Journal of Clinical Monitoring and Computing
https://doi.org/10.1007/s10877-021-00713-0

ORIGINAL RESEARCH

Comparison of a modified Story approach to traditional evaluation of acid–base disturbances in patients with shock: a cohort study

Matheus Golenia dos Passos[1] · Luciana Bergamini Blaya[1] · Márcio Manozzo Boniatti[2]

Received: 11 December 2020 / Accepted: 23 April 2021

Abstract
To compare whether the diagnostic evaluation of metabolic acidosis can be improved by using a modified Story method compared to the traditional evaluation in a population of critically ill patients with shock. This prospective cohort study included shock patients admitted to the ICU of a tertiary hospital in Brazil between May 2018 and November 2019. We collected laboratory data necessary for traditional evaluation and the simplified Stewart's method. During the study period, 149 patients were included in the final analysis. Of the 17 patients with a normal SBE and $AG_{corrected}$, 13 (76.5%) presented with metabolic acidosis according to the modified Story assessment. Therefore, of the 149 patients included in the study, the traditional approach failed to identify metabolic acidosis that was identified by the modified Story assessment in 13 (8.7%) patients. In addition, the determination of the severity of metabolic acidosis also differed between the two methods by a mean of − 7.8 mEq/L. We found that a modified Story method can identify and quantify metabolic acidosis in patients with disorders that were not revealed by the traditional approach.

Keywords Acid–base disorders · Metabolic acidosis · Traditional approach · Simplified Stewart · Shock

1 Introduction

Acid–base disorders, especially metabolic acidosis, are frequently found in critically ill patients [1]. These disorders might be described by a traditional approach, adapted from Henderson and Hasselbach, in which the metabolic component of acid–base physiology is based on the analysis of plasma concentrations of bicarbonate (HCO_3^-). This might be further completed with the use of base excess (BE), which was proposed by Siggaard-Andersen through the Van Slyke equation. These variables, with the addition of the anion gap (AG), are widely used to identify the presence and degree of metabolic acidosis [2]. An advantage of this method is that it is easy to understand and apply in common clinical situations. However, traditional assessment may be insufficient for complex acid–base disorders, as commonly seen in critically ill patients [3–5]. An alternative evaluation is the mathematical model based on the physicochemical principles described by Stewart [6] and modified by Figge [7, 8]. This theory states that three independent variables determine the plasma pH: PCO_2; the strong ion difference (SID), which is the difference between fully dissociated plasma anions and cations; and weak nonvolatile acids (albumin and phosphorus). This method allows the quantification of the components of acid–base disorders individually and, thus, offers a better understanding of the pathogenesis. Several studies have shown that this approach, compared to the traditional approach, can be more accurate in identifying acid–base disorders in critically ill patients [3–5]. However, Stewart's approach is a complex method to apply bedside. Story recently described Stewart's simplified method, which combines the assessment of standard base excesso (SBE) with the original Stewart assessment [9]. Thus, the objective of our study was to compare whether the diagnostic evaluation of metabolic acidosis can be improved by using a modified Story method compared to the traditional evaluation in a population of critically ill patients with shock. We chose this population because it represents a subset of critically ill patients who, in general, have complex acid–base disorders.

✉ Márcio Manozzo Boniatti
mboniatti@hcpa.edu.br

[1] Department of Critical Care, Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil

[2] Department of Critical Care, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

Published online: 02 May 2021

2 Methods

This is a prospective cohort study that included patients admitted to the ICU of Hospital Nossa Senhora da Conceição (HNSC) in Porto Alegre, Brazil, from May 2018 to November 2019. HNSC is a public tertiary hospital with 843 beds and approximately 26,000 hospitalizations per year. The ICU has 59 beds, of which 14 are postoperative beds used after major surgery and the others are medical beds.

The study was approved by the HNSC Research Ethics Committee. Blood samples were collected in the context of usual care for patients with shock. Thus, consent was waived due to the observational nature of the study.

