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Clinical Investigation

CLINICAL PRACTICE

Improving interpretation of metabolic acid–base disorders by correcting pH-dependent bias in base excess partitioning

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Abstract

Background: Base excess (BE) partitioning is an established tool for bedside interpretation of metabolic acid–base disorders. However, this method assumes that changes in plasma strong ion difference, estimated as $[Na^+]-[Cl^-]$, directly relate to changes in standard BE. This assumption holds in isolated plasma but fails *in vivo*, where pH-dependent redistribution between body compartments alters plasma strong ion difference without producing an equivalent change in standard BE. We hypothesised that this introduces a clinically relevant pH-dependent bias into BE partitioning and that adjusting the $[Na^+]-[Cl^-]$ reference value for pH would correct it.

Methods: Unmeasured ions were quantified using conventional BE partitioning and a novel pH-corrected version, in which the $[Na^+]-[Cl^-]$ reference was adjusted by $+1.5$ mEq L^{-1} for every -0.1 change in pH. Agreement with strong ion gap was assessed in 5976 ICU patients from AmsterdamUMCdb using Bland–Altman analyses (including pH-stratified subgroups) and linear regression to quantify the independent effect of pH.

Results: The conventional method demonstrated wide limits of agreement (-5.6 to 2.9 mEq L^{-1}) and a strong confounding effect of pH (1.45 mEq L^{-1} per 0.1 pH unit). The pH-corrected algorithm markedly improved agreement with the strong ion gap (limits of agreement -4.4 to 0.4 mEq L^{-1}) and substantially reduced the confounding effect of pH (0.15 mEq L^{-1} per 0.1 pH unit).

Conclusions: Conventional base excess partitioning is subject to a clinically relevant pH-dependent error. A variable, pH-adjusted $[Na^+]-[Cl^-]$ reference value eliminates this error and provides a more reliable assessment of metabolic acid–base disturbances, especially in patients with severe acidaemia or alkalaemia.

Keywords: acid–base imbalance; base excess; critical care; diagnostic techniques and procedures; hydrogen ion concentration; ions

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Editor's key points

- Conventional base excess (BE) partitioning is pH-dependent and could introduce clinically relevant inaccuracies in assessment of metabolic acid–base disturbances.
- In 5976 ICU patients, the conventional method showed wide disagreement with strong ion gap and a major confounding effect of pH (1.45 mEq/L per 0.1 pH unit).
- A pH-adjusted $[Na^+]-[Cl^-]$ reference markedly improved agreement with strong anion gap, providing more reliable assessment especially among patients with abnormal pH.

Analysis of acid–base status is a cornerstone of intensive care and is becoming increasingly important across other medical fields. In the 1980s, the traditional bicarbonate-based approaches of the Copenhagen and Boston schools were joined by Stewart's physicochemical concept.[1] A milestone that facilitated the broader application of physicochemical principles was publication of detailed equations characterising albumin dissociation.[2,3] This enabled development of a precise tool for detecting unmeasured ions (UI), later popularised as the strong ion gap (SIG),[4] and laid the groundwork for Stewart-inspired systematic approaches to the diagnosis of acid–base disturbances.[5,6] In these models, metabolic disorders are classified as alterations in the strong ion difference (SID) or the content of weak non-volatile acids (albumin and phosphate); variations in SID can be further divided into water excess/deficit, relative chloride excess/deficit, and presence of UI. Gradually, these considerations are being integrated into modern diagnostic algorithms.[7–9]

A popular algorithm benefiting from the physicochemical insight is base excess (BE) partitioning, originally developed by Gilfix and colleagues[6] and later simplified by Story and colleagues[10] for bedside use through mental arithmetic. Story's[11] method uses the standard BE (SBE) as an indicator of the overall metabolic acid–base status and evaluates whether it can be fully explained by measured strong ions (sodium, chloride, and lactate) and albumin. If not, a BE gap is detected, indicating the accumulation of UI (Table 1, column A).

While simple and informative, BE partitioning has been criticised for a major conceptual flaw: it applies Stewart's concept of plasma SID (in its simplified form of the $[Na^+]-[Cl^-]$ difference) as an independent determinant of acid–base status, despite this holding true only in isolated plasma and not in multicompartment systems such as whole blood and *in vivo*.[12,13] In these settings, strong ions redistribute across compartments, leading to changes in plasma SID and $[Na^+]-[Cl^-]$ difference that are not accompanied by equivalent changes in blood BE or SBE.[14,15] For example, plasma SID changes during acute respiratory disorders *in vivo* (Fig. 1),[13,14,16] while SBE is designed to remain stable. In metabolic disorders such as hyperchloraemic acidosis, both SBE and plasma SID change concordantly, but electrolyte redistribution causes ΔSBE to progressively diverge from ΔSID.[14] Consequently, any algorithm that assumes every alteration in plasma SID is accompanied by an equal change in SBE may lead to diagnostic error. Our recent work in isolated whole blood showed that the redistribution of electrolytes is predictable and pH-dependent, allowing true SID-driven acid–base disturbances to be identified using a pH-dependent plasma SID reference[17].

