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ARTIGO ORIGINAL

Partitioning Evolutive Standard Base Excess Determinants in Septic Shock Patients*

Determinantes da Evolução do Standard Base Excess em Pacientes com Choque Séptico

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RESUMO

JUSTIFICATIVA E OBJETIVOS: A acidose metabólica diagnosticada pela mensuração do *standard base excess* (SBE) é indicadora de maior mortalidade e sua melhora temporal é associada à maior sobrevida em pacientes críticos. O objetivo deste estudo foi esclarecer o mecanismo de variação do SBE, em pacientes com choque séptico, durante os três primeiros dias de internação na unidade de terapia intensiva (UTI), através da avaliação físico-química do equilíbrio ácido básico.
MÉTODO: Os dados foram coletados de pacientes com choque séptico a partir de um banco de dados, prospectivamente, diariamente até o terceiro dia de internação na UTI. Correlações entre o SBE e outras variáveis físico-químicas independentes foram realizadas, assim como um modelo matemático multilinear foi desenhado para revelar os determinantes independentes da variação do SBE.
RESULTADOS: A variação do SBE em pacientes sépticos nos primeiros três dias de internação na UTI foi fracamente correlacionado ao *strong ion gap* (SIG), lactato, albumina, creatinina e $PaCO_2$ quando analisados individualmente. Quando analisados de forma concomitante, as variáveis albumina, *strong ion difference* (SIDa), SIG, $PaCO_2$ e diurese foram independentemente associados à variação do SBE com um coeficiente de determinação de 0,866.
CONCLUSÔES: A variação do SBE durante os três primeiros dias de internação na UTI foi resultante da interação de alguns fatores independentes como $PaCO_2$, diurese, SIG, SIDa e albumina
Unitermos: Acidose metabólica, choque séptico, lactato, monitorização, sepse grave

SUMMARY

BACKGROUND AND OBJECTIVES: The amount of metabolic acidosis measured through the standard base excess (SBE) has been shown to be an outcome marker and its improvement has been associated with better survival. We studied the mechanism of standard base excess variation in the first three days of intensive care unit (ICU) stay through the evaluation of independent variables of physico-chemical approach.
METHODS: Data were retrieved from our prospective collected data base from patients with diagnosis of septic shock, daily up to the third day after the ICU admission. Single correlations between SBE and independent variables were performed as well as a mathematical multilinear model was built to disclose the SBE variation determinants.
RESULTS: We have shown that in septic shock patients the standard base excess variation during the first three days of ICU stay is weakly correlated to strong ion gap (SIG), lactate, creatinin and $PaCO_2$ when individually analyzed. Analyzing concomitantly those independent variables, we built a mathematical model with a stepwise multilinear regression composed by apparent strong ion difference (SIDa), SIG, $PaCO_2$, albumin and diuresis that resulted in a R^2 coefficient of 0.866 to determine SBE variation.

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CONCLUSIONS: Variations of metabolic acidosis measured through the standard base excess in septic shock patients when analyzed until the third day after intensive care unit admission, is resultant of interaction of several independent determinants as $PaCO_2$, diuresis, SIG, SIDa and albumin.
Key Words: lactate, metabolic acidosis, monitorization, septic shock, severe sepsis

INTRODUCTION

Base excess is the quantity of metabolic acidosis or alkalosis, defined as the amount of acid or base that must be added to a sample of whole blood in vitro in order to restore the pH of the sample to 7.40 while the PCO_2 is held at 40 mmHg[1]. Currently the most commonly used methodology for acquire base excess is the Van Slyke equation which takes into account the bicarbonate serum level, hemoglobin and pH[2]. Base excess is quite accurate *in vitro*, although inaccuracy has always been a problem when Van Slyke is applied *in vivo*, where base excess changes slightly with changes in arterial carbon dioxide partial pressure ($PaCO_2$)[3]. Thus, the base excess equation has been modified to standardize the effect of hemoglobin in order to improve the accuracy of base excess *in vivo*[2]. The term standard base excess (SBE) has been given to this last described variable, which better quantifies the change in metabolic acid base status in multicompartment systems, highlighting the plasmatic compartment[2,3].

