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Quantitative relationships among plasma lactate, inorganic phosphorus, albumin, unmeasured anions and the anion gap in lactic acidosis

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ABSTRACT

Background: Quantitative relationships among plasma [Lactate], [Pi], [Albumin], unmeasured anions ([UA]) and the anion gap (AG_K) in lactic acidosis (LA) are not well defined.
Methods: A mathematical model featuring compensatory potassium and chloride shifts and respiratory changes in LA demonstrated: (1) AG_K = [Lactate] + Zp × [Pi] + 2.4 × [Albumin] + constant1 + *e*, where Zp is a function of pH, and *e* reflects unmeasured anions and cations plus pH-related variations. Eq. (1) can be algebraically rearranged to incorporate the albumin-corrected anion gap, cAG_K: (2) cAG_K = [Lactate] + Zp × [Pi] + constant2 + *e*. Eq. (1) was tested against 948 data sets from critically ill patients with [Lactate] 4.0 mEq/L or greater. AG_K and cAG_K were evaluated against 12,341 data sets for their ability to detect [Lactate] > 4.0 mEq/L.
Results: Analysis of Eq. (1) revealed $r^2 = 0.5950$, $p < 0.001$. cAG_k > 15 mEq/L exhibited a sensitivity of 93.0% [95% CI: 91.3–94.5] in detecting [Lactate] > 4.0 mEq/L, whereas AG_K > 15 mEq/L exhibited a sensitivity of only 70.4% [67.5–73.2]. Additionally, [Lactate] > 4.0 mEq/L and cAG_K > 20 mEq/L were each strongly associated with intensive care unit mortality ($\chi^2 > 200$, $p < 0.0001$ for each).
Conclusions: In LA, cAG_K is more sensitive than AG_K in predicting [Lactate] > 4.0 mEq/L.

1. Introduction

The anion gap, $AG_k = [Na^+] + [K^+] - [Cl^-] - [HCO_3^-]$, as described in detail by Emmett and Narins in 1977 [1], is often used as a simple bedside scanning tool to signal the presence of unmeasured anions (UA) [2]. The anion gap can be calculated with (AG_k) or without potassium (AG). The normal ranges for AG_k and AG are highly dependent on the underlying technology for measurement of electrolytes and must be established for each laboratory [3]. For example, Winter et al., using ion-selective electrodes, established a normal range of 3 to 11 mEq/L for AG in one laboratory, but found that the majority of healthy volunteers had an AG of 6 mEq/L or less in two other laboratories [3]. The calculated values of AG_k and AG are also dependent on the exact functionality of the ion-selective electrodes for sodium, potassium and chloride and reflect the precision, specificity and use of these electrodes [4,5]. It is widely recognized that there are many pitfalls in the use of the anion gap in clinical practice [6,7]. As one example, albumin carries a net negative charge and hypoalbuminemia can falsely lower the calculated AG_k and AG [1]. The albumin-corrected anion gap (cAG_k), was introduced by Figge and colleagues in 1998, to correct the anion gap for fluctuations in the albumin concentration [8-10]. However, despite widespread clinical use and recent recommendations on such corrections [11], little is known about the quantitative relationships among plasma [Lactate], inorganic phosphorus concentration ([Pi]), [Albumin], [UA] and AG_k in critically ill patients with lactic acidosis and varying degrees of metabolic and respiratory compensation.

2. Methods

2.1. Overview

To develop theoretical relationships between [Lactate], [Pi], [Albumin], [UA] and AG_k, we employed a mathematical model that describes the acid-base behavior of plasma [12]. Monte-Carlo simulations incorporating varying levels of [Lactate], [Pi], [Albumin], [UA], compensatory potassium shifts from "tissue buffering" [13] and chloride shifts into red blood cells [13], as well as varying levels of compensatory respiratory changes, were modeled in a computer program [described further in the Appendix 1]. Two theoretical relationships were developed for lactic acidosis with varying degrees of compensatory ion shifts and varying

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degrees of respiratory compensation. The first relationship, involving AG_K, [Lactate], [Pi] and [Albumin], was tested using a large, unselected data base of consecutive prospectively collected laboratory measurements in patients admitted to an intensive care unit (ICU) at a major academic center. We identified a subgroup of 948 data sets from critically ill patients with [Lactate] levels of 4.0 mEq/L or greater. The predicted relationship was tested in regression analyses against this subgroup. The second relationship, incorporating the albumin-corrected anion gap, cAG_K, was algebraically derived from the first relationship. We then tested both AG_k and cAG_K against the entire database of 12,341 data sets for their ability to detect [Lactate] > 4.0 mEq/L.

2.2. Institutional review

The study was approved by the Institutional Ethics Committee of Austin Hospital, Heidelberg, Victoria, Australia with waiver of informed consent.

2.3. Study population

The study population consisted of consecutive patients admitted to the ICU of Austin Hospital during five consecutive calendar years (2000–2004). All patients with arterial catheters as part of their ICU care were included in the study. Demographic, clinical, and biochemical data were collected for each patient.

2.4. Blood samples

For each data set, two blood samples were drawn through an arterial catheter. The first sample (3 mL) was collected in a heparinized blood-gas syringe (Rapidlyte; Chiron Diagnostics, East Walpole, MA). This sample was used for measurement of sodium, potassium, chloride, arterial pH, pCO_2, and lactate. The second arterial sample was drawn on a daily basis using a vacuum technique with lithium heparin tubes (Vacuette; Greiner Labortechnik, Kremsmunster, Austria). This sample was used for measurement of inorganic phosphorus and albumin. Hence, in each data set, most analytes were measured contemporaneously, but albumin and phosphorus were measured daily.

2.5. Directly measured quantities

Arterial samples collected in blood-gas syringes were analyzed immediately after collection in a point-of-care blood-gas and electrolyte analyzer (Bayer Diagnostics Rapilab 865; Bayer Australia, Sydney, Australia) at 37 °C. Sodium, potassium, and chloride were measured by the analyzer using ion selective electrodes, as previously described [4], without sample pre-dilution. Lactate was measured using a biosensor responding to changes induced by lactate oxidase.

Inorganic phosphorus and albumin concentrations were analyzed by staff at the hospital central laboratory by means of a Hitachi multichannel biochemical analyzer (Hitachi 747; Hitachi Ltd., North Ryde, New South Wales, Australia). Inorganic phosphorus concentration was measured using a phosphomolybdate complex colorimetric technique. Serum albumin concentration was measured using a colorimetric assay featuring Bromcresol Purple. Samples were processed within 2 h of being drawn and were not stored on ice.

All data were stored in computerized records.

2.6. Derived quantities

The bicarbonate concentration, $[HCO_3^-]$, was calculated from the measured pH and pCO_2 using the Henderson-Hasselbalch equation:

$$pH = 6.1 + \log_{10}([HCO_3^-]/(0.0307 \times pCO_2)) \quad (1)$$

where $[HCO_3^-]$ is in mEq/L and pCO_2 is given in mm Hg.

The anion gap including potassium (AG_K) was calculated as:

$$AG_K = [Na^+] + [K^+] - [Cl^-] - [HCO_3^-] \quad (2)$$

where all quantities are in mEq/L.