Building on these observations, the current study aims to introduce a *pH-corrected* BE partitioning into clinical practice and to validate this approach using a large retrospective dataset. We hypothesised that (1) a pH-dependent bias would arise during application of the conventional BE partitioning method *in vivo*, (2) its magnitude would be sufficient to impair acid–base interpretation across clinically relevant pH ranges, and (3) the pH-corrected modification would eliminate this bias, thereby enabling a more accurate assessment of metabolic acid–base disturbances *in vivo*.

Methods

Development of the pH-corrected base excess partitioning algorithm

The pH-corrected BE partitioning algorithm was derived from the conventional algorithm by Story,[11] which uses a fixed $[Na^+]-[Cl^-]$ reference value of 35 mEq L^{-1} (Table 1, column A).

The novel pH-corrected variant of BE partitioning was constructed by adjusting the $[Na^+]-[Cl^-]$ reference value for pH. This modification was informed by our previous findings in isolated whole blood, which demonstrated that the change in plasma SID attributable to electrolyte redistribution is equal to the product of the non-carbonic buffer power of whole blood (β_{WB}) and the deviation of pH from 7.4 (ΔpH).[17] Translating this principle to *in vivo* conditions, we set the expected $[Na^+]-[Cl^-]$ reference value to vary with the product of non-carbonic buffer power of extracellular fluid (β_{ECF}=16.2 mmol L^{-1})[18] and ΔpH (Table 1, column B).

To enable practical bedside use, we also derived and assessed a bedside-friendly version of the algorithm with rounded coefficients (Table 1, column C).

Evaluation of the base excess partitioning algorithms

We used data from AmsterdamUMCdb, a publicly available database containing 23 106 ICU admissions to Amsterdam University Medical Centres between 2003 and 2016.[19] Ethical approval and patient consent were not required because the data are fully de-identified. All eligible admissions were included; no formal sample size calculation was performed.

The three BE partitioning algorithms were evaluated according to their ability to quantify UI. This is done in the final step of each algorithm (Table 1) and therefore reflects their overall performance. SIG, an established measure of UI in both experimental and clinical settings,[20–27] was used as the reference standard.

Data extraction and processing

The following routinely collected laboratory values were extracted using Structured Query Language (SQL) queries (Supplementary file 1): pH, P_{CO_2}, $[Na^+]$, $[K^+]$, $[Cl^-]$, $[Ca^{2+}{}_i]$, $[Lac^-]$, total $[Mg^{2+}]$, phosphate, and albumin. Ion concentrations measured by the blood gas analyser, (i.e. using direct ion-selective electrodes), were used where possible ($[Na^+]$, $[K^+]$, $[Cl^-]$, $[Ca^{2+}{}_i]$, and $[Lac^-]$). Total $[Mg^{2+}]$, phosphate, and albumin were measured in the central laboratory.

Using a Python script (Supplementary file 2), each extracted pH value was aggregated with the nearest available laboratory

Table 1 The BE partitioning algorithm by Story[11] (A) and the proposed pH-corrected variants with exact (B) and rounded (C) coefficients. Albumin (Alb) concentration is in g L^{-1}, all other concentrations are in mmol L^{-1}. BE, base excess; BE_{UI}, BE effects of unmeasured ions; SBE, standard base excess; SIG, strong ion gap.

	A algorithm by Story[11] (uncorrected)	B pH-corrected algorithm, exact coefficients	C pH-corrected algorithm, rounded coefficients
Effect of strong ions	$BE_{SID}=[Na^+]-[Cl^-]-ref$	$BE_{SID}=[Na^+]-[Cl^-]-ref$	$BE_{SID}=[Na^+]-[Cl^-]-ref$
$[Na^+]-[Cl^-]$ reference value	ref=35	ref=35+16.2×(7.4−pH)	ref=35+15×(7.4−pH)
Effect of lactate	$BE_{Lac}=1-[Lac^-]$	$BE_{Lac}=1-[Lac^-]$	$BE_{Lac}=1-[Lac^-]$
Effect of albumin	$BE_{Alb}=0.25\times(42-Alb)$	$BE_{Alb}=0.25\times(42-Alb)$	$BE_{Alb}=0.3\times(40-Alb)$
BE gap	$BE_{UI}=SBE-BE_{SID}-BE_{Lac}-BE_{Alb}$		