The study included patients who were admitted to the ICU for shock (distributive, obstructive, cardiogenic or hypovolemic) or who had a diagnosis of shock within 6 h of admission to the ICU. Shock was defined as the need to use vasoactive drugs for a minimum period of 1 h. Patients who did not have the necessary laboratory data for the proposed acid–base disorder analysis at the time of admission were excluded.

The following clinical and demographic variables were collected: age, sex, SAPS III, comorbidities, predominant type of shock, unit of origin, previous renal dysfunction (using the KDIGO classification [10]), duration of mechanical ventilation, length of ICU stay, length of hospital stay and need for dialysis during hospitalization. Patients were followed up until discharge from the hospital to determine ICU mortality and hospital mortality.

The laboratory variables measured at admission and 24 h afterwards were pH and PCO_2 (Rapilab 865, Chiron Diagnostics), Na^+, K^+ and Cl^- (ion selective electrode, Roche Diagnostics), albumin (bromocresol green colorimetric technique, Roche Diagnostics) and lactate (colorimetric kinetics, Roche Diagnostics). The bicarbonate concentration and SBE were calculated using the Henderson-Hasselbach [11] and the Van Slyke equations [12], respectively.

The anion gap (AG) was calculated as follows:

$$AG = \left(Na^+ + K^+\right) - \left(Cl^- + HCO_3^-\right).$$

The anion gap corrected ($AG_{corrected}$) for abnormal albumin values was calculated according to the formula:

$$AG_{corrected} = AG + 2.5 \times (4.2 - \text{observed albumin})\,(g/dL).$$

In the analysis based on the SBE and $AG_{corrected,}$ we obtained the following diagnoses [13]:

(1) Simple disorders:

Metabolic acidosis: ↓ SBE (< − 2.0 mEq/L).

Metabolic acidosis with an increased AG: ↑ $AG_{corrected}$ (> 16.0 mEq/L)

Metabolic acidosis with a normal AG: $AG_{corrected} \leq 16.0$ mEq/L

(2) Mixed disorders (when the secondary response to the primary process appears outside expected range): $\Delta AG_{corrected} > \Delta HCO_3^-$.

In the analysis using the modified Story method, SBE variations are explained by the variation of chloride (in relation to sodium), lactate, albumin and other ions. The SBE variation attributable to these components was calculated as follows:

$$SBE_{Cl} = Na^+ - Cl^- - 35(\text{in mEq/L})$$

$$SBE_{Lac} = 1 - \text{lactate (in mEq/L)}$$

$$SBE_{Alb} = 2.5 \times (4.2 - \text{albumin in g/dL})$$

$$SBE_{OI} = SBE - SBE_{Cl} - SBE_{Lac} - SBE_{Alb}$$

From this analysis, we defined hyperchloremic acidosis, acidosis due to an increase in lactate or acidosis due to an increase in unmeasured anions, as when the SBE attributable to chloride (in relation to sodium, not an absolute chloride effect), lactate or other ions showed a value < − 2.0 mEq/L, respectively. A value < − 2.0 mEq/L in the sum of the negative SBE values attributable to these three components was used to define the presence of metabolic acidosis using the modified Story method; this variable is called $SBE_{acidosis\_Story}$.

$$SBE_{acidosis\_Story} = SBE_{Cl}(\text{if } < 0 \text{ mmol/L}) + SBE_{Lac}(\text{if } < 0 \text{ mmol/L}) + SBE_{OI}(\text{if } < 0 \text{ mmol/L})$$

It is important to note here that positive values (alkalizing effects) were not considered in this sum, since the intention was to show the presence of metabolic acidosis without being masked by the concomitant presence of metabolic alkalosis. The theoretical advantage of this variable is that it quantifies the presence of the 3 components of metabolic acidosis, while excluding the possible contribution of an alkalinizing effect, for example, hypoalbuminemia or hypochloremia, which may be present masking metabolic acidosis.