The albumin-corrected anion gap including potassium (cAG_K), was calculated using the Figge-Jabor-Kazda-Fencl [8–10] equation:

$$cAG_K = AG_K + \boldsymbol{z} \times (4.4 - [\text{Albumin}]) \quad (3)$$

where [Albumin] is in g/dL, and the normal albumin concentration is considered to be 4.4 g/dL.

In Eq. (3), the parameter, $\boldsymbol{z}$, represents the net negative charge (in mEq/L) contributed by 1 g/dL (or 10 g/L) of albumin (including the charge contributed by bound calcium). In this study we employ a value of 2.4 for $\boldsymbol{z}$, representing the net negative charge contributed by 1 g/dL of albumin at pH 7.40 in the presence of a physiologic concentration of ionized calcium [10]. The net negative charge includes the charge contributed by ionized amino acid side chains in the albumin macromolecule, as well as the charge contributed by albumin-bound calcium ions [10]. The value, 2.4, is confirmed by a regression analysis using the current data set, and is similar to the value of 2.5 previously published by Figge et al. [8], and the value of 2.3 published by Feldman et al. [14].

2.7. Statistical analyses

Sensitivity, specificity and negative predictive value (NPV) were calculated for AG_K and cAG_K with respect to detection of [Lactate] > 4.0 mEq/L. This cutoff value was pre-specified before the analysis of data.

The strength of a linear correlation was assessed with Pearson's product moment, r. The overall criterion for significance was $p < 0.01$. Because six relationships were tested, we used the Bonferroni correction which resulted in a criterion of $p < 0.0017$ for a given relationship.

A receiver operating characteristic curve (ROC curve) was determined for cAG_K with respect to the detection of [Lactate] > 4.0. The area under the ROC curve (AUC) was calculated by numerical integration.

Bayes' theorem was utilized to calculate the odds of a patient having [Lactate] > 4.0 in the setting of a negative test (i.e., an anion gap or corrected anion gap at or below a given threshold value). A quantity called the likelihood ratio associated with a negative test (LR^-) was utilized in this analysis. Bayesian calculation of the post-test odds of [Lactate] > 4.0, given a negative test, was according to:

$$\text{posterior odds} = (LR^-) \times \text{prior odds} \quad (4)$$

where $(LR^-) = (1 - \text{sensitivity}) / \text{specificity}$.

The closer the (LR^-) is to zero, the greater the informational value of a negative test, because a highly informative negative test greatly lowers the posterior odds of [Lactate] > 4.0. If the posterior odds value is converted to a posterior probability of [Lactate] > 4.0 given a negative test, and if the prior probability is taken as the prevalence of the given condition in the sample, then it can be shown algebraically that:

$$\text{posterior probability} = 1 - \text{NPV} \quad (5)$$

2.8. Bootstrapping procedure

The original sample of 12,341 data sets was randomly re-sampled (with replacement) to create a new sample with 12,341 data sets. Hence, any given data set from the original sample might be included once, more than once, or not at all in the new sample. This process was repeated for a total of 1000 iterations. Values for sensitivity, specificity, NPV, and (LR^-) were recalculated each iteration. This process yielded a distribution of 1000 values each for sensitivity, specificity, NPV and

(LR^-) for each threshold level of the anion gap. The 95-percent confidence interval for each statistic was derived from the respective distribution. Bootstrapping was performed in order to estimate 95-percent confidence limits for the detection of [Lactate] > 4.0 mEq/L by AG_K and cAG_K.

2.9. Mortality data

The vital status at the conclusion of each ICU admission was recorded (alive or deceased). [Lactate], AG_K and cAG_K were each tested for an association with in-ICU mortality using the two-tailed Chi-square (χ^2) statistic with 1 degree of freedom. The pre-specified threshold value for [Lactate] was a level > 4.0 mEq/L. Two pre-specified threshold values for AG_K and cAG_K were employed: >15 mEq/L, and >20 mEq/L. The overall criterion for significance was $p < 0.01$. Since there were a total of five comparisons, application of the Bonferroni correction resulted in a criterion of $p < 0.002$ for a given relationship.

Table 1
ICU admission diagnoses/conditions (N = 3201 ICU admissions).

Diagnosis/condition	Number of ICU admissions
Acute myocardial infarction	30
Aortic aneurysm	12
Aspiration pneumonia	47
Asthma	26
Bacterial/viral pneumonia	166
Cardiac arrest	135
Cardiogenic shock	72
Carotid endarterectomy	7
Cholecystitis/cholangitis	22
Coagulopathy/neutropenia	2
Congestive heart failure	38
COPD	60
CABG	16
Craniotomy for neoplasm	11
Diabetic ketoacidosis	26
Dissecting/ruptured aorta	67
Drug overdose	65
Elective AAA	44
GI bleeding	112
GI inflammatory disease	65
GI neoplasm	117
GI perforation/obstruction/rupture	123
Head trauma	56
Hepatic Failure	80
Hip or extremity fracture	36
Hypertension	13
Intracerebral hemorrhage	54
Isolated cervical spine injury	62
Laminectomy/spinal cord surgery	30
Liver transplant	81
Mechanical airway obstruction	3
Metabolic coma	9
Multiple trauma	133
Neurologic infection	21
Neurologic neoplasm	2
Neuromuscular diseases	8
Other cardiovascular diseases	112
Other GI diseases	46
Other hematologic disorders	8
Other metabolic disorders	26
Other neurologic disease	33
Other renal diseases	24
Other respiratory diseases	234
Peripheral vascular disease	58
Pregnancy related disorder	3
Pulmonary embolism	26
Pulmonary edema (non-cardiac)	46
Renal disorders	43
Renal neoplasm	14
Respiratory arrest	49
Respiratory infection	16
Respiratory neoplasm	116
Rhythm disturbance	10
Seizure	37
Sepsis	321
Stroke	33
Subarachnoid hemorrhage	68
Subdural/epidural hematoma	14
Valvular heart surgery	9
Undefined	4
Total	3201

2.10. Mathematical model of plasma acid-base balance

The mathematical model is described in detail in Appendix 1. The first theoretical relationship derived from the model is:

$$AG_K = [\text{Lactate}] + Zp \times [\text{Pi}] + 2.4 \times [\text{Albumin}] + \text{constant1} + e \quad (6)$$

where AG_K and [Lactate] are in mEq/L, [Pi] is in mmol/L, [Albumin] is in g/dL, Zp is a function of pH (see Appendix 1), and e is an error term that reflects unmeasured anions and cations plus pH-related variations.

The relationship in Eq. (6) can be algebraically rearranged to incorporate cAG_K and an adjusted value for the constant:

$$cAG_K = [\text{Lactate}] + Zp \times [\text{Pi}] + \text{constant2} + e \quad (7)$$

If the pH is not known, the default value of 1.85 can be assigned to Zp without introducing significant error.

3. Results

3.1. Data from ICU admissions

A total of 12,341 data sets were collected from 3201 ICU admissions (1935 males, 1266 females) during the study period. Patients ranged in age from 9 to 98 years (mean 61.5 years). The majority of patients were critically ill, and a variety of acute admitting diagnoses were recorded (Table 1).

