Gamblegram shows the acid–base variables calculated according to the physicochemical approach. If we include [Lac^-] in the calculation equation of [SID_{app}], [SID_{app}] decreases and the value of [SIG] becomes negative† (this is represented as an expansion of the anion column above the upper limit of the cation column). In other words, the measured negative ions are more than the corresponding positive ions in the Gamblegram. This assumes that there is an additional amount of positively charged ions in plasma (to maintain electrical neutrality) that are initially imperceptible (and are not taken into account in the ion balance calculations), e.g. IgG paraproteins or lithium, resulting in the compensatory increase in [Cl^-] (hyperchloremic acidosis is ruled out-see text). This additional amount of cations is indicated by an upward expansion of the cation column (shown with stripes). Spurious hyperchloremia, e.g. due to the ingestion of bromide preparations, would lead to the same result; in this case, the additional positive charges would correspond to the cations of the bromide salts. †[SID_{app}]: apparent strong ion difference; [SID_{eff}]: effective strong ion difference; [SIG]: strong ion gap.

The fact that we arrive at conceptually similar conclusions using the two methods should not surprise us. A strong correlation has been established between [AG] values (corrected for albumin) and [SIG] values, showing that their change is determined by the same factors [16].

As a final remark, we should emphasize that in the presence of metabolic acidosis of both types, i.e. hyperchloremic acidosis coexisting with increased [X^-] acidosis, the increase in [AG] and [SIG] *persists*. Both [AG] and [SIG] should increase quantitatively in proportion to the X^- excess; the gap-gap ratio and the $\Delta[AG]-\Delta[HCO_3^-]$ difference [17] simply change.[6]

The base excess

Continuing our analysis, we note that for the experienced clinician, the significant increase in lactate together with the picture of hyperchloremic acidosis, which at first glance

6 If lactic acidosis is accompanied by hyperchloremic acidosis, the decrease in bicarbonate concentration would correspond to the increase in lactate concentration plus the increase in chloride –we ignore for the moment the presumed deviations from the one-to-one ratio in these quantitave relationships. Let as assume that $[HCO_3^-]_o$ and $[Cl^-]_o$ are the basal/normal bicarbonate and chloride concentrations respectively, $\Delta[Cl^-]$ is the primary increase in chloride concentration (hyperchloremic acidosis), $\Delta[HCO_3^-]_{Lac}$ is the decrease in bicarbonate due to lactic acidosis and $\Delta[HCO_3^-]_{Cl}$ is the decrease in bicarbonate due to hyperchloremic acidosis. Then, $[AG]=[Na^+]-([Cl^-]_o+\Delta[Cl^-]+[HCO_3^-]_o-\Delta[HCO_3^-]_{Lac}-\Delta[HCO_3^-]_{Cl})$. But, theoretically, $\Delta[Cl^-]=\Delta[HCO_3^-]_{Cl}$. Therefore $[AG]=[Na^+]-([Cl^-]_o+[HCO_3^-]_o-\Delta[HCO_3^-]_{Lac})$. Thus, [AG] increases by $\Delta[HCO_3^-]_{Lac}$, i.e. an increase in [AG] is observed as expected in high anion gap metabolic acidosis (HAGMA). The same applies to the calculation of [SIG]: $[SIG]=[Na^+]+[K^+]+[Ca^{2+}]+[Mg^{2+}]-[Cl^-]_o-\Delta[Cl^-]-([HCO_3^-]_o-\Delta[HCO_3^-]_{Lac}-\Delta[HCO_3^-]_{Cl}+[Alb^-]+[Pi^-])=[Na^+]+[K^+]+[Ca^{2+}]+[Mg^{2+}]-[Cl^-]_o-([HCO_3^-]_o-\Delta[HCO_3^-]_{Lac}+[Alb^-]+[Pi^-])$. Thus, [SIG] increases by $\Delta[HCO_3^-]_{Lac}$, i.e. an increase in [SIG] is observed as expected during acidosis due to an increase in [X^-].

In the event that the increase in chloride is secondary, i.e. offsetting a primary increase in unknown positive charges in plasma to maintain 'ionic balance', [HCO_3^-] is not expected to be affected by the change in [Cl^-] and the [AG]/[SIG] will be altered (decreased), i.e. the observed increase, if any, will not correspond to (and will not reveal) the actual increase in unknown anions in serum.