2.1 Statistical analysis

The analysis of the collected data was performed through descriptive statistics with calculation of the mean and

standard deviation or median and interquartile range, frequency and percentage. The analysis of the variation between the measurements was performed with a paired Student's t test. Pearson's correlation coefficient was used to assess the correlation between SBE and $SBE_{acidosis\_Story}$. The degree of agreement between SBE and $SBE_{acidosis\_Story}$ was assessed using the agreement limits of the Bland–Altman analysis. According to Bland and Altman [14], 95% of the points must be within ± 1.96 of the standard deviation of the mean difference, thus defining the upper and lower limits of agreement. A value of $p < 0.05$ was considered statistically significant. The statistical analysis was performed using SPSS software version 20.0.

3 Results

During the study period, 154 patients were admitted to the ICU with a diagnosis of shock. Five patients were excluded for not having all the necessary laboratory variables on admission. Thus, 149 patients were included in the final analysis. Demographic, clinical and outcome characteristics are described in Table 1.

Table 2 describes the measured and calculated variables for assessing acid–base disorder at admission and after 24 h after admission to the ICU.

On admission to the ICU, 107 (71.8%) patients with metabolic acidosis (SBE < − 2.0 mEq/L) were identified by traditional assessment. Of these, 82 (76.6%) had an increased $AG_{corrected}$, and 69 (64.5%) had $\Delta AG_{corrected} > \Delta HCO_3^-$, showing a mixed disorder. According to modified Story assessment, 145 (97.3%) patients had metabolic acidosis ($SBE_{acidosis\_Story}$ < − 2.0 mEq/L). Of these, 56 (38.6%) had relative hyperchloremia (SBE_{Cl} < − 2.0 mEq/L), 48 (33.1%) had hyperlactatemia (SBE_{Lac} < − 2.0 mEq/L), and 99 (68.3%) had unmeasured anions (SBE_{OI} < − 2.0 mEq/L).

Of the 42 patients without metabolic acidosis according to the traditional assessment (SBE > − 2.0 mEq/L), 25 (59.5%) presented with an increased $AG_{corrected}$. Of the 17 patients with SBE > − 2.0 mEq/L and without an increased $AG_{corrected}$, 13 (76.5%) presented with metabolic acidosis according to the modified Story assessment. All of these cases had relative hyperchloremia and hypoalbuminemia. Therefore, of the 149 patients included in the study, the assessment based on SBE and $AG_{corrected}$ failed to identify metabolic acidosis that was identified by the modified Story assessment in 13 (8.7%) patients. Table 3 shows two examples of metabolic disorder detected using the modified Story assessment. In patient 1, we did not identify a metabolic disorder using the traditional evaluation (normal HCO_3, $AG_{corrected}$ and SBE). However, when we applied the modified Story method, we noticed that there is a hyperchloremic metabolic acidosis. SBE misses this disorder due to the alkalinizing effect of hypoalbuminemia. $AG_{corrected}$ does not identify the disorder because hyperchloremia does not increase the anion gap. In patient 2, SBE underestimated the degree of metabolic acidosis due to coexistence of metabolic alkalosis (hypoalbuminemia and sodium-chloride difference > 35). When we separate the acidifying and alkalinizing effects, we see severe metabolic acidosis due to unmeasured anions. In this case, the AG identifies the presence of unmeasured anions. However, HCO_3 and SBE, variables used to assess the degree of metabolic acidosis, underestimate the severity of the disorder.