Table 2 shows reference ranges and the ranges of patient values for pH, pCO_2, electrolytes, albumin, and lactate. The ICU patients displayed a wide variety of critical disturbances in acid-base variables and electrolytes. Disturbances in pH ranged from severe acidemia to severe alkalemia, due to metabolic, respiratory, or mixed derangements. As demonstrated in Table 2, lactate levels ranged up to 24.69 mEq/L. A value of [Lactate] 4.0 mEq/L or greater in patients without diabetic ketoacidosis was demonstrated in 948 data sets (7.7%). Albumin levels ranged from 2 to 55 g/L. Hypoalbuminemia was common in ICU patients, and 10,248 data sets (83%) featured an albumin level of <30 g/L. An albumin level of <20 g/L was demonstrated in 2995 data sets (24%).

3.2. Regression analyses

The subset of 948 data sets in patients without diabetic ketoacidosis featuring [Lactate] of 4.0 mEq/L or greater was selected for testing the proposed relationship in Eq. (6). The regression analysis of AG_k versus the proposed model is shown in Fig. 1 and reveals a strong linear

Table 2
Laboratory measurements (N = 12,341).

Analyte	Reference range	ICU patients
pH	7.35–7.45	6.74–7.75
pCO_2 (mm Hg)	35–45	8–183
$[Na^+]$ (mEq/L)	135–145	102.1–179.2
$[K^+]$ (mEq/L)	3.5–4.5	1.45–15.3
$[Cl^-]$ (mEq/L)	95–106	69–153
$[Ca^{++}]$ (ionized) (mmol/L)	1.12–1.32	0.50–2.26
[Pi] (mmol/L)	0.6–1.4	0.06–6.29
[Albumin] (g/L)	35–45	2–55
[Lactate] (mEq/L)	0.00–2.00	0–24.69

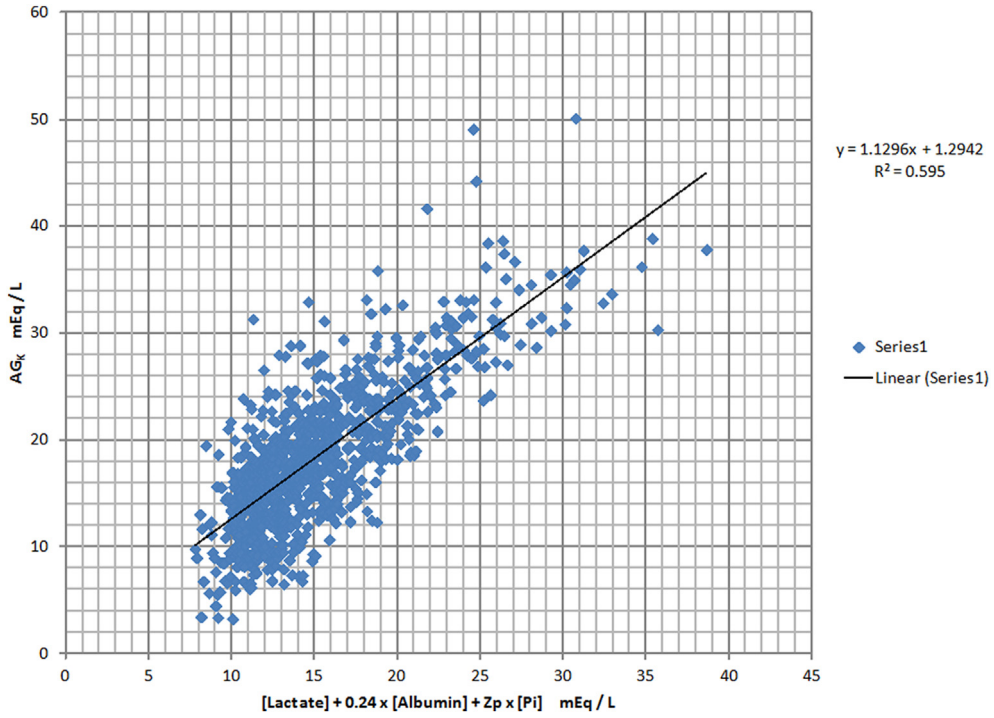

Fig. 1. Regression analysis of AG_K versus the charge contributed by Lactate, Albumin and Pi. The analysis was performed on a subgroup of 948 data sets from critically ill patients with [Lactate] levels of 4.0 mEq/L or greater. The Y-axis is AG_K in mEq/L. The X-axis is [Lactate] + 0.24 × [Albumin] + Zp × [Pi] in mEq/L. The analysis reveals a strong linear correlation with a slope of 1.1 ($r^2 = 0.5950$; $p < 0.001$).

correlation with a slope close to 1.0 ($r^2 = 0.5950$; $p < 0.001$; slope 1.1). Table 3 shows the results of regression analyses against partial versions of the model. For AG_K versus [Lactate], the regression yields: $r^2 = 0.4934$; $p < 0.001$; slope 1.3. When the contribution of albumin is added to lactate, the regression of AG_K versus [Lactate] + 2.4 × [Albumin] yields a stronger correlation and a slope closer to 1.0: $r^2 = 0.5270$; $p < 0.001$; slope 1.2. Likewise, when the contribution of phosphate species is added to lactate, the regression of AG_K versus [Lactate] + Zp × [Pi] also yields a stronger correlation and a slope closer to 1.0: $r^2 = 0.5484$; $p < 0.001$; slope 1.2. As noted, the correlation is strongest and the slope closest to 1.0 when all three components are included in the regression analysis. Hence, the contributions from albumin and from phosphate species each independently improve the linear fit compared to lactate alone.

Moreover, the proposed relationship in Eq. (7) was tested by the regression analysis of cAG_K versus [Lactate] + Zp × [Pi], yielding $r^2 = 0.5842$; $p < 0.001$; slope 1.2 (Table 3).

3.3. Detection of [Lactate] > 4.0 mEq/L

The sensitivity, specificity, negative predictive value and (LR^-) of AG_K and cAG_K were calculated at varying upper normal threshold values with respect to detection of [Lactate] > 4.0 mEq/L (Table 4). The area under the receiver operating characteristic (ROC) curve for cAG_K was 0.84 (Fig. 2). The sensitivity of the albumin-corrected measure, cAG_K, was 93.0% [95% CI: 91.3–94.5] when a threshold of 15 mEq/L was used for cAG_K (this corresponds to a threshold of 11 mEq/L if one uses

Table 3
Regression analyses in data sets without diabetic ketoacidosis demonstrating [Lactate] of 4.0 mEq/L or greater.[a]

Test	Slope	r^2	r	p
AG_K versus				
[Lactate]	1.3479	0.4934	+0.7024	<0.001
[Lactate] + 2.4 × [Albumin]	1.2348	0.5270	+0.7259	<0.001
[Lactate] + Zp × [Pi]	1.1766	0.5484	+0.7405	<0.001
[Lactate] + 2.4 × [Albumin] + Zp × [Pi]	1.1296	0.5950	+0.7714	<0.001
cAG_K versus				
[Lactate]	1.3592	0.5233	+0.7234	<0.001
[Lactate] + Zp × [Pi]	1.1892	0.5842	+0.7643	<0.001

[a] N = 948. The value for p refers to the statistical significance of the linear correlation coefficient, r, with 946 degrees of freedom, using a two-tailed test.