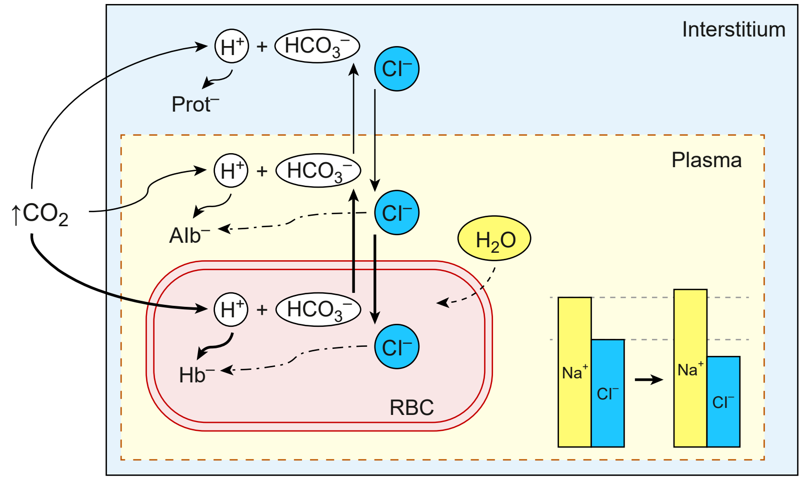


Fig 1. Schematic representation of three mechanisms altering plasma ion concentrations during respiratory acidosis. First, in all compartments, CO_2 hydration generates bicarbonate and protons, most of which are rapidly buffered by non-carbonic buffers [haemoglobin (Hb^-), albumin (Alb^-), and interstitial proteins ($Prot^-$)]. Bicarbonate production is most pronounced inside red blood cells (RBCs) as a result of the high buffering capacity of haemoglobin. This drives bicarbonate–chloride exchange and lowers extracellular chloride (solid arrows). Second, the formation of bicarbonate adds new osmotically active particles, raising osmolarity in all compartments, but most prominently in RBCs. This draws water from plasma and thereby increases plasma sodium (dashed arrow). Third, protonation of haemoglobin and albumin reduces their negative charge and enhances chloride binding (dash-dotted arrows). None of these processes alters standard base excess (SBE).

measurements within predefined time windows of plus or minus 1 h for $[Na^+]$, $[K^+]$, $[Cl^-]$, $[Ca^{2+}{}_i]$, $[Lac^-]$, and pCO_2; plus or minus 2 h for total $[Mg^{2+}]$ and phosphate; and plus or minus 4 h for albumin. Records lacking valid measurement timestamps or containing values clearly outside reasonable ranges (indicative of data entry errors) were excluded. Only the earliest record for each patient within the first 24 h of admission was retained for analysis.

Calculations

Actual bicarbonate concentration $[HCO_3^-]$ and SBE were calculated from P_{CO_2} (in kPa) and pH as[18]:

$$[HCO_3^-] = 0.23 \times pCO_2 \times 10^{pH-6.095} \tag{1}$$

$$SBE = [HCO_3^-] - 24.8 + 16.2 \times (pH - 7.4) \tag{2}$$

The BE effects of UI (BE_{UI}) derived by the uncorrected and the two pH-corrected BE partitioning algorithms were calculated using the equations specified in Table 1. SIG was calculated with the equation proposed by Kellum and colleagues,[4] excluding urate because of its negligible contribution and to avoid reducing the sample size as a result of missing values:

$$\begin{aligned} SIG = & \left([Na^+] + [K^+] + 2 \times \left[Ca^{2+}\right] + 2 \times \left[Mg^{2+}\right] - [Cl^-] \right. \\ & \left. - [Lac^-]\right) - [HCO_3^-] - Alb \times (0.123 \times pH - 0.631) \\ & - Pi \times (0.309 \times pH - 0.469) \end{aligned} \tag{3}$$

To enable statistical comparison of conceptually different methods, the midpoint of the typical reference range (2 mEq L^{-1})[24,28,29] was subtracted from SIG as only UI values exceeding physiological levels are relevant in acid–base diagnostics. For the same reason, BE_{UI} values were multiplied by -1 to align their directionality with SIG, as negatively charged UI increase SIG but decrease BE_{UI}. Similar normalisation strategies have been applied previously.[12,30]

Statistical analysis

Agreement between SIG and BE_{UI} was assessed primarily using Bland–Altman analyses.[31] For each of the three evaluated methods, we calculated the mean difference (mean bias), standard deviation of the differences (SD), limits of agreement (LoA=mean bias [1.96 SD]), and the slope of the regression line of differences *vs* averages (proportional bias).