Table 1 Clinical, demographic and outcome characteristics

Variables	n 149
Age, mean ± SD	62.0 ± 15.2
Sex, male, n,%	81 (54.4)
SAPS 3, mean ± SD	72.5 ± 18, 1
Origin, n (%)	
Surgical room	54 (36.2)
Emergency	51 (34.2)
Ward	41 (27.5)
Other	3 (2.0)
Type of admission, n (%)	
Surgical	57 (38.3)
Medical	92 (61.7)
Comorbidities, n (%)	
Hypertension	81 (54.4)
Diabetes	49 (32.9)
Heart failure	22 (14.8)
Chronic renal disease	23 (15.4
Solid neoplasia	23 (15.4)
Hematological neoplasia	6 (4.0
Cirrhosis	9 (6.0)
Shock type, n (%)	
Cardiogenic	21 (14.1)
Distributive	105 (70.5)
Hypovolemic	22 (14.8)
Obstructive	1 (0.7)
Acute renal failure at admission	
KDIGO, n (%)	
0	64 (43.0)
1	28 (18.8)
2	19 (12.8)
3	38 (25, 5)
Dialysis during hospitalization, n (%)	58 (38.9)
MV, n (%)	124 (83.2)
MV duration, days, median (IQR)	3.0 (1.0–11.0)
ICU LOS, days, median (IQR)	7.0 (3.0–15.0)
Hospital LOS, days, median (IQR)	27.0 (15.0–39, 5)
ICU mortality, n (%)	65 (43.6)
Hospital mortality, n (%)	76 (51.0)

Table 2 Acid–base characterization of patients at admission and after 24 h

	Admission	24 h	P
pH	7.32 ± 0.1	7.38 ± 0.1	< 0.001
PCO_2, mmHg	42.2 ± 14.8	39.3 ± 10.6	0.02
HCO_3, mEq/L	20.6 ± 5.3	22.5 ± 5.0	< 0.001
SBE, mEq/L	− 4.6 ± 5.7	− 2.0 ± 5.3	< 0.001
Sodium, mEq/L	138.3 ± 6.7	137.5 ± 6.4	0.07
Potassium, mEq/L	4.3 ± 0.8	4.1 ± 0.6	0.007
Chloride, mEq/L	105.0 ± 6.8	105.8 ± 7.0	0.70
Lactate, mEq/L	3.1 ± 2.5	2.7 ± 2.6	0.12
Albumin, g/dL	2.6 ± 0.6	2.6 ± 0.6	0.23
$AG_{corrected,}$ mEq/L	21.0 ± 8.4	18.3 ± 9.1	0.003
$SBE_{Cl,}$ mEq/L	− 1.7 ± 7.7	− 2.3 ± 7.5	0.47
SBE_{Lac}, mEq/L	− 2.1 ± 2.5	− 1.7 ± 2.6	0.12
SBE_{OI}, mEq/L	− 4.9 ± 8.3	− 1.9 ± 8.6	0.001
SBE_{Alb}, mEq/L	4.0 ± 1.5	4.0 ± 1.5	0.23
$SBE_{acidosis\_Story}$, mEq/L	− 12.4 ± 5.8	− 10.8 ± 5.5	0.003

Table 3 Examples of acid–base disorders

	Patient 1	Patient 2
Sodium, mEq/L	127	138
Potassium, mEq/L	4.1	2.5
Albumin, g/dL	2.5	3.5
Chloride, mEq/L	99	97
pH	7.38	7.21
Lactate, mEq/L	1.3	1.0
HCO3, mEq/L	24.2	23.1
SBE, mEq/L	− 0.2	− 3.7
$AG_{corrected}$, mEq/L	12.1	22.2
$SBE_{acidosis\_Story}$, mEq/L	− 7.3	− 11.5
$SBE_{Cl,}$ mEq/L	− 7.0	6.0
SBE_{Lac}, mEq/L	− 0.3	0
SBE_{Alb}, mEq/L	4.3	1.8
SBE_{OI}, mEq/L	2.9	− 11.5

The determination of the severity of metabolic acidosis also differed between the two methods. The correlation between SBE and $SBE_{acidosis\_Story}$ was weak ($r^2 = 0.53$). According to the Bland–Altman analysis, the mean (SBE—$SBE_{acidosis\_Story}$) was 7.8 mEq/L, with lower and upper agreement limits of 16.05 mEq/L and − 0.49 mEq/L, respectively (Fig. 1). Although there is good agreement, with 146 out of 149 (98.0%) points between 1.96 standard deviations of the mean, the mean difference between the two methods is large. Among the 33 patients with an SBE between − 2.0 and − 5.0 mEq/L, 16 (48.5%) had $SBE_{acidosis\_Story} < -10.0$ mEq/L.