Table 4
Predictive performance of AG_K and cAG_K for detection of [Lactate] > 4.0 mEq/L.[a]

Test	Threshold	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	NPV (%) [95% CI]	(LR^-) [95% CI]
AG_K	$AG_K > 11$	89.9 [87.8–91.7]	50.3 [49.4–51.2]	98.4 [98.0–98.7]	0.200 [0.165–0.241]
	$AG_K > 12$	86.3 [84.2–88.5]	60.2 [59.4–61.1]	98.2 [97.8–98.5]	0.227 [0.191–0.263]
	$AG_K > 13$	82.2 [79.7–84.6]	69.3 [68.4–70.1]	97.9 [97.6–98.2]	0.257 [0.222–0.292]
	$AG_K > 14$	76.1 [73.3–78.6]	76.5 [75.7–77.2]	97.5 [97.1–97.8]	0.312 [0.278–0.348]
	$AG_K > 15$	70.4 [67.5–73.2]	82.6 [81.9–83.3]	97.1 [96.8–97.4]	0.358 [0.325–0.393]
	$AG_K > 16$	64.3 [61.4–67.1]	87.3 [86.8–88.0]	96.7 [96.4–97.1]	0.409 [0.376–0.442]
	$AG_K > 17$	57.1 [54.2–59.9]	90.8 [90.3–91.3]	96.2 [95.9–96.6]	0.473 [0.442–0.505]
cAG_K	$cAG_K > 11$	99.5 [99.0–99.9]	8.9 [8.4–9.4]	99.5 [99.1–99.9]	0.060 [0.012–0.117]
	$cAG_K > 12$	98.5 [97.7–99.2]	14.3 [13.7–14.9]	99.1 [98.7–99.6]	0.104 [0.053–0.158]
	$cAG_K > 13$	97.0 [95.9–98.0]	21.5 [20.8–22.3]	98.9 [98.4–99.2]	0.138 [0.092–0.189]
	cAGK > 14	95.7 [94.3–96.9]	31.3 [30.5–32.2]	98.9 [98.5–99.2]	0.139 [0.099–0.180]
	$cAG_K > 15$	93.0 [91.3–94.5]	42.5 [41.7–43.4]	98.7 [98.3–99.0]	0.165 [0.128–0.205]
	$cAG_K > 16$	89.0 [86.9–90.9]	53.1 [52.1–54.0]	98.3 [98.0–98.6]	0.208 [0.171–0.248]
	$cAG_K > 17$	84.4 [82.1–86.6]	62.9 [62.1–63.8]	98.0 [97.7–98.3]	0.248 [0.212–0.284]

[a] N = 12,341. There were 943 positive observations.

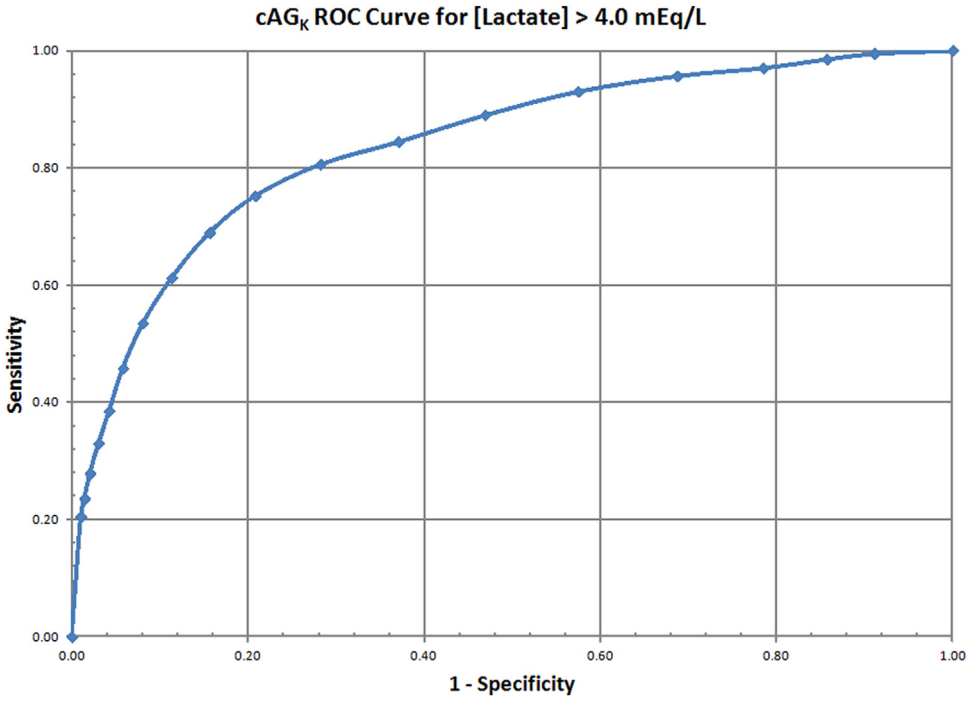

Fig. 2. Receiver operating characteristic (ROC) curve for cAG_K as an indicator of [Lactate] > 4.0 mEq/L. The analysis was performed on the complete group of 12,341 data sets from critically ill patients. The Y-axis is sensitivity. The X-axis is (1 — specificity). The area under the curve as determined by numerical integration is 0.84.

cAG). The corresponding negative predictive value was 98.7% [95% CI: 98.3–99.0]. In contrast, the traditional AG_K had a sensitivity of only 70.4% [95% CI: 67.5–73.2%]. Fig. 3 demonstrates that the albumin correction increases the sensitivity of the anion gap at a given anion gap threshold.

3.4. Bayesian analysis for [Lactate] > 4.0 mEq/L

Fig. 4 demonstrates that the albumin correction decreases the value of (LR^-) approximately 2-fold for any given anion gap threshold. From a power regression model (Fig. 4), the albumin-corrected value of (LR^-)