Overall, in metabolic acidosis of both types, i.e. AG and non-AG acidosis, the increase in [AG] is not hidden; the gap-gap ratio and the $\Delta[AG]-\Delta[HCO_3^-]$ difference [17] (which is between –5 and + 5 mEq/l in pure HAGMA) simply change (the difference becomes <–5). In particular, in lactic acidosis, the difference of $0.6\times\Delta[AG]-\Delta[HCO_3^-]$ is more likely to be true (the gap-gap ratio increases, i.e. [AG] increases more than [HCO_3^-] decreases, in contrast to diabetic ketoacidosis, for example, possibly due to differences in the distribution space of H^+ and Lac^- and/or renal handling of H^+ and Lac^- –lower renal loss of Lac^-). In our case, if we assume that the increase in [Lac^-] corresponds to an approximately equal increase in [AG], we obtain $0.6\times\Delta[AG]-\Delta[HCO_3^-]=2.08$ mEq/l; this corresponds to a pure HAGMA. However, if we assume that the usual ratio of one-to-one between the decrease in [HCO_3^-] and the increase in [AG]applies, then $\Delta[AG]-\Delta[HCO_3^-]=6.6$ mEq/l; this corresponds to an imposed metabolic alkalosis.

seems to be coexistent, does not justify a moderate metabolic acidosis (as deduced from the moderate decrease in pH and bicarbonate concentration); he would certainly expect a much more severe acidosis. Since the pCO_2 is close to normal, one might suspect an imposed metabolic alkalosis attenuating the pH change.

To investigate the relationship between ion concentrations and pH change, it would be appropriate to use the standard base excess (SBE) method,[7] as its measurement is originally based on blood titration tests (i.e. normalization of pH under physiological pCO_2 conditions) [18] and thus conceptually fits and can answer the clinician's question: i.e. *given the measured ion concentrations and the value of the SBE, what is the expected concentration of the unknown ions/charges?*

Here, too, there is a significant difference between the SBE value (=−6.2 mmol/l, it refers to the overall change in the metabolic part of the acid–base disorder) and the increase in lactate that the SBE should indicate.

An easy-to-use method for the investigation of acid–base disorders based on the SBE has been proposed [19]. This method was proposed to help physicians reach clinical conclusions more easily. It essentially combines the concept of base excess [18] with the basic principle of electrical neutrality of aqueous solutions on which the [AG] and the Stewart's physicochemical approach are –partly– based.

According to this method, different fractions of the SBE are distinguished, which are calculated using the concentrations of known ions and compared with the measured SBE to determine the contribution of unknown ions/charges to shaping the SBE value. We therefore apply the following equations:

$$SBE_{FW} = 0.3 \times ([Na^+] - 140) = 2.1\, mEq/l$$

$$SBE_{Cl} = 104 - \{[Cl^-] \times (140/[Na^+])\} = -6.476\, mEq/l$$

$$SBE_{Alb} = (0.148 \times pH - 0.818) \times (40 - [Alb^-]) = 0.798\, mEq/l$$

$$SBE_{UA} = SBE - SBE_{FW} - SBE_{Cl} - SBE_{Alb} = -2.62\, mEq/l$$

where SBE_{FW}, SBE_{Cl}, SBE_{Alb} and SBE_{UA} are the fractions of SBE attributable to water excess/deficit and the concentrations of chloride, albumin and unknown anions, respectively. In view of the fact that [Lac^-]=11.3 mEq/l, i.e. SBE_{UA} should correspond to at least (since other unknown anions can coexist) −11.3 mEq/l, one comes to the conclusion that this method was also unable to detect the increased [X^-] acidosis. Predictably, part of the SBE is due to unknown cations (SBE_{UC}), i.e. additional positive charges that exert an alkaline effect.[8] It is noteworthy that if the lactate concentration were unknown, the metabolic acidosis could reasonably be attributed to hyperchloremia, since SBE_{Cl} and total SBE have almost identical values and SBE_{UA} is not significantly elevated (in absolute values). Assuming that the increase in [Cl^-] balances the concentration of additional positive charges, the initial [Cl^-] would be 107.32 mEq/l (close to normal). Furthermore, in the case where lactic acidosis and hyperchloremic acidosis simply coexisted (no other positive charges are present at elevated concentrations), the expected value of SBE based on the above equations would be as follows: $SBE=SBE_{FW} + SBE_{Cl} + SBE_{Alb} + SBE_{UA}$ = −14.878 mEq/l. Finally, the observed increase in [Cl^-] and the increase in 'unknown' cations in the blood (a conclusion