The hypothesised confounding effect of pH on diagnostic performance was evaluated using three complementary approaches. First, Bland–Altman analyses were stratified by pH (near-normal: 7.3–7.5 *vs* abnormal: <7.3 or >7.5). Second, we performed linear regression of differences against pH. Third, univariate and multivariable linear regression analyses were conducted, with BE_{UI} as the primary predictor of SIG and pH added as a covariate to quantify its independent effect.

Reporting compliance

We applied Standards for Reporting Diagnostic Accuracy (STARD) guidelines for reporting diagnostic accuracy studies[32] where appropriate and supplemented them with Guidelines for Reporting Reliability and Agreement Studies (GRRAS) recommendations for reporting agreement and reliability.[33] To ensure full reproducibility of our analyses, we provide the data extraction and handling scripts in Supplementary files.

Results

A total of 684 801 unique pH measurements were extracted from AmsterdamUMCdb. After aggregation with other relevant variables within the predefined time windows, 5976 complete records remained (Supplementary file 3). Demographic, clinical, and laboratory characteristics of the analysed cohort are presented in Table 2.

Bland–Altman analyses demonstrated substantial differences in performance between the three evaluated variants of BE partitioning (Fig. 2). The uncorrected algorithm showed a mean bias of -1.4 mEq L^{-1} with SD of 2.2 mEq L^{-1} (LoA -5.6 to 2.9 mEq L^{-1}). In contrast, the pH-corrected algorithm with exact coefficients demonstrated improved precision, with a mean bias of -2.3 mEq L^{-1} and a substantially smaller SD of 1.2 mEq L^{-1} (LoA -4.7 to 0.0 mEq L^{-1}). The bedside-friendly rounded-coefficient version showed similar performance: a mean bias of -2.0 mEq L^{-1} and SD of 1.3 mEq L^{-1} (LoA -4.4 to 0.4 mEq L^{-1}).

Stratified Bland–Altman analyses (Fig. 3) demonstrated that all three algorithms performed similarly within the near-normal pH range (7.3–7.5), with comparable mean bias (-2.4 to -2.1 mEq L^{-1}) and SD (1.1–1.3 mEq L^{-1}). In contrast, substantial divergence emerged in patients with abnormal pH (<7.3 or >7.5): the uncorrected method showed markedly reduced precision (SD 2.5 mEq L^{-1}), whereas the pH-corrected variants maintained performance similar to that observed in near-normal pH range (SD 1.3 and 1.4 mEq L^{-1}).

Multivariable linear regression confirmed a strong independent effect of pH on the relationship between the uncorrected BE partitioning and SIG, quantified as 1.45 mEq L^{-1} per 0.1 pH unit. By contrast, this effect was markedly attenuated in the pH-corrected algorithms with exact and rounded coefficients (0.03 and 0.15 mEq L^{-1} per 0.1 pH unit, respectively). Detailed statistical results are presented in Supplementary file 4.

Table 2 Demographic, clinical, and baseline laboratory characteristics of the study cohort. Data are presented as *n* (%) or median (25–75th percentile). SBE, standard base excess.

n		5976
Sex	*n* (%)	
- Male		1991 (33.3)
- Female		3983 (66.6)
- Unknown		2 (0.0)
Age	yr	65 (55–75)
Height	cm	175 (165–185)
Weight	kg	75 (65–95)
Body mass index	kg m^{-2}	24.8 (23.8–27.8)
ICU admission specialty	*n* (%)	
- Cardiac surgery		1893 (31.7)
- Cardiology		563 (9.4)
- Internal medicine		474 (7.9)
- Abdominal surgery		470 (7.9)
- Neurosurgery		419 (7.0)
- Traumatology		367 (6.1)
- Vascular surgery		290 (4.9)
- Neurology		266 (4.5)
- Pulmonology		215 (3.6)
- Adult intensive care		158 (2.6)
- Nephrology		117 (2.0)
- Other		648 (11.4)
- Unknown		60 (1.0)
ICU mortality	*n* (%)	789 (13.2)
pH		7.4 (7.3–7.4)
P_{CO_2}	kPa	5.3 (4.8–6.0)
SBE	mEq L^{-1}	-2.5 (-5.6 to -0.5)
$[Na^+]$	mmol L^{-1}	138 (136–140)
$[K^+]$	mmol L^{-1}	4.2 (3.8–4.6)
$[Cl^-]$	mmol L^{-1}	107 (103–110)
$[HCO_3^-]$	mmol L^{-1}	22.8 (20.4–24.7)
$[Lac^-]$	mmol L^{-1}	1.6 (1.1–2.6)
$[Ca^{2+}{}_i]$	mmol L^{-1}	1.1 (1.1–1.2)
[total Mg^{2+}]	mmol L^{-1}	0.8 (0.7–1.0)
Albumin	g L^{-1}	25 (21–29)
Phosphate	mmol L^{-1}	1.1 (0.8–1.4)