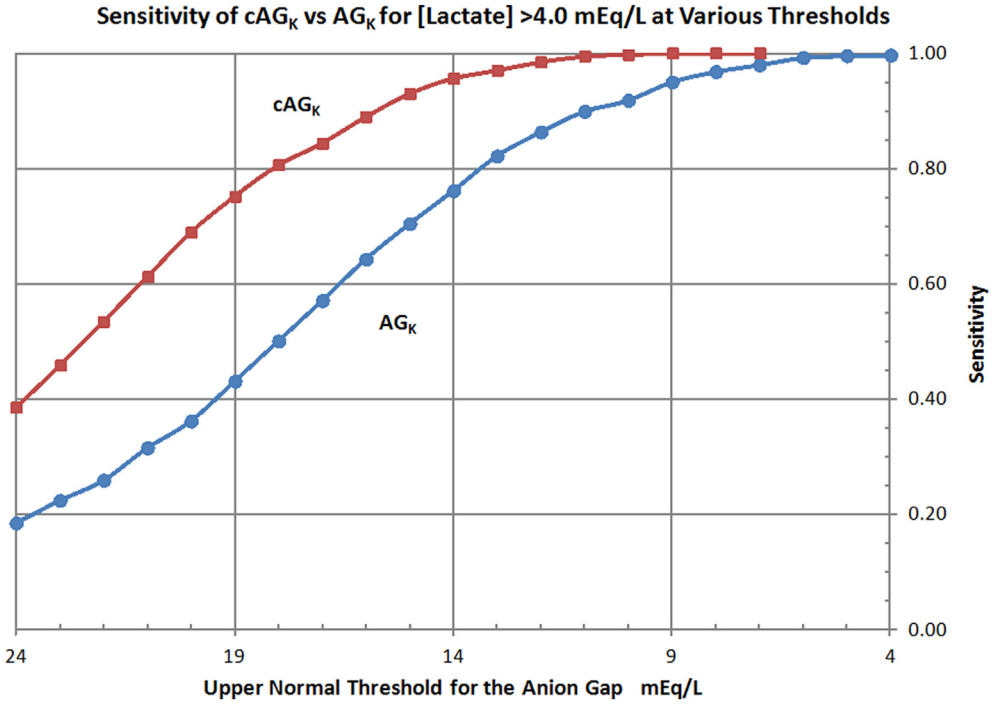

Fig. 3. Sensitivity of cAG_K vs AG_K as an indicator of [Lactate] > 4.0 mEq/L at various upper normal anion gap thresholds. The analysis was performed on the complete group of 12,341 data sets from critically ill patients. The Y-axis is sensitivity. The X-axis is the upper normal threshold in mEq/L for both cAG_K and AG_K. For example, if the upper normal threshold for cAG_K and AG_K is set at 15 mEq/L, then the chart demonstrates that cAG_K (upper curve) has a sensitivity of 93% in detecting [Lactate] > 4.0 mEq/L, whereas AG_K (lower curve) has a sensitivity of only 70.4%. An upper normal threshold of 15 mEq/L for cAG_K and AG_K corresponds to an upper normal threshold of 11 mEq/L for cAG and AG.

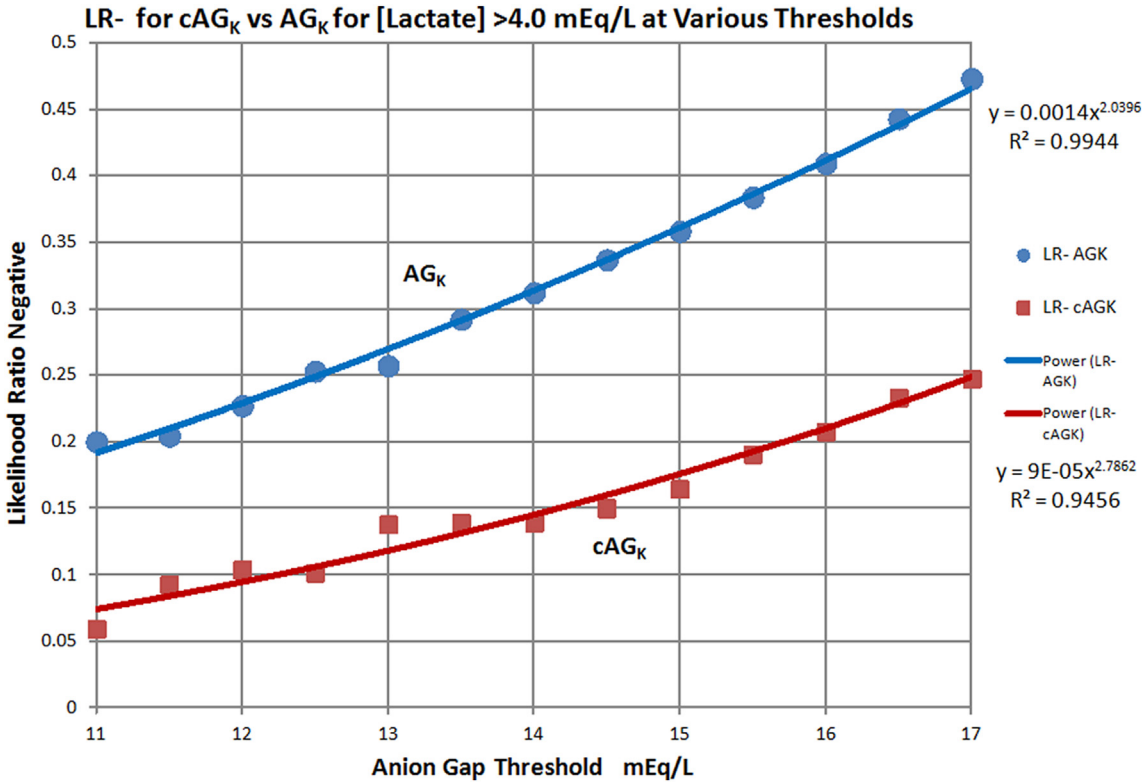

Fig. 4. Likelihood ratio negative (LR^-) as an indicator of [Lactate] > 4.0 mEq/L at various anion gap thresholds. The analysis was performed on the complete group of 12,341 data sets from critically ill patients. The Y-axis is the Likelihood Ratio Negative. The X-axis is the threshold in mEq/L for both cAG_K and AG_K. The smooth curve in each case depicts the best fit to a power function. At any given anion gap threshold value, the value of LR^- can be determined from the chart for either cAG_K or AG_K. The posterior odds of [Lactate] being >4.0 mEq/L is determined by multiplying the prior odds by LR^-. For example, using $cAG_K \leq 13$, the value of LR^- as estimated from the curve is approximately 0.12. If the prior odds of detecting a lactate level of >4.0 mEq/L is 0.083, then the posterior odds is reduced to 0.01.

at any given threshold, X, in the range of 11 through 17 for cAG_K is given as:

$$(LR^-) = (0.000092771)X^{2.7862} \quad (8)$$

For example, a value of $cAG_K \leq 13$ reduced the odds of detecting a lactate level of >4.0 mEq/L from 0.083 pre-test to 0.01 post-test. In terms of probabilities, this is algebraically equivalent to a reduction from 7.6 percent pre-test probability to 1 percent post-test probability.

3.5. Associations with in-ICU mortality

The overall in-ICU mortality among the 3201 ICU admissions was 23.5%. Each of [Lactate] > 4.0 mEq/L, AG_K > 15 mEq/L, AG_K > 20 mEq/L, cAG_K > 15 mEq/L, and cAG_K > 20 mEq/L were positively associated with mortality in the ICU ($p < 0.0001$ for each). The strongest associations were with [Lactate] > 4.0 mEq/L ($\chi^2 = 249.984$, $p < 0.0001$) and cAG_K > 20 mEq/L ($\chi^2 = 218.920$, $p < 0.0001$). For example, a value of cAG_K > 20 mEq/L was associated with an in-ICU mortality of 37%, versus 14% when cAG_K was ≤20 mEq/L. Similarly, a value of [Lactate] > 4.0 mEq/L was associated with an in-ICU mortality of 49%, versus 18% when [Lactate] was ≤4.0 mEq/L.