In 1981, Dr. Peter Stewart, a Canadian physiologist, proposed a novel physico-chemical theory of acid base balance based mainly on an explicit master fourth-order polynomial equation that relates the pH to three independent variables: 1. SID which is the difference of charge of all strong ions (cations – anions), 2. PCO_2 and 3. Atot which is the total concentration of weak acids, represented in the human physiology by albumin and phosphate[4,5]. This new theory has brought new light to the area of acid base disturbances of critically ill patients.

In critically ill subjects, the presence of metabolic acidosis is very common, particularly in septic shock patients[6]. The amount of metabolic acidosis measured through the SBE has been shown to be an outcome marker, when it is evaluated isolated on admission or during the first days after ICU admission[7]. Its improvement has been associated with better survival. However, so far it is not clear which are the factors associated with SBE variations in critically ill septic patients.

In this study, we splitted septic shock patients in two groups, one group of patients who improved SBE from the day of ICU admission to the third day of ICU stay, and one group who worsened SBE in the same period. The aim of this study was to characterize the acid-base variables, according to the Stewart's theory, responsible for SBE improvement and worsening within the first three days of ICU stay.

METHODS

Data were retrieved from our prospective collected data base of a tertiary teaching seven beds intensive care unit (ICU) in São Paulo – Brazil. The period investigated was from January 2004 to May 2004. Age, gender, APACHE II score, length of stay in ICU, clinical outcome, needing for mechanical ventilation, previous diagnosis of chronic renal failure, needing for dialysis, fluids handling, general laboratorial data and infection source were collected from patients with diagnosis of septic shock daily up to the third day after ICU admission. The diagnosis of septic shock was performed according to the consensus conference criteria[8].

Blood samples and fluids handling data were obtained at the end of each day. The arterial line was used to collect blood samples. Albumin, phosphate and serum Mg^{2+} were analyzed by colorimetric techniques, and other serum electrolytes were measured with an ion-selective electrode. Arterial blood gases and lactate were measured by the OMNI analyzer (Roche Diagnostics System, F. Hoffmann - La Roche Ltd, Basel, Switzerland) and to determine SBE value the Van Slyke method was used[2]. All standard formulas used to calculate physico-chemical variables are described in the appendix.

Data were considered normal using Shapiro-Wilk goodness-of-fit model, and are shown as means and standard deviation. Means between groups were compared using Student *t* test and categorical data were compared using Fisher or Chi-square analysis as indicated. Determinants of metabolic acidosis according to Stewart`s physico-chemical approach were independently correlated with variations SBE using Pearson's correlation and afterward a mathematical model was built to correlate SBE variations with the components of physico-chemical approach using a stepwise multilinear regression model. The commercially available SPSS 10.0 statistical package was used, considering $p < 0.05$ as a significant level.

RESULTS

During five months, thirty eight patients with septic shock treated according to the surviving sepsis campaign, were observed. General characteristics and infection sites of whole group are shown in table 1.

The SBE evolution was linear beyond the three first days in both groups (Figure 1 - Panel A). A slight variation around 35 mmol/L was the feature of SIDa behavior, and lactate also had a small variation. Unmeasured anions, disclosed by SIG, fall in the group who improved SBE and rise in the group who worsened SBE (Figure 1 - Panel B). Albumin levels fall in the group who worsened SBE, and initially fall in the first day rising in the second day in the group who improved SBE (Figure 1 - Panel C).

The SBE variation was individually correlated with lactate, $PaCO_2$, creatinin and SIG (Table 4). When a stepwise multilinear regression model with SBE as a dependent variable was built, the independent variables albumin, $PaCO_2$, SIDa, SIG and diuresis have composed an equation with the determination coefficient (R^2) of 0.866. Beta unstandardized coefficients of the multilinear regression model are shown in table 4. When analyzing the group of patients who SBE improved or worsened individually the results are similar.