Discussion

We investigated whether the conventional BE partitioning method, which uses a fixed $[Na^+]-[Cl^-]$ reference, is systematically biased by pH-dependent electrolyte redistribution, a limitation inherent in applying plasma-based principles to multicompartment physiology. Our analyses confirmed that such a bias exists *in vivo*, increases progressively with deviation from normal pH, and is clinically relevant in severe acid–base disturbances. For example, at a pH of 7.0, base excess effects of SID (BE_{SID}) and therefore the BE_{UI} estimated by the uncorrected and pH-corrected algorithms differ by ~6 mEq L^{-1}, as demonstrated in a real case from the analysed cohort (Fig. 4).

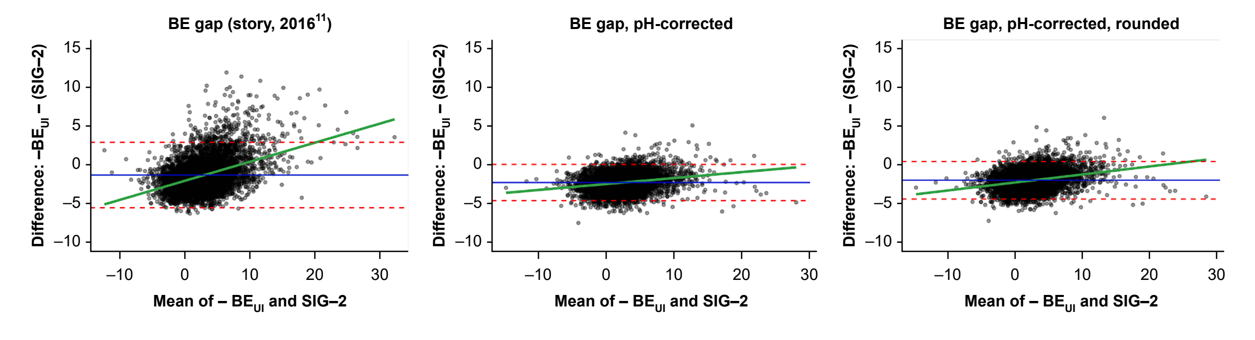


Fig 2. Bland–Altman plots visualising the agreement between SIG and the three evaluated BE partitioning algorithms. Solid blue lines indicate the mean bias, red dashed lines represent the limits of agreement, and solid green lines depict the regression line assessing proportional bias. BE, base excess; BE$_{UI}$, BE effects of unmeasured ions; SIG, strong ion gap.