4. Discussion

4.1. Statement of key findings

A mathematical model of plasma acid-base behavior [12] was used to develop a theoretical relationship between [Lactate], [Pi], [Albumin] and AG_k in lactic acidosis. The model accounts for compensatory potassium shifts ("tissue buffering") and chloride shifts into red blood cells, as well as compensatory respiratory changes. The theoretical relationship was tested against 948 data sets from critically ill patients with [Lactate] 4.0 mEq/L or greater. We found that in lactic acidosis, AG_K more accurately reflects increasing levels of [Lactate] in critically ill patients when charge contributions from [Pi] and [Albumin] are incorporated. We also conducted a retrospective analysis of a large database containing detailed information on electrolytes and serum albumin from critically ill patients to assess the ability of the anion gap to detect [Lactate] > 4.0 mEq/L in comparison with its albumin-corrected version. We found that the albumin-corrected anion gap (cAG_K) was more sensitive than AG_K in predicting the presence of [Lactate] > 4.0 mEq/L.

4.2. Previous studies

Several authors have studied the analytical performance of AG and/or cAG to detect hyperlactatemia in small cohorts of patients. Iberti and colleagues [15] studied 56 adult surgical intensive care unit (ICU) patients and found that AG lacked adequate sensitivity to exclude a lactate level ≥2.5 mEq/L. Levraut and colleagues [16] reached the same conclusion but found that AG exhibited higher sensitivity for a lactate level ≥5 mEq/L. Dinh et al. [17], in a retrospective study of 639 data sets, similarly found that neither AG nor cAG has adequate sensitivity to exclude a lactate ≥2.5 mEq/L. Moviat et al. [18] studied 50 ICU patients with metabolic acidosis defined by standard base excess less than or equal to −5. In this highly selected series, AG was not useful for detection of a lactate of ≥2.0 mEq/L, but cAG exhibited high sensitivity. Chawla and colleagues [19], in a series of 497 highly selected lab values, demonstrated that both AG and cAG lacked adequate sensitivity to exclude a lactate concentration >2.5 mEq/L and that cAG, but not AG, had sufficient sensitivity to exclude a lactate >4.0 mEq/L [20-22].

4.3. Implications of study findings

Our findings imply that AG_K more accurately reflects increasing levels of [Lactate] in critically ill patients when [Pi] and [Albumin] are incorporated into the analysis. As expected, the albumin-corrected anion gap, cAG_K, performs with markedly higher sensitivity than the traditional anion gap, AG_K, in its ability to detect [Lactate] > 4.0 mEq/L. This implies that clinical laboratories should routinely provide albumin levels when AG_K is used to assess patients so that cAG_K can be calculated.

These findings are useful in the assessment of illness severity and the need to measure lactate concentrations. For example, in ambulatory and ward settings the concentration of lactate may not be routinely measured or be rapidly available and cAG_K can be calculated without the need for a blood gas measurement. This approach is useful because cAG_K relies on charge balance rather than specific chemical identity to signal the presence of excess anions. Moreover, our findings can be applied to deteriorating emergency department or ward patients [23-25] and in helping identify patients who are developing end-of-life illness [26,27]. Our findings may also be useful in ICU settings where a direct measurement of [Lactate] is not readily available [28].

In the ICU, we recommend that critically ill patients be evaluated with cAG_K together with [Pi], [Ca^{2+}], [Mg^{2+}], [Lactate], and an arterial blood gas (ABG). This approach permits detection of elevated levels of lactate and phosphate species together with unmeasured anions. A similar approach has been advocated by Mallat et al. [29] who recommended calculation of cAG_K − [Lactate] to estimate elevated levels of anions other than lactate. Using the results of our model, a calculation of [UA] is given by the equation:

$$[UA] = AG_K + \left[Ca^{2+}\right] + \left[Mg^{2+}\right] - [Lactate] - 10 \times [Albumin] \times (0.123 \times pH - 0.631) - Zp \times [Pi] \quad (9)$$

This equation permits an estimate of levels of unmeasured anions other than lactate and phosphate species. In 800,000 model simulations, the root-mean-square-deviation (RMSD) of [UA] as calculated by Eq. (9) was 0.07 mEq/L. This result indicates that this approach is highly precise from a theoretical perspective. In actual clinical practice, however, the precision will be affected by measurement error involving multiple analytes. Eq. (9) could be calculated by a computerized application at the bedside in the ICU. The upper normal limit for [UA] should be determined for each clinical laboratory as its value might be sensitive to the exact functionality of the ion-selective electrodes that are employed (see Appendix 1 for further discussion).

Finally, we note that [Lactate] > 4.0 as well as elevated levels of AG_K or cAG_K are positively associated with mortality during the ICU admission. In particular, the strongest associations with mortality during the ICU admission were [Lactate] > 4.0, followed by cAG_K > 20 mEq/L. These findings are in accord with the results of Lipnick et al. [30], who noted that [Lactate] and cAG had the best discriminating power for predicting 30-day mortality.

4.4. Study strengths and limitations

This study has several strengths. It is based on the findings from the largest cohort to date of patients, arterial blood gases, electrolytes, albumin, and lactate concentrations for which a detailed physicochemical analysis could be applied and where all necessary variables were measured. It performed such analysis in a diverse group of patients with a broad and deep range of acid-base disorders, electrolyte disturbances and variable albumin concentrations, making its findings widely applicable. Its findings appear robust, reproducible and logical and have clinical implications. However, there are also several limitations. For example, we studied a cohort of critically ill patients rather than general ward patients, or ambulatory patients. However, although the clinical characteristics of such patients are different, the principles of acid-base physiology and anion gap and corrected anion gap calculations are likely independent of the clinical context. In addition, the albumin and inorganic phosphorus concentration measurements were performed only once a day. The application of such morning levels of albumin to the calculations obtained from each blood gas and electrolyte measurement implies a relatively constant albumin value. This assumption may lead to minor errors but is unlikely to impact the key findings of this study. Furthermore, our observations are consistent with previous published [19] modeling of the albumin effects on the anion gap.

5. Conclusions

In lactic acidosis, AG_K more accurately reflects increasing levels of [Lactate] in critically ill patients when charge contributions from [Pi] and [Albumin] are also considered. This suggests that correcting AG_K for variations in the albumin concentration will improve its sensitivity. Our data demonstrate that the albumin-corrected anion gap, cAG_K, performs with markedly higher sensitivity than AG_K in its ability to detect [Lactate] > 4.0 mEq/L. Hence, clinical laboratories should routinely provide albumin concentrations when AG_K is used to assess patients, so that cAG_K can be calculated. cAG_K can be calculated in ambulatory, ward and emergency room patients without the need for a blood gas measurement. This approach is useful by virtue of the fact that cAG_K relies on charge balance rather than specific chemical identity to signal the presence of excess anions. Finally, In the ICU, we recommend that critically ill patients be evaluated with cAG_K together with [Pi], [Ca^{2+}], [Mg^{2+}], [Lactate], and an arterial blood gas (ABG). This approach permits detection of elevated levels of lactate and phosphate species together with unmeasured anions. [UA] can be calculated with the equation:

$$[UA] = AG_K + \left[Ca^{2+}\right] + \left[Mg^{2+}\right] - [Lactate] - 10 \times [Albumin] \times (0.123 \times pH - 0.631) - Zp \times [Pi].$$

We suggest that the calculation of [UA] be automated by computerized applications at the bedside. The upper normal limit for [UA] should be determined for each clinical laboratory.