4 Discussion

Our main findings are that, in a cohort of critically ill patients with shock, the assessment based on SBE and $AG_{corrected}$ failed to identify metabolic acidosis that was identified by the modified Story assessment in 8.7% of patients. In addition, the severity of the disorder is underestimated by SBE in relation to $SBE_{acidosis\_Story}$.

Although SBE and AG (including $AG_{corrected}$ for serum albumin level) are commonly used to assess acid–base disorders, it is recognized that this method may fail to identify the complex metabolic disorders seen in critically ill patients and is often insufficient for explaining them [3–5]. An alternative approach is the application of basic physicochemical principles of aqueous solutions to plasma, as in Stewart's method. Several studies have demonstrated the potential superiority of the Stewart method over traditional assessment [15–18], identifying disorders in patients with normal pH, SBE and AG. SBE represents the sum of all disorders (alkalosis and acidosis). The presence of hypoalbuminemic alkalosis is very common in critically ill patients [3, 5], decreasing the sensitivity of SBE in identifying metabolic acidosis. The $AG_{corrected}$, a variable that would increase the sensitivity of traditional assessment [13], does not change with hyperchloremic acidosis. In this scenario, patients with hypoalbuminemia and relative hyperchloremia may have normal SBE and $AG_{corrected}$ levels, as shown in our results. On the other hand, the complexity of applying the Stewart method bedside is a limitation. Story [9] recently described a simplified method. We found that the a modified Story method maintains the greatest sensitivity in relation to the traditional assessment.

In addition to the identification of metabolic acidosis in patients with apparently normal acid–base status by traditional evaluation, the quantification of the disorder by the new method allows us to determine its severity that was masked by other factors. The $SBE_{acidosis\_Story}$, a variable that represents the sum of the different etiologies of metabolic acidosis (chloride, lactate or unmeasured anions), already excluding the possible alkalinizing effects (either from hypoalbuminemia or an increase in the sodium-chloride difference), differed, on average, by 7.8 mEq/L of the SBE. In this way, disorders previously identified by the traditional assessment, but classified as mild, may, in fact, be serious disorders that are underestimated.

Another advantage of using a quantitative physical–chemical approach is that a better understanding of the causes of acid–base disorders is achieved. Noritomi et al. [19] found that patients with severe sepsis and septic shock exhibit complex metabolic acidosis on admission to the ICU, caused predominantly by relative hyperchloremia and unmeasured anions. The same results were presented by Mallat [3], with