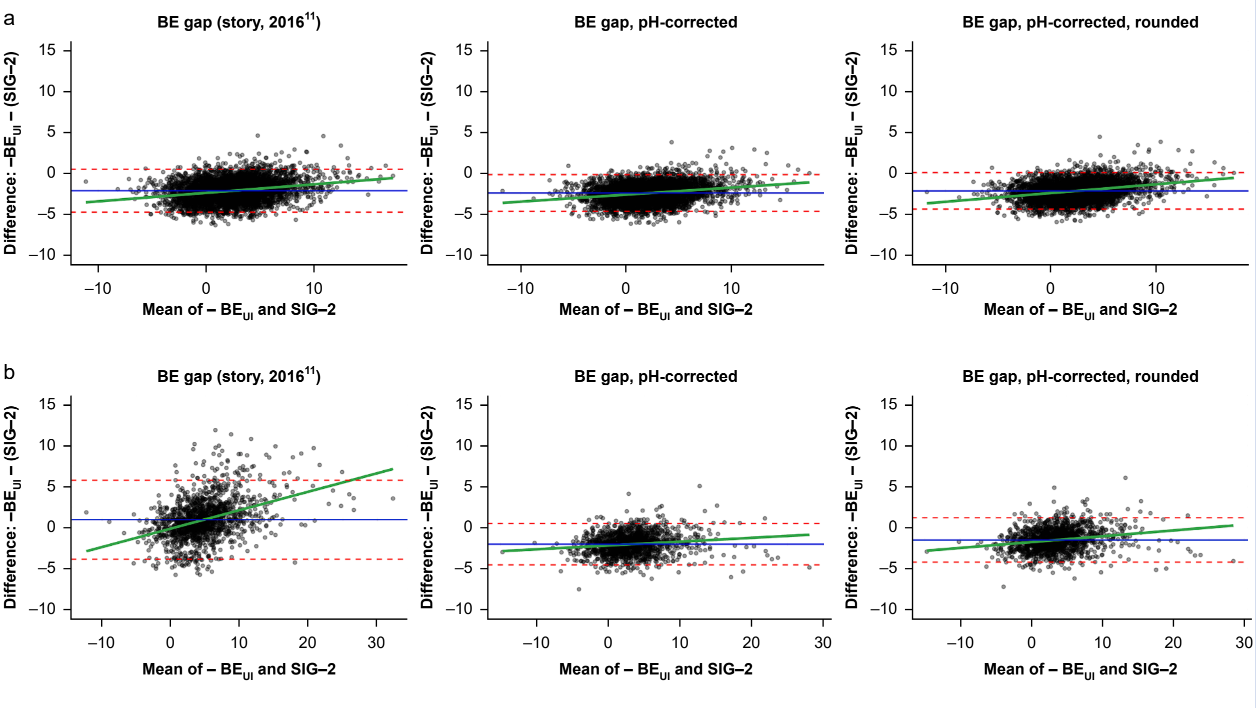
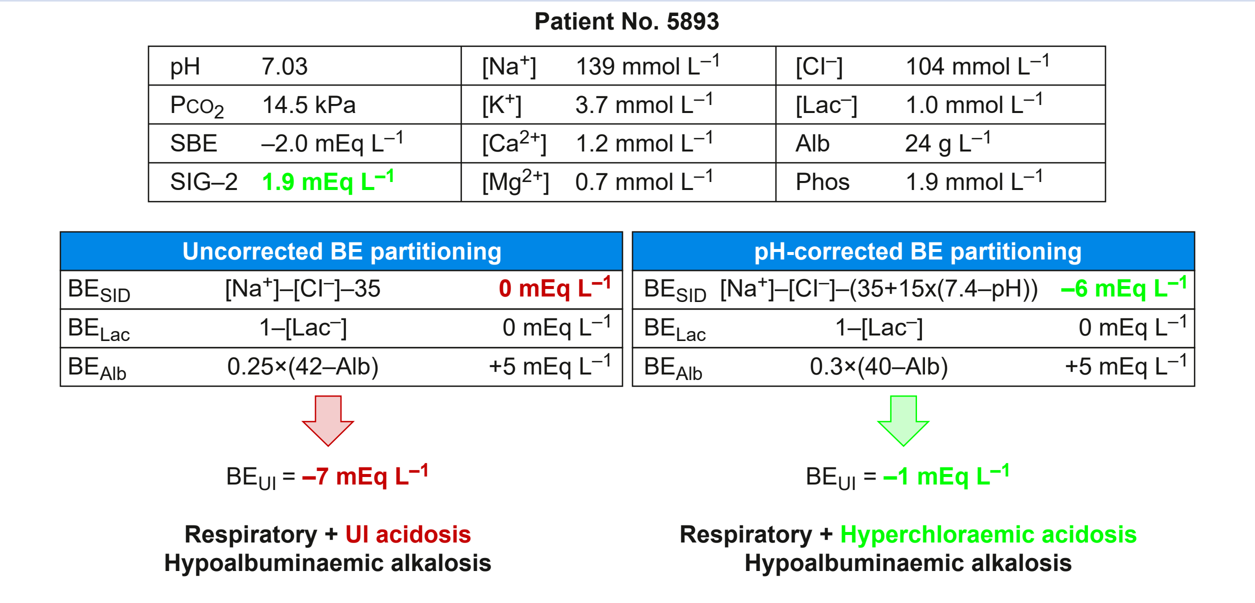


Fig 3. Bland–Altman plots demonstrating agreement between SIG and the three evaluated BE partitioning algorithms in patient subgroups stratified by pH. (a) Near-normal pH (7.3–7.5). (b) Abnormal pH (<7.3 or >7.5). Solid blue lines indicate the mean bias, red dashed lines represent the limits of agreement, and solid green lines depict the regression line assessing proportional bias. BE, base excess; BE$_{UI}$, BE effects of unmeasured ions; SIG, strong ion gap.