Appendix 1

Mathematical model of human acid-base physiology in blood plasma

Figge, Rossing and Fencl [31] produced electrolyte solutions resembling human serum that contained albumin as the sole protein moiety. Data collected from these solutions were used in a least-squares algorithm to develop a quantitative physicochemical model of acid-base status in blood plasma. This model treated albumin as a polyprotic macromolecule with multiple equilibrium dissociation constants corresponding to different classes of amino acid side chains (i.e., Arg, Lys, Asp, Glu, Cys, His, Tyr, amino terminus, carboxyl terminus). The expression employed for the carbon dioxide - bicarbonate equilibrium was mathematically equivalent to the Henderson-Hasselbalch equation. Apparent equilibrium dissociation constants from the work of Sendroy and Hastings [32] for the phosphoric acid - phosphate system ([H_3PO_4], [$H_2PO_4^-$], [HPO_4^{2-}], and [PO_4^{3-}]), as applicable to plasma at 38 °C, were explicitly included. This model was successful in calculating the pH of albumin-containing electrolyte solutions as well as the pH of filtrands of serum.

Figge, Mydosh and Fencl [12] further refined the quantitative physicochemical model by incorporating pK_A values for albumin histidine residues as determined by NMR spectroscopy [33]. The pK_A values were temperature-corrected to 37 °C in the model. This

model accounted for the effects of the microenvironments within the macromolecule of albumin on the pK_A values of individual histidine residues. Although the Figge-Mydosh-Fencl model was successful in many aspects, it did not account for the presence of all 59 lysine residues in human serum albumin. Because of this limitation, the model provides useful results restricted to the pH range of biologic interest (6.9 to 7.9); outside of this range the model is unreliable.

The model was further refined in 2009 [34] to account for all 59 lysine residues in human serum albumin. It was found that 9 lysine residues had unusually low pK_A values, in accord with the prior work of Halle and Lindman [35], and as suggested by data from tryptophan and tyrosine fluorescence emission spectroscopy studies [36]. The 2009 model revision also accounted for the N-B (neutral-to-base) structural transition of human serum albumin. The N-B transition occurs between pH 6 and 9, which is important because this includes the physiologic pH range. There are most likely five conformation-linked histidine residues that undergo a downward pK shift as albumin transitions from the N to the B conformation [33]. The predicted titration curve of human serum albumin as calculated by the 2009 model closely tracks with the independent experimental data of Fogh-Andersen, Bjerrum and Siggaard-Andersen [37] over the pH range of approximately 5 to 9.

The physicochemical model of human acid-base physiology was updated in 2012 and published online [38] as the Figge-Fencl model version 3.0. The 2012 model incorporates key enhancements from earlier models, and features an improved least-squares fit ($S^2 = 0.0700$) to the original data of Figge, Rossing and Fencl, compared with the Figge-Mydosh-Fencl model ($S^2 = 0.0728$) and the model of 2009 ($S^2 = 0.0768$). The 2012 model improves the performance down to pH 4, extending the useful range from pH 4 to 9. The titration curve of human serum albumin at 37 °C as predicted by the 2012 model closely tracks with the experimental data points of Niels Fogh-Andersen and colleagues [37] over the pH range of approximately 4 to 9. In this model, the predicted isoelectric point of human serum albumin (pI, the pH at which albumin's intrinsic charge is zero) is 5.44 [38], in agreement with the experimental value of 5.4 determined by Fogh-Andersen and colleagues [37]. The 2012 model version gives results equivalent to those of the Figge-Mydosh-Fencl model within the pH range of biologic interest (6.9 to 7.9). Micro environmental pK_A values of amino acid side chains in human serum albumin as featured in the 2012 model are given in Table A1 [38], and the model is completely described in Table A2 [38].

Monte Carlo simulations of lactic acidosis

The 2012 physicochemical model of human acid-base physiology [38], as described above, was employed for the simulations. In each computer simulation, plasma was assigned a normal set of starting electrolyte values along with a normal or low albumin level. There were eight sets of starting conditions, corresponding to normal albumin (4.4 g/dL) with low-normal, mid-normal, or high-normal cAG_K, as well as low albumin (2.0 g/dL) with low-normal, mid-normal, or high-normal cAG_K. The starting pCO_2 was 40 mm Hg, and the starting pH was 7.40 in each of the eight sets. A total of 100,000 simulations were run for each of the starting conditions, for a total of 800,000 Monte Carlo simulations. In each simulation, the system was perturbed by the introduction of a random amount of lactic acid and undefined organic acids, resulting in an acute drop in pH and bicarbonate, with accumulation of lactate and undefined anions (UA). The pH was then partially restored back towards 7.40 by the introduction of compensatory ion shifts, including potassium shifts ("tissue buffering") and chloride shifts into red blood cells. The pCO_2 was modified to provide respiratory compensation, also partially restoring the pH back towards 7.40. The final pH of the system was then calculated by the model. The computer tracked compliance with the Winters formula [11]. Approximately 37 to 38% of the simulations in each of the eight groups were compliant with the Winters formula, indicating that these simulations provided a realistic portrayal of compensated lactic acidosis.

The model simulations demonstrated that AG_K can be expressed as the sum of the following components:

$$AG_K = [\text{Lactate}] + Zp \times [\text{Pi}] + 2.4 \times [\text{Albumin}] + [\text{UA}] + \text{constant1} + e \quad \text{(A1)}$$

where AG_K, [UA], and [Lactate] are in mEq/L, [Pi] is in mmol/L, [Albumin] is in g/dL, Zp is a function of pH (as discussed in references [12,31,32,34], and in Table A2; the default value for Zp = 1.85 at pH 7.40), and *e* reflects unmeasured cations plus pH-related variations. In actual clinical samples, the level of unidentified anions, [UA], will be unknown, so this term is incorporated into *e*.

Eq. (A1) can be rearranged as follows, to derive an expression employing the albumin-corrected anion gap and a recalculated value for the constant:

$$cAG_K = [\text{Lactate}] + Zp \times [\text{Pi}] + \text{constant2} + e \quad \text{(A2)}$$

The optimal value of the constant for Eq. (A2) ranges from 5.3 to 6.7 mEq/L and depends on the buffer composition.

Based on the Monte Carlo simulations, we compared two different methods for determining unmeasured anions. The first method is the full physicochemical calculation as discussed by Figge, Mydosh and Fencl [12]. This method should exactly reproduce the results of the Monte Carlo simulations because it serves as the underlying theory for those simulations. The second method is a variant of the simplified equation given by Figge, Mydosh and Fencl [12] which includes [Lactate]:

$$[\text{UA}] = AG_K + \left[Ca^{2+}\right] + \left[Mg^{2+}\right] - [\text{Lactate}] - 10 \times [\text{Albumin}] \times (0.123 \times \text{pH} - 0.631) - Zp \times [\text{Pi}] \quad \text{(A3)}$$

In Eq. (A3), the quantities AG_K, $[Ca^{2+}]$, $[Mg^{2+}]$, [Lactate], and [UA] are in mEq/L. The quantities $[Ca^{2+}]$ and $[Mg^{2+}]$ refer to the total concentrations (not ionized concentrations) of calcium and magnesium, respectively, in mEq/L. [Albumin] is in g/dL. [Pi] is the inorganic phosphorus concentration in mmol/L.