Table 1 – General Characteristics at Admission and Infection Site of Patients

Characteristics	Whole Group (n = 38)	SBE Improved (n = 22)	SBE Worsened (n = 16)	P value*
Age (years)	50 ± 20	48 ± 22	50 ± 17	0.742
Gender - females (%)	17 (45)	10 (45)	7 (44)	0.821
APACHE II	23 ± 9	22 ± 9	24 ± 16	0.355
Death - no (%)	11 (30)	6 (27)	5 (31)	1.000
Mechanical ventilation - no (%)	31 (82)	17 (77)	14 (88)	0.675
Chronic renal failure - no (%)	8 (21)	5 (23)	3 (19)	1.000
Dialysis - no (%)	4 (11)	3 (14)	1 (6)	0.624
LOS (days)#	11 ± 7	11 ± 7	12 ± 8	0.743
Creatinin (mg/dL)	1.9 ± 2.2	2.0 ± 3.4	1.6 ± 1.85	0.692
pH	7.33 ± 0.09	7.32 ± 0.09	7.34 ± 0.09	0.432
$PaCO_2$ (mmHg)	32 ± 9	32 ± 9	33 ± 9	0.594
SBE (mEq/L)	-7.5 ± 5.40	-8.7 ± 5.2	-5.8 ± 5.4	0.109
Lactate (mmol/L)	2.3 ± 1.7	2.4 ± 2.1	2.1 ± 1.2	0.577
Albumin (mg/dL)	21.7 ± 6.7	21.2 ± 6.7	22.3 ± 6.8	0.613
Phosphate (mmol/L)	0.70 ± 0.29	0.67 ± 0.27	0.74 ± 0.32	0.226
Hemoglobin	9.0 ± 1.8	9.2 ± 1.8	8.8 ± 1.9	0.343
$PaCO_2$ (mmHg)	32 ± 9	31 ± 9	33 ± 9	0.324
CRP (ng/dL)‖	179 ± 113	174 ± 99	189 ± 138	0.681
SIDa (mmol/L)	35.0 ± 6.7	34.8 ± 6.2	34.9 ± 7.6	0.941
SIG (mmol/L)	11.0 ± 7.5	11.8 ± 7.2	9.9 ± 8.1	0.463
Chloride (mmol/L)	106 ± 17.3	104 ± 6.8	108 ± 6.3	0.758
Infection Site				
Pneumonia - no (%)	21 (55)	12 (55)	9 (57)	0.821
Peritonitis - no (%)	6 (16)	3 (12)	3 (19)	0.682
Urinary – no (%)	3 (8)	2 (9)	1 (6)	1.000
Mediastinitis - no (%)	1 (3)	1 (5)	0 (0)	1.000
Fungemia - no (%)	2 (5)	1 (5)	1 (6)	1.000
Soft tissue - no (%)	3 (8)	2 (9)	1 (6)	1.000
Catheter - no (%)	2 (5)	1 (5)	1 (6)	1.000

no denotes number of patients.
*P value denotes the significance of comparisons between SBE worsened and SBE improved groups.
LOS denotes lenght of stay.
‖ CRP denotes c-reactive protein.

Table 2 – Fluids Handling During the First Three Days

Characteristics	Whole Group (n = 38)	SBE Improved (n = 22)	SBE Worsened (n = 16)	P value*
Day 1				
Diuresis (mL)	1312 ± 1462	1402 ± 1450	1445 ± 1842	0.950
Hydric balance (mL)	3822 ± 4542	2880 ± 2570	5313 ± 5899	0.201
Fluid intake (mL)	5134 ± 4482	4281± 2907	6597 ± 6390	0.290
Day 2				
Diuresis (mL)	1608 ± 1639	1792 ± 2097	1437 ± 1129	0.599
Hydric balance (mL)	4565 ± 4171	4306 ± 4573	4804 ± 3937	0.773
Fluid intake (mL)	6172 ± 3912	6098 ± 3921	6240 ± 4026	0.930
Day 3				
Diuresis (mL)	1852 ± 1884	2192 ± 2241	1585 ± 1584	0.435
Hydric balance (mL)	1761 ± 3192	645 ± 3242	2639 ± 2974	0.123
Fluid intake (mL)	3613 ± 2506	2836 ± 1785	4224 ± 2869	0.174
First 3 days				
Diuresis (mL)	1630 ± 1664	1784 ± 1920	1491 ± 1509	0.433
Hydric balance (mL)	3505 ± 4092	2666 ± 3779	4212 ± 4454	0.244
Fluid intake (mL)	5084 ± 3765	4450 ± 3249	5703 ± 4274	0.142

no denotes number of patients.
* P value denotes the significance of comparisons between SBE worsened and SBE improved groups.