Relation to previous studies

Our findings in the unstratified population align with prior studies that evaluated the precision of uncorrected BE partitioning *in vivo*. Specifically, a bias of 1.8 mEq L^{-1} and LoA of −0.9 to 4.4 mEq L^{-1} were reported for the agreement between BE$_{UI}$ and SIG in 135 cardiac surgery patients.[12] Note that this study used the opposite sign convention, so their negative values correspond to positive values in our analysis. In another study, SBE partitioning demonstrated only moderate accuracy in detecting UI in 15 patients during acute haemodilution on cardiopulmonary bypass.[27]

The uncorrected BE partitioning algorithm by Gilfix was reported to accurately reflect SIG in a mixed cohort of 21 patients from medical and surgical ICU and emergency room.[6] However, most of the measurements were obtained within the near-normal pH range, and the analysis was performed using linear regression, a method known to overestimate agreement when compared with Bland–Altman analysis.[30,31] Gilfix's BE partitioning algorithm was also tested against SIG in 300 patients recruited from the general ICU population, demonstrating a bias of 3.5 mEq L^{-1} and wide LoA of −1.6 to 8.5 mEq L^{-1}.[30]



Patient No. 5893

pH	7.03	$[Na^+]$	139 mmol L^{-1}	$[Cl^-]$	104 mmol L^{-1}
P_{CO_2}	14.5 kPa	$[K^+]$	3.7 mmol L^{-1}	$[Lac^-]$	1.0 mmol L^{-1}
SBE	–2.0 mEq L^{-1}	$[Ca^{2+}]$	1.2 mmol L^{-1}	Alb	24 g L^{-1}
SIG–2	**1.9 mEq L^{-1}**	$[Mg^{2+}]$	0.7 mmol L^{-1}	Phos	1.9 mmol L^{-1}

Uncorrected BE partitioning		
BE_{SID}	$[Na^+]–[Cl^-]–35$	**0 mEq L^{-1}**
BE_{Lac}	$1–[Lac^-]$	0 mEq L^{-1}
BE_{Alb}	0.25×(42–Alb)	+5 mEq L^{-1}

BE_{UI} = **–7 mEq L^{-1}**

Respiratory + UI acidosis
Hypoalbuminaemic alkalosis

pH-corrected BE partitioning		
BE_{SID}	$[Na^+]–[Cl^-]–(35+15x(7.4–pH))$	**–6 mEq L^{-1}**
BE_{Lac}	$1–[Lac^-]$	0 mEq L^{-1}
BE_{Alb}	0.3×(40–Alb)	+5 mEq L^{-1}

BE_{UI} = **–1 mEq L^{-1}**

Respiratory + Hyperchloraemic acidosis
Hypoalbuminaemic alkalosis

Fig 4. Example case demonstrating the effect of pH correction on BE partitioning in severe acidaemia. The uncorrected method fails to detect acidosis attributable to relative hyperchloraemia (BE_{SID}) and incorrectly indicates the presence of unmeasured ions (BE_{UI}). In contrast, the pH-corrected approach remains robust under this extreme pH deviation and correctly reports only an insignificant accumulation of unmeasured ions, consistent with an increase in SIG of 1.9 mEq L^{-1} above the 2 mEq L^{-1} reference value. BE, base excess; BE_{ALB}; base excess effects of albumin; BE_{LAC}; base excess effects of lactat; BE_{SID}; base excess effects of SID; BE_{UI}, BE effects of unmeasured ions; SBE, standard base excess; SIG, strong ion gap.

Sources of error in base excess partitioning

The mean bias across the three evaluated BE partitioning methods was approximately −2 mEq L^{-1}. This error is correctable by adjusting the value 35 (see Table 1) accordingly and indicates that acid–base calculations benefit from local calibration with the specific equipment in use.

The low precision (high SD and wide LoA) observed in the uncorrected BE partitioning method was driven by patients with abnormal pH. Adjusting the $[Na^+]–[Cl^-]$ reference value for pH effectively eliminated this error. Both the exact and rounded-coefficient versions of the pH-corrected algorithm demonstrated substantially improved agreement with SIG across the full pH range, reducing the SD and narrowing the LoA by ~45% compared with the uncorrected method.

The imprecision that remained after the pH correction reflected the fact that BE partitioning deliberately disregards minor strong cations (K^+, Ca^{2+}, and Mg^{2+}) and phosphate. In individual cases, this may introduce a clinically relevant error. For example, in a patient with a $[K^+]$ of 8 mmol L^{-1}, the $[Na^+]–[Cl^-]$ difference underestimates the true BE_{SID} by ~4 mEq L^{-1}, which has led some authors to include $[K^+]$ in the estimation of BE_{SID}.[34] Elevated phosphate is typically considered in the differential diagnosis of UI.[6,10,11,34] Alternatively, if phosphate concentration is known, its contribution can be calculated analogously to base excess effects of lactate (BE_{Lac}) and base excess effects of albumin (BEAlb) (Table 1) as 2×(1−phosphate), where the factor of 2 approximates the 1.82 mEq $mmol^{-1}$ of charge contributed by phosphate at pH 7.4 and 1 mmol L^{-1} represents its reference concentration.