Because the level of "unknown anions" was actually known by the computer in each Monte-Carlo simulation, we can compare the performance of both methods using the root-mean-square-deviation (RMSD). As expected, the full physicochemical calculation yields a RMSD of zero mEq/L across all simulation runs (n = 800,000 simulations); this serves as an internal check on the validity of the Monte Carlo simulations. The Figge-Mydosh-Fencl Eq. (A3) also performs extremely well and yields a RMSD of 0.06–0.07 mEq/L in the eight sets of simulation runs. Both of these methods require knowledge of the pH.

Eq. (A3) provides a very useful method for calculation of [UA], and could be easily automated on a computer application. The upper normal limit for [UA] should be determined by each clinical laboratory for several reasons. First, our model was optimized against experimental data where sodium was determined by flame photometry, and chloride by a titration methodology [12,31,34,38]. These methods will likely provide slightly different results than ion-selective electrodes. Second, our model is based on albumin as the sole protein moiety, and does not include globulins. Even though globulins are thought to have minimal net charge near pH 7.4, they are likely to contribute to plasma buffering [12,31,34]. Third, we used a calculated value of $[HCO_3^-]$ based on the Henderson-Hasselbalch equation. Some laboratories calculate the anion gap using a measurement of total CO_2, which will differ slightly from the value of bicarbonate calculated using the Henderson-Hasselbalch equation. For these reasons, we recommend that individual laboratories determine their own applicable value of the upper normal limit for [UA].

Table A1
Microenvironmental pK_A values of amino acid side chains of human serum albumin as featured in the 2012 quantitative physicochemical model of human acid-base physiology in blood plasma [38].

Amino acid	Number of side chains	Micro environmental pK_A
Cys	1	8.5
Glu and Asp	98	3.9
Tyr	18	11.7
Arg	24	12.5
Lys	2	5.8
	2	6.15
	2	7.51
	2	7.685
	1	7.86
	50	10.3
His	1	7.12[a]
	1	7.22[a]
	1	7.10[a]
	1	7.49[a]
	1	7.01[a]
	1	7.31
	1	6.75
	1	6.36
	1	4.85
	1	5.76
	1	6.17
	1	6.73
	1	5.82
	1	5.10
	1	6.70
	1	6.20
Amino terminus	1	8.0
Carboxyl terminus	1	3.1

[a] Note: The pK_A's of the first five His residues will each downshift by 0.4 pH units due to the structural rearrangement associated with the neutral-to-base (N-B) transition. See discussion in reference [34] and formula in Table A2.

Table A2
Mathematical description of the 2012 quantitative physicochemical model of human acid-base physiology in blood plasma [38].

$$\begin{aligned}
&\mathrm{SID} + 1000 \times ((aH^+) - \mathrm{Kw}/(aH^+) - \mathrm{Kc1} \times pCO_2/(aH^+) - \mathrm{Kc1} \times \mathrm{Kc2} \times pCO_2/(aH^+)^2) \\
&- [\mathrm{Pi}] \times \mathrm{Zp} \\
&+\{-1/(1+10^{-(pH-8.5)}) \\
&-98/(1+10^{-(pH-3.9)}) \\
&-18/(1+10^{-(pH-11.7)}) \\
&+24/(1+10^{(pH-12.5)}) \\
&+2/(1+10^{(pH-5.80)}) \\
&+2/(1+10^{(pH-6.15)}) \\
&+2/(1+10^{(pH-7.51)}) \\
&+2/(1+10^{(pH-7.685)}) \\
&+1/(1+10^{(pH-7.86)}) \\
&+50/(1+10^{(pH-10.3)}) \\
&+1/(1+10^{(pH-7.12+NB)}) \\
&+1/(1+10^{(pH-7.22+NB)}) \\
&+1/(1+10^{(pH-7.10+NB)}) \\
&+1/(1+10^{(pH-7.49+NB)}) \\
&+1/(1+10^{(pH-7.01+NB)}) \\
&+1/(1+10^{(pH-7.31)}) \\
&+1/(1+10^{(pH-6.75)}) \\
&+1/(1+10^{(pH-6.36)}) \\
&+1/(1+10^{(pH-4.85)}) \\
&+1/(1+10^{(pH-5.76)}) \\
&+1/(1+10^{(pH-6.17)}) \\
&+1/(1+10^{(pH-6.73)}) \\
&+1/(1+10^{(pH-5.82)}) \\
&+1/(1+10^{(pH-5.10)}) \\
&+1/(1+10^{(pH-6.70)}) \\
&+1/(1+10^{(pH-6.20)}) \\
&+1/(1+10^{(pH-8.0)}) \\
&-1/(1+10^{-(pH-3.1)})\} \times 1000 \times 10 \times [\mathrm{Albumin}]/66,500 = 0.
\end{aligned}$$

where:
$(aH^+) = 10^{-pH}$; (aH^+) is the hydrogen ion activity, also used as an approximation of hydrogen ion concentration, $[H^+]$;

Table A2 (*continued*)

$$\begin{aligned}
&\mathrm{Zp} = (\mathrm{K1} \times (aH^+)^2 + 2 \times \mathrm{K1} \times \mathrm{K2} \times (aH^+) + 3 \times \mathrm{K1} \times \mathrm{K2} \times \mathrm{K3})/((aH^+)^3 \\
&\quad + \mathrm{K1} \times (aH^+)^2 + \mathrm{K1} \times \mathrm{K2} \times (aH^+) + \mathrm{K1} \times \mathrm{K2} \times \mathrm{K3}); \\
&\mathrm{NB} = 0.4 \times (1 - 1/(1+10^{(pH-6.9)}));
\end{aligned}$$

Strong ion difference, SID, is given in mEq/L;
pCO_2 is given in Torr;
Total concentration of inorganic phosphorus-containing species, [Pi], is given in mmol/L;
[Albumin] is given in g/dL;

$$\begin{aligned}
&\mathrm{Kw} = 4.4 \times 10^{-14}\,(\mathrm{Eq/L})^2; \\
&\mathrm{Kc1} = 2.44 \times 10^{-11}\,(\mathrm{Eq/L})^2/\mathrm{Torr}; \\
&\mathrm{Kc2} = 1.1 \times 10^{-10}\,(\mathrm{Eq/L}); \\
&\mathrm{K1} = 1.22 \times 10^{-2}\,(\mathrm{mol/L}); \\
&\mathrm{K2} = 2.19 \times 10^{-7}\,(\mathrm{mol/L}); \\
&\mathrm{K3} = 1.66 \times 10^{-12}\,(\mathrm{mol/L});
\end{aligned}$$

66,500 g/mol is the molecular weight of albumin.

The above expression defines a function, f_{pH}, which can be used to calculate the pH of plasma for any valid set of values for SID, pCO_2, [Pi], and [Albumin]:
$pH = f_{pH}\{\mathrm{SID}, pCO_2, [\mathrm{Pi}], [\mathrm{Albumin}]\}$

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