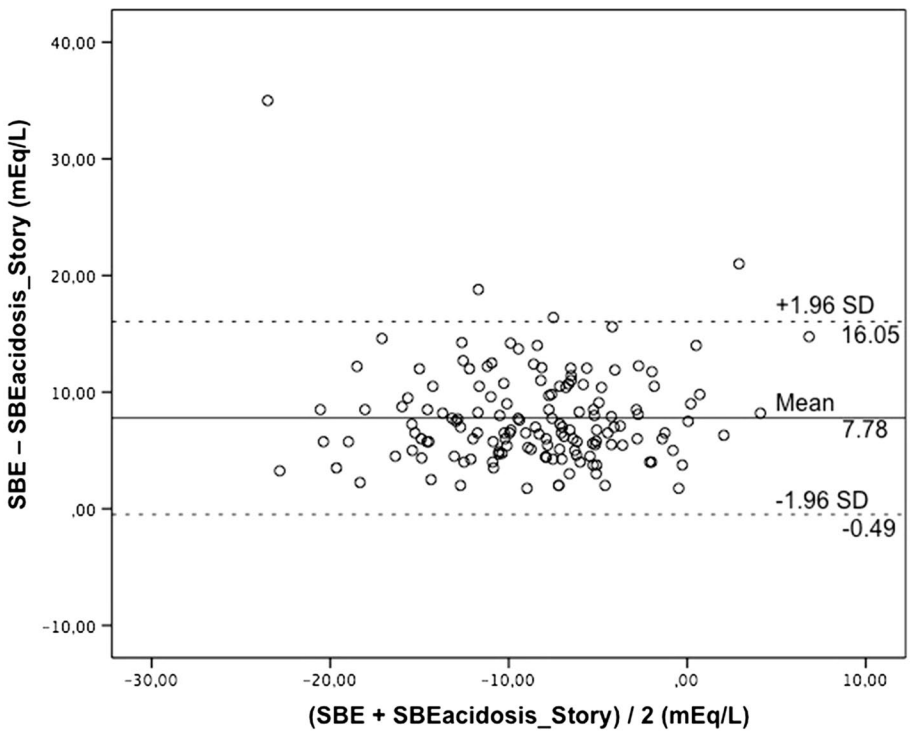

Fig. 1 Bland–Altman analysis for agreement between SBE and $SBE_{acidosis\_Story}$

relative hyperchloremia and unmeasured anions affecting 70% of the septic patients analyzed. In our study, the main etiology of metabolic acidosis at admission was an increase in unmeasured anions, with a decrease in this contribution within 24 h. Bruegger et al. had already demonstrated, in an experimental study, that there is a large amount of unmeasured anions generated from hemorrhagic shock [20]. Intermediate metabolites of the Krebs Cycle, particularly acetate and citrate, have been observed with unmeasured anions metabolic acidosis, suggesting mitochondrial dysfunction as an etiology [21]. Another potential source of unmeasured anions during hypoperfusion states is shedding of the endothelial glycocalyx rich in negatively charged heparan sulfate [22, 23]. All of these potential etiologies may explain the higher prevalence of unmeasured anions in our patients with shock. The lower prevalence of hyperchloremic acidosis in our study may be due to the preferential use of ringer lactate as a resuscitation fluid, instead of normal saline, in our institution.

This study has some limitations. First, this is a single-center study with a limited number of patients, which makes it difficult to generalize the results. Second, we did not use healthy volunteers to determine reference laboratory values. Third, the study design and sample size do not allow us to determine the clinical significance of our findings. However, we believe that identifying and quantifying disorders masked by other factors, which may possibly go unnoticed by some methods, is a potential first step towards having a clinical impact with the method chosen to address acid–base disorders, especially in critically ill patients. Finally, we just compared this new method with the traditional assessment. Other methods and different cutoff points can alter the results and should be evaluated in future studies.

We found that a modified Story method, applied to patients with shock, can identify metabolic acidosis in patients with disorders that are not revealed by the traditional approach. In addition, the method allows us to quantify the severity of the disturbance that was masked by other factors. Further studies should investigate the clinical significance of these advantages.

Author contributions MGP, LBB and MMB have made substantial contributions to the conception and design of the study and to acquisition of data; MGP and MMB performed the analysis and the interpretation of data; all authors read and approved the final manuscript.

Data availability The datasets used and/or analysed during the current study are available from the corresponding author on request.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This study protocol was consistent with the ethical principles of the Declaration of Helsinki and was previously approved by the Committee of Research Ethics of Hospital Nossa Senhora da Conceicao. Informed consent was waived.