Table 3 – Vasopressors and Inotropics Used

Characteristics	Whole Group (n = 38)	SBE Improved (n = 22)	SBE Worsened (n = 16)	P value*
Norepinephrine – no (%)	38 (100)	22 (100)	16 (100)	
Mean maximal dosis (µg/kg/min)	0.81 ± 1.68	0.96 ± 1.89	0.69 ± 1.35	0.270
Dobutamine – no (%)	33 (87)	19 (86)	14 (88)	0.831
Mean maximal dosis (µg/kg/min)	13.7 ± 6.1	13.1 ± 5.9	14.1 ± 6.2	0.617

no denotes number of patients.
*P value denotes the significance of comparisons between SBE worsened and SBE improved groups.

Table 4 – Linear and Multilinear Correlation between SBE and Metabolic Acidosis Determinant Variables

	Single Correlation		Stepwise Multilinear Regression *	
Variables	Pearson Coefficient	P value	Beta Unstandardized Coefficient	P value
Lactate	-0.211	0.024	-	-
Albumin	-0.059	0.534	-34.5	< 0.001
Phosphate	-0.226	0.016	-	-
$PaCO_2$	0.364	<0.001	-0.2	< 0.001
Creatinin	-0.346	<0.001	-	-
Hemoglobin	0.064	0.524	-	-
SIDa	-0.124	0.187	1.2	< 0.001
SIG	-0.368	< 0.001	-1.2	< 0.001
Diuresis#	0.044	0.711	0.03	0.014
C-reactive protein	-0.242	0.105	-	-
Hydric balance#	-0.101	0.390	-	-
Fluids received#	-0.090	0.441	-	-

*The final model with five variables resulted in a determination coefficient (R^2) of 0.866. The inclusion criteria of the model was an F probability of 0.05 and exclusion criteria was an F probability of 0.1. C-reactive protein was not included in the initial multilinear model due to a high collinearity with albumin (Pearson coefficient of 0.550).
#Numbers respective to each day.