The proportional bias seen with the uncorrected BE partitioning algorithm also appeared to be driven by pH. This interpretation was supported by the marked reduction in proportional bias after application of the pH correction, both in the overall Bland–Altman analysis (Fig. 2) and in the subgroup with abnormal pH (Fig. 3). Importantly, the proportional bias that persists after correction appears unrelated to pH, as demonstrated by the regression of differences *vs* pH presented in Supplementary file 4.

The value of the pH correction factor

Electrolyte and water shifts are governed by multiple processes (e.g. the Hamburger effect and the accompanying osmotically driven water transfers,[35] the Donnan effect, and ion–protein binding[36]), making a full analytical description infeasible. The correction factors we applied and tested in this study (1.62 and 1.5 mEq L^{-1} per 0.1 pH unit) had therefore been derived from the agreement between β_{WB} and redistribution of strong ions observed in whole blood *in vitro*,[17] and extrapolated to β_{ECF} and extracellular fluid *in vivo*. The applicability of the correction coefficients was supported by two findings: first, the pH-corrected BE partitioning algorithm achieved similar precision in patients with near-normal and abnormal pH (Fig. 3); and second, the coefficients were closely matched by the regression coefficient for pH from the multivariable linear regression analysis of the uncorrected BE partitioning method (1.45 mEq L^{-1} per 0.1 pH unit).

Of note, the value of β_{ECF} has been challenged.[37] However, β_{ECF} not only reflects the rate of strong ion redistribution *in vivo* but is also an integral part of SBE calculation. If the value of β_{ECF} were to be revised in the future, the correction factor for the $[Na^+]–[Cl^-]$ reference would need to be adjusted accordingly, but the general principle of pH-corrected BE partitioning would remain valid.

Clinical implications

Finding the optimal balance between simplicity and accuracy in acid–base evaluation algorithms is a subjective matter and depends on the clinical context. Our data show that no correction is needed at near-normal pH levels. By contrast, it is advisable to consider applying the pH correction at moderate and severe pH deviations. A practical rule of thumb is that for every 0.2 change in pH, the reference $[Na^+]-[Cl^-]$ value should be adjusted by 3 mEq L^{-1} in the opposite direction.

We recognise that many clinicians may prefer to retain the simple, uncorrected BE partitioning approach. In such cases, our results highlight the limitations of this method at extreme pH values and the potential for misclassification of metabolic disturbances. Outside the context of BE partitioning, our findings are relevant to clinicians who use plasma SID (or its surrogate $[Na^+]-[Cl^-]$) to guide therapeutic decisions such as fluid selection, demonstrating that *in vivo* some degree of SID alteration accompanies every deviation of pH and represents a predictable passive response of the multicompartment system rather than renal compensation or a standalone metabolic disorder.

Strengths and limitations

A major strength of this study is the use of a large, real-world dataset comprising nearly 6000 patients from a diverse and unselected ICU population. Moreover, the proposed correction factor for $[Na^+]-[Cl^-]$ reference value is grounded in both physiological principles and the presented data.

This study also has several limitations. The retrospective design limits control over confounding factors, and external generalisability is restricted because the results are derived from a single open-access database from one country. Only about one-quarter of admitted patients had a complete set of necessary parameters within the first 24 h, possibly reflecting clinicians' selective ordering of tests when UI were not suspected. A timing mismatch between laboratory variables, although restricted to narrow time windows, may have introduced variability in calculated values. The validity of our findings also depends on the reliability of the reference standard itself. While SIG is the most widely accepted and validated method, it may be outperformed by advanced computer-based multicompartment models.[27] These, however, lack clinical validation and are challenging to implement. Finally, the proposed correction factor requires prospective validation before it can be adopted in clinical practice.

Conclusions

Our findings demonstrate that the conventional BE partitioning method, which uses a fixed $[Na^+]-[Cl^-]$ reference, is affected by a clinically relevant pH-dependent bias. Incorporating a pH-adjusted $[Na^+]-[Cl^-]$ reference value eliminates this bias, producing an algorithm that preserves the conceptual logic of BE partitioning but remains accurate across the full pH range. More broadly, our findings emphasise the importance of accounting for pH-driven electrolyte shifts when applying Stewart's principles *in vivo*.

Authors' contributions

Conceptualisation: MK, LG, FD
Methodology: all authors
Formal analysis: MK, MV, PW
Data curation: MV, PW, MLAH, PWGE
Visualisation: MK, MV, PW, LG
Writing—original draft: MK
Writing—review and editing: all authors
Funding acquisition: MLAH, PWGE, FD

Data availability statement

The AmsterdamUMCdb dataset is available upon request at https://amsterdammedicaldatascience.nl/. SQL queries and Python script used to derive the analysed cohort are provided as supplementary files.

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Declaration of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2026.02.001.

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