7 The base excess (BE) [18] is defined as the change in the concentration of all buffer anions, mainly bicarbonateand proteinate ions(buffer base, BB) [27], compared to the normal value, i.e. $BE=BB - BB_{normal}$. It is originally determined by blood titration to achieve a pH of 7.4 at a pCO_2 of 40 mmHg. The BB space conceptually represents the 'internal content' of [SID], with which it is quantitatively identified [28]. Thus, Wooten [28] expresses [SID] as a function of the concentration of the bicarbonate buffer anion (i.e. [HCO_3^-]) and the sum of the concentrations of the non-carbonate buffers:

$$[SID] = [HCO_3^-] - \sum_i C_i \bar{z}_i$$

where C_i is the concentration of (non-carbonate) species i and $\bar{z}_i$ is the average charge per molecule for species i.

8 The National Committee for Clinical Laboratory Standards [29] recommends using the following formula to access the SBE: $SBE= HCO_3^-$ act $-24.8 + [16.2 \times (pH-7.40)]$ (this results in an SBE value that is close to the value provided by the blood gas analyzer, i.e. −6.73); i.e. it is calculated on the basis of the difference between the actual bicarbonate concentration and its normal level and the approximate value of the concentration of non-bicarbonate buffers in the extracellular space (16.2 mEq/l). If we assume that the effect of excess lactate anions on *bicarbonate reduction* (and hence on the *change in SBE*) is equal to the ratio 0.6:1 (as in footnote 'e'), then the *corresponding changein SBE* (which, at least partially, accounts for the total SBE_{UA}) is $0.6 \times 11.3 = -6.78$ *mEq*/l (i.e. an absolute value that is clearly greater than the previously calculated SBE_{UA}).This means that the previously calculated SBE_{UA} should contain both the negative charges due to the increase in [Lac^-] and a certain amount of positive charges due to unknown cations in order to obtain the observed lower value for SBE_{UA} compared to the expected value. If part of the increase in [Cl^-] compensates for this amount of unknown, positively charged ions, the remaining effect of [Cl^-] on the formation of SBE (SBE_{Cl}) is −2.316 mEq/l; this is approximately equal to the sum of SBE_{FW} + SBE_{Alb} (+2.898 mEq/L) and can also beconsidered as compensation for their alkaline effect. Thus, the increase in [Cl^-] (assuming that it actually compensates for the alkaline disturbances, i.e., positive charge excesses) is not really involved in the acidosis, i.e. in our case a pure [X^-] increase acidosis is present. On the other hand, if the ratio between the decrease in bicarbonate (and SBE) and the increase in lactate is 1:1, then the SBE_{UC}=8.68 mEq/l; moreover, the increase in [Cl^-] falls behind the increase in [X^-] and we have an additional (i.e. above the SBE_{Cl}) SBE_{UC} of + 2.2 mEq/l (there is an imposed metabolic alkalosis). The conclusions compared to footnote 'e' are therefore similar.

drawn from the change in SBE and the associated calculations) can also be considered as independent metabolic disturbances that have a cumulative effect on SBE, i.e. the increase in [Cl^-] can be considered as corresponding to hyperchloremic acidosis and not as compensation for a primary increase in positive charges and their alkalizing effect; this is a matter of interpretation. However, even if the cumulative effect on SBE is small, the correct diagnosis of the causes of metabolic acid–base disturbances is crucial.

In summary, the three methods used cannot accurately detect metabolic acidosis due to unknown anions (i.e. due to the increase in lactate) when an increase in positive charges in plasma occurs together with hyperchloremia. After all calculations have been done we know that we should go back to the clinical information to come to a final acid–base diagnosis.

Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Use of Large Language Models, AI and Machine Learning Tools: None declared.
Conflict of interest: None declared.
Research funding: No funding.
Data availability: Not applicable.

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