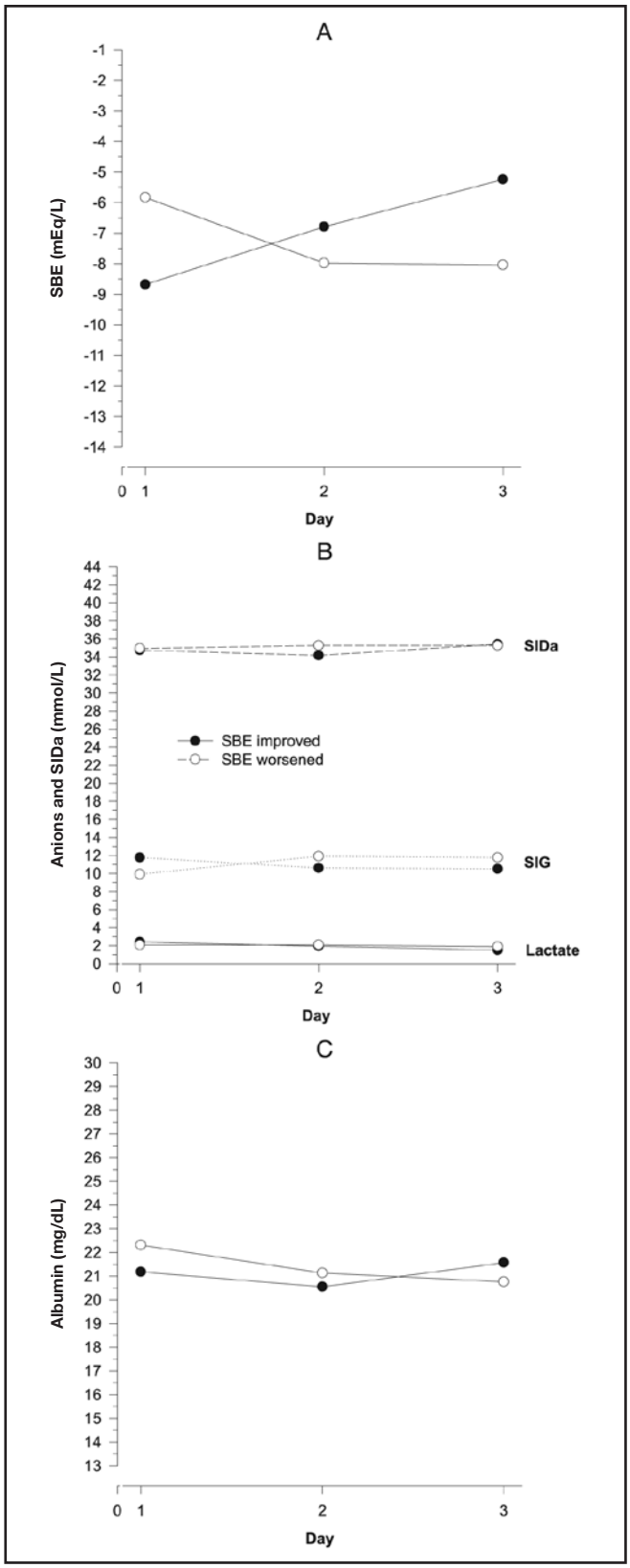

Figure 1 – Panel A shows the Evolution of SBE during the Three First Days. Panel B shows the Evolution of SIDa, SIG and Lactate. Panel C shows the Evolution of Albumin.

DISCUSSION

In our study, we have shown that in septic shock patients the SBE variation during the first three days of ICU stay is weakly correlated to SIG, lactate, creatinin and $PaCO_2$ when individually analyzed. Analyzing concomitantly those independent variables, we built a mathematical model with a stepwise multilinear regression composed by SIDa, SIG, $PaCO_2$, albumin and diuresis that resulted in a R^2 coefficient of 0.866 to determine SBE variations.

Since the description of base excess in 1960[1], it has been largely used in the clinical practice to disclose and measure metabolic acidosis[3,4,9]. However, base excess or its clinical derivation SBE are limited to detect true metabolic acidosis in adult critically ill patients and in pediatric cardiac postoperative[10,11]. This limitation has been ascribed to hypoalbuminemia, which can cause metabolic alkalosis hiding or attenuating any kind of installed metabolic acidosis[11]. In spite of the apparent limited information's given by the SBE, low values of SBE at the admission to ICU has been associated with poor outcome[12-15], and in the same way the improvement of SBE by the third day after the ICU admission has been independently correlated with better prognosis[7]. In the hemodynamic early goal directed therapy study performed by Rivers et al.[16] to severe sepsis and septic shock patients, the interventional group improved SBE close to normal values by the third day, starting from very low initial values. Those characteristics turn SBE an important clinical physiological tool to be used in the modern ICU.

It is interesting to note that among our patients there were not admission characteristics that have identified the subjects who could improve or worse SBE until the third day. The amount and quality of fluids used in resuscitation of shock can, theoretically, be related to acid base state modifications[3,9]. In our study, the amount of fluids used in both groups were similar (Table 2) and the standard fluid used was ringer lactate, in this way, the great acid base derangements expected using crystalloids would be SIDa variations, by contrast, our finding point out to SIG as a correlate with SBE in the univariate analysis (Table 4). SIG actually quantify unmeasured anions[3,5], and it can be raised by colloids[3], which were not used in our patients. Other possible sources of SIG acidosis in septic shock patients are: 1. mitochondrial dysfunction, which can be secondary to oxygen deprivation[17] or inflammatory mediators[18], and 2. renal dysfunction by reducing clearance of non volatile

acids[19]. Currently, there are some investigations about the unmeasuble anions components of SIG acidosis, and some metabolic intermediates of Krebs` cycle as isocitrate, α-ketoglutarate and malate has been associated with SIG acidosis[20], although, the definitive list of endogenous anions that can cause metabolic SIG acidosis in sepsis and shock states is far from complete[21]. There are some evidences that SIG acidosis is correlated with outcome[13,14], and it is additive with prognostic information of serum lactate level[12].

Serum lactate level is a well known cause of metabolic acidosis in critically ill patients[22], but its clinical and physiological importance has been shared with other unmeasured anions[12,14]. It has been associated with oxygen deprivation, inflammation and hepatic dysfunction[22]. Our correlation finding between SBE and lactate is physiologically rational (Table 4)[9], and the lactate exclusion of the final stepwise regression model can be explained by the fact that the unmeasured anions calculated by SIG physiologically behave quite similar to lactate[17,20], likewise, in the mathematical model the inclusion of lactate could not be of great importance in the modification of F probability statistics, and this fact is an acquard reflection of clinical association among SIG, SBE and lactate[12,14,20].