References

1. Gunnerson KJ, Saul M, He S, Kellum JA. Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. Crit Care. 2006;10:R22.
2. Sirker AA, Rhodes A, Grounds RM, Bennett ED. Acid-base physiology: the "traditional" and the "modern" approaches. Anaesthesia. 2002. https://doi.org/10.1046/j.0003-2409.2001.02447.x.
3. Mallat J, Michel D, Salaun P, Thevenin D, Tronchon L. Defining metabolic acidosis in patients with septic shock using Stewart approach. Am J Emerg Med. 2012. https://doi.org/10.1016/j.ajem.2010.11.039.
4. Fencl V, Jabor A, Kazda A, Figge J. Diagnosis of metabolic acid-base disturbances in critically ill patients. Am J Respir Crit Care Med. 2000;162:2246–51.
5. Szrama J, Smuszkiewicz P. An acid-base disorders analysis with the use of the Stewart approach in patients with sepsis treated in an intensive care unit. Anestezjol Intensiv Ther. 2016. https://doi.org/10.5603/ait.a2016.0020.
6. Stewart PA. Modern quantitative acid–base chemistry. Can J Physiol Pharmacol. 1983. https://doi.org/10.1139/y83-207.
7. Figge J, Rossing TH, Fencl V. The role of serum proteins in acid-base equilibria. J Lab Clin Med. 1991;117:453–67.
8. Figge J, Mydosh T, Fencl V. Serum proteins and acid-base equilibria: a follow-up. J Lab Clin Med. 1992;120:713–9.
9. Story DA. Stewart acid-base. Anesth Analg. 2016. https://doi.org/10.1213/ane.0000000000001261.
10. Stevens PE, Levin A. Kidney disease: improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013;158:825–30.
11. Henderson LJ. The theory of neutrality regulation in the animal organism. Am J Physiol Leg Content. 1908. https://doi.org/10.1152/ajplegacy.1908.21.4.427.
12. Astrup F, Siggaard Andersen O, Jørgensen K, Engel K. The acid-base metabolism. Lancet. 1960. https://doi.org/10.1016/s0140-6736(60)90930-2.
13. Dubin A, Menises MM, Masevicius FD, Moseinco MC, Kutscherauer DO, Ventrice E, et al. Comparison of three different methods of evaluation of metabolic acid-base disorders. Crit Care Med. 2007. https://doi.org/10.1097/01.ccm.0000259536.11943.90.
14. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res. 1999. https://doi.org/10.1191/096228099673819272.
15. Boniatti MM, Cardoso PRC, Castilho RK, Vieira SRR. Acid-base disorders evaluation in critically ill patients: we can improve our diagnostic ability. Intensiv Care Med. 2009;35:1377–82.
16. Antonogiannaki E-M, Mitrouska I, Amargianitakis V, Georgopoulos D. Evaluation of acid-base status in patients admitted to ED—physicochemical vs traditional approaches. Am J Emerg Med. 2015. https://doi.org/10.1016/j.ajem.2014.12.010.
17. Morgan TJ, Anstey CM, Wolf MB. A head to head evaluation of 8 biochemical scanning tools for unmeasured ions. J Clin Monit Comput. 2017. https://doi.org/10.1007/s10877-016-9861-5.
18. Shen X, Ke L, Yang D, Sun J, Tong Z, Li B, et al. The prognostic value of the strong ion gap in acute pancreatitis. J Crit Care. 2016. https://doi.org/10.1016/j.jcrc.2016.06.035.
19. Noritomi DT, Soriano FG, Kellum JA, Cappi SB, Biselli PJC, Libório AB, et al. Metabolic acidosis in patients with severe sepsis and septic shock: a longitudinal quantitative study. Crit Care Med. 2009. https://doi.org/10.1097/ccm.0b013e3181a59165.
20. Bruegger D, Kemming GI, Jacob M, et al. Causes of metabolic acidosis in canine hemorrhagic shock: role of unmeasured ions. Crit Care. 2007;11:R130.
21. Forni LG, McKinnon W, Lord GA, Treacher DF, Peron JM, Hilton PJ. Circulating anions usually associated with the Krebs cycle in patients with metabolic acidosis. Crit Care. 2005;9:R591-595.
22. Annecke T, Rehm M, Bruegger D, et al. Ischemia-reperfusion-induced unmeasured anion generation and glycocalyx shedding: sevoflurane versus propofol anesthesia. J Investig Surg. 2012;25:162–8.
23. Chappell D, Jacob M, Becker BF, Hofmann-Kiefer K, Conzen P, Rehm M. Expedition glycocalyx. A newly discovered "Great Barrier Reef." Anaesthesist. 2008;57:959–69.