ORIGINAL RESEARCH PAPER

Volume-8 | Issue-4 | April-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

PLASMA LACTATE AND BASE EXCESS LEVELS AS PREDICTORS OF OUTCOME IN PATIENTS WITH SEPSIS AND SEPTIC SHOCK ADMITTED IN PEDIATRIC INTENSIVE CARE UNIT – A PROSPECTIVE OBSERVATIONAL STUDY AND AN INSTITUTIONAL EXPERIENCE FOR A TERTIARY CARE CHILDREN'S HOSPITAL IN THE PRIVATE SECTOR.

Paediatrics

Dr. Malavika B. G. DNB Resident Pediatrics, Lotus Children's Hospital, Lakdikapul - 500004 Hyderabad, Telangana, India.

Dr. VSV Prasad Chief Pediatric Intensivist and Consultant Neonatologist, Lotus Children's Hospital, Lakdikapul - 500004 Hyderabad, Telangana, India.

Dr. Pushpendra N Renjen* Sr. Consultant Neurologist & Academic Coordinator, Institute of Neurosciences, Indraprastha Apollo Hospitals *Corresponding Author

Dr. Abhas Kumar DNB Neurology, Institute of Neurosciences, Indraprastha Apollo Hospitals – 110076

Dr. Anjali Mishra FNB Critical Care, Max Super Specialty Hospital, New Delhi

Dr. Dinesh Chaudhari Associate Consultant, Institute of Neurosciences, Indraprastha Apollo Hospitals – 110076

ABSTRACT

Severe sepsis and septic shock are the major causes of morbidity and mortality in the PICU, killing at least one in four. In order to monitor the metabolic consequences of shock and hemodynamic management, plasma lactate levels and standard base excess are being used in critical illness.

Goal: To determine plasma lactate and base excess levels in sepsis and septic shock patients at the time of admission to the PICU; if they are accurate predictors of morbidity and mortality; and if there is a substantive correlation between the two.

Methodology: Conducted at the PICU of Hyderabad's Lotus Children's Hospital, the study population was restricted to children between the ages of 1 month and 18 years with the sample size being 100. To determine plasma lactate and base excess levels, venous blood was collected at the time of admission.

Results: The mean lactate levels among the non survivors were significantly higher (mean: 52.45 +38.81 mg/dl) than the mean lactate levels among the survivors (mean: 21.86+ 8.25 mg/dl) and $p < 0.01$. There was also a significant correlation between elevated plasma lactate and days of hospital stay and ICU stay ($p < 0.01$).The mean venous base excess levels were more negative i.e., lesser among non survivors (mean: -16.86 + 8.25 meq/l) compared to survivors (mean: -9.91 + 5.62 meq/l) and $p < 0.01$. However, there was no statistically significant correlation between venous base excess levels and number of days of hospital stay ($p= 0.025$) and ICU stay ($p = 0.15$). Furthermore, there was an inverse correlation between plasma lactate and base excess levels with an increased morbidity and mortality rate with increasing trend in lactate or corresponding decreasing (more negative) base excess levels ($p < 0.01$).

Conclusion: Hyperlactatemia and decreased venous base excess levels are significant predictors of outcome in critically ill children at presentation with initial plasma lactate being a better predictor in comparison to initial base excess levels.

KEYWORDS

Plasma lactate, Base excess levels, Septic shock, Sepsis, PICU

INTRODUCTION:

Severe sepsis and septic shock are the major causes of admission and deaths in the ICU, killing one in four (and often more) and increasing in incidence [1]. Approximately 60% of these cases are first diagnosed and treated in the ED [2,3]. In order to improve the clinical outcomes in these patients, it is crucial to obtain early recognition of patients who are at risk of death and to optimize the clinical decision making in a timely manner[4-6]. Although early identification and prompt antibiotic administration are essential, successful hemodynamic resuscitation and continued monitoring are key components of the management of sepsis in the ED. The primary goal of hemodynamic monitoring in sepsis is to ensure adequate tissue perfusion pressure and oxygen delivery. Impaired tissue oxygen delivery can rapidly lead to cardiovascular instability, multi-organ dysfunction and death. Unfortunately, traditional methods of monitoring such as noninvasive blood pressure, pulse rate, pulse oximetry and urine output, are insensitive and unreliable markers of ongoing tissue hypo perfusion and hypoxia. It is well documented that microvascular flow alterations and organ hypoxia can exist despite normalization of vital signs [7,8]. In order to monitor the metabolic consequences of shock and hemodynamic management, plasma lactate levels and standard base excess (SBE) can be used in critical illness.

Lactate measurement in critically ill patients is practical and can provide information on illness severity and prognosis, because a high lactate level is most frequently, but not always, interpreted as resulting from anaerobic metabolism related to cellular hypoxia and is thought to be an important marker of impaired tissue perfusion in patients with sepsis particularly when associated with metabolic acidosis [9, 10]. For this reason, current guidelines on the ED management of sepsis recommend measuring and monitoring serum markers of tissue ischemia [11].

The present study aims to check whether plasma lactate levels and venous base excess levels at admission to PICU show any correlation with mortality and morbidity in critically ill patients and the levels which best correlate with mortality and which could be used prospectively to identify patients who are likely to develop multi-organ failure.

MATERIAL AND METHODS

Study area: State of Art 16 bedded PICU of a Tertiary care referral hospital at Hyderabad – Lotus Children's Hospital. This was a prospective observational study conducted in PICU. Maximum number of patients admitted in our PICU had sepsis and septic shock. The profile of these patients was variable with variable outcomes. Measuring admission blood lactate and base excess levels is a routine practice at our PICU. The correlation of initial lactate and base excess levels in these patients with respect to their outcome is not well documented in literature. For this reason, we enrolled these patients and followed up them till discharge or death. The parameters like need for inotropes, ventilator requirement, number of days of ICU stay and the final outcome in terms of survival or death were recorded. These parameters were compared with initial lactate and base excess levels with respect to outcome.