Creatinin was other finding associated with SBE variation. Low renal clearance is associated with increments in SIG[19], but in our patients it is hard to affirm that SIG acidosis has been caused by low renal clearance or SIG acidosis has been epiphenomena which has resulted from the critical illness and multiorgan dysfunction[18,23]. Diuresis is an immediate reflection of renal clearance and can disclose renal impairment earlier than creatinin elevations[24]. Otherwise, few patients can present oliguria without elevations of creatinin, but acidosis will be present only if renal failure is present[19]. In this way, we can understand why diuresis was associated with SBE variations only in the mathematical multilinear model[25].

Partial pressure of carbon dioxide was positively associated with SBE variations as expected by the mathematical calculus using the Van Slyke equation, where bicarbonate concentration is one of the independent variables besides pH[2]. Thus, from the stoichiometric point of view, one can expect that rising $PaCO_2$ the bicarbonate and then SBE will also rise[1]. Otherwise, in our multilinear mathematical model, an interesting finding was the negative correlation of $PaCO_2$ and SBE variations, contrasting with the single correlation. This finding can represent the clinical status of patients, where higher the severity of the disease, higher the probability to be on mechanical ventilation, reflecting in low SBE due to the severity of disease and $PaCO_2$ dependent of mechanical ventilation strategy. In this way, we would like to stress that fourteen patients (37%) accomplished acute respiratory distress syndrome (ARDS) criteria of consensus conference[26], and in our patients the open lung approach with permissive hypercapnia has been used to ventilate ARDS patients[27]. The advantage of the mathematical stepwise multilinear regression in this case was the representation of SBE as a multicomponent tool, reproducing the complex clinical acid base environment[25].

Albumin and phosphate have been considered as the main weak acids in organic systems that are responsible for acid base modulation[10,28-30]. Hypoalbuminemia is a frequent finding in critically ill patients and also in our patients (Table 1, Figure 2), being an important source of metabolic alkalosis and pH and SBE neutralization in this setting as we can observe in table 4, in the mathematical model[11].

Funk et al.[31] studied the acid base behavior in a general ICU population, showing chloride and SIDa as the main determinants of acid base behavior. By contrast, in septic shock patients, according to our findings the acidosis variation measured by the SBE results from a complex situation, and SIDa was important only in the mathematical multilinear model when analyzed together with other components associated with metabolic acidosis.

We would like to stress that the physico-chemical approach is not superior to the traditional approach at bedside to diagnose acid-base derangements[32]. However, this methodology allows the quantification of respiratory and / or metabolic shifts to statistical measurement. In this way, we have used the physico-chemical approach in our study.

In conclusion, variations of metabolic acidosis measured through the SBE in septic shock patients when analyzed until the third day after ICU admission, is resultant of interaction of several independent determinants as $PaCO_2$, diuresis, SIG, SIDa and albumin.

APPENDIX – STANDARD FORMULAS

1. Standard base excess (Van Slyke`s equation) (SBE_{VS}) (mEq/L) = $0.9287 \times (HCO_3 - 24.4 + 14.83 \times [pH - 7.4])$
2. Apparent strong ion difference (SID_a) (mEq/L) = $Na^+ + K^+ + Ca^{2+} + Mg^{2+} - Cl^-$ - Lactate
3. Effective strong ion difference (SID_e) (mEq/L) = 2.46

$\times 10^{-8} \times PCO_2/10^{-pH}$ + [albumin (g/dL)] × (0.123 × pH – 0.631) + [phosphate (mg/dL)/3 × (pH – 0.469)]

4. SIG (mEq/L) = SIDa – SIDa

5. Albumin (mEq/L) = 10 x Albumin (g/dL) x (0.123 x pH – 0.631)

6. Inorganic phosphate (Pi)(mEq/L) = (PO_4(mg/dL) x 10/30,97) x (0.309 x pH - 0.469)

7. The unit of all strong ions was mEq/L

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