Study population: Children with age of 1 month to 18 years admitted to the PICU with sepsis and septic shock based on the criteria of International Consensus definitions of Pediatric sepsis.

Sample size and Sample technique: The sample size has been determined taking margin of error (confidence interval) of +/- 5%, confidence level of 95% with corresponding Z score of 1.96 and prevalence of 0.075.

Sample size has been calculated using the formula:

$(\text{Z score})^2 \times \text{prevalence} (1 - \text{prevalence}) / (\text{margin of error})^2$

$= 1.96 \times 1.96 \times 0.075 \times (1 - 0.075) / 0.05 \times 0.05$
$= 106.60$ (approx 100)
Hence a sample size of 100 was taken in the present study.

Data collection technique and tools: All patients with sepsis and septic shock had their blood samples collected for lactate and blood gas at the time of admission to the PICU.

Method of collection: To determine plasma lactate, venous blood was collected at the time of admission in green top vacutainer with heparin as anticoagulant and the sample was processed by the GenX Lactate kit using STAT FAX 3300 semi auto analyzer within 30 minutes of sample collection.

To determine base excess levels, venous blood was collected at the time of admission in a heparinized 1 cc nipro syringe anaerobically and sample was processed by ABL 800 Blood gas analyzer within 30 minutes of sample collection and venous base excess levels were determined.

Data analysis: Data were statistically described in terms of mean (±SD), frequencies (number of cases) and percentages when appropriate. Data were tested first for normal distribution by Klomogorov – Smirnov test. Comparison of quantitative variables between the study groups was done using Student t test for independent samples if normally distributed. Mann–Whitney U test was used for non-normally distributed quantitative data. For comparing categorical data, Chi square test was performed. Exact test was used instead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. ROC curves were made to find the efficacy of Plasma lactate and Base excess levels as screening tests for predicting outcome. Binary logistic regression analysis was also performed to find the significant predictors of outcome by taking outcome as dependent variable and Plasma lactate and Base excess levels as Independent variables.

All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 17.

RESULTS:

In the present study, the mortality rate was 56 % (Figure 1). The mean lactate levels among the non survivors were significantly higher (mean: 52.45 $\pm$ 38.81 mg/dl) than the mean lactate levels among the survivors (mean: 21.86 $\pm$ 8.25 mg/dl) and $p < 0.01$. Correlation between plasma lactate and morbidity indicators showed that the mean lactate levels in the patients requiring inotropic support were significantly higher (mean: 42.60 $\pm$ 34.39 mg/dl) than the patients who did not require inotropic support (mean: 16.79 $\pm$ 4.40 mg/dl) (Figure 2). Similarly lactate levels were significantly higher in the patients requiring mechanical ventilation (mean: 42.77 $\pm$ 34.80 mg/dl) compared to those who did not require ventilatory support (mean: 19.16 $\pm$ 7.31 mg/dl) and $p < 0.01$ (Figure 3). There was also a significant correlation between elevated plasma lactate and days of hospital stay and ICU stay ($p < 0.01$) (Figure 4). For a minimum cut off value of plasma lactate of **15 mg/dl**, the sensitivity was 94.6 % and specificity was 27.3 % with a positive predictive value of 62.4 % and negative predictive value of 80% for outcome i.e., death.

The mean venous base excess levels were more negative i.e., lesser among non survivors (mean: -16.86 $\pm$ 8.25 meq/l) compared to survivors (mean: -9.91 $\pm$ 5.62 meq/l) and $p < 0.01$. The mean base excess levels in the patients requiring inotropic support (mean: -15.14 $\pm$ 7.80 meq/l) were significantly lesser i.e., more negative implying elevated base deficit than the patients who did not require inotropic support (mean: -5.61 $\pm$ 1.58 meq/l) (Figure 2). Similarly, base excess levels were significantly higher in the patients requiring mechanical ventilation (mean: -15.31 $\pm$ 7.65 meq/l) compared to those who did not require ventilator support (mean: -5.88 $\pm$ 3.96 meq/l) and $p < 0.01$ ((Figure 3). However, there was no statistically significant correlation between venous base excess levels and number of days of hospital stay ($p = 0.025$) and ICU stay ($p = 0.15$) (Figure 5). For a minimum cut off value of venous base excess level of **- 8 meq/l**, the sensitivity was 45.5 % and specificity was 91.1% with a positive predictive value of 68% and negative predictive value of 80% for outcome i.e., death. Further there was an inverse correlation between plasma lactate and base excess levels i.e., higher the plasma lactate levels, more negative or lesser the base excess levels (Figure 6). There was an increased morbidity and mortality rate with increasing trend in lactate or corresponding decreasing (more negative) base excess levels ($p < 0.01$) (Figure 7).

DISCUSSION:

The first hours following the diagnosis of severe sepsis and septic shock are known as the "golden hours". In this period, aggressive hemodynamic resuscitation is related to higher survival rates and reduced organ dysfunctions[12]. The match between oxygen delivery/consumption is the rationale for this phenomena[13,14]. After the "golden hours", the aggressive hemodynamic resuscitation is no longer efficient in restoring organ function or in decreasing mortality. It may be surmised that following this initial period, irreversible endothelial and organ cellular dysfunctions sets in and consequently the benefits of aggressive hemodynamic resuscitation are lost[15,16]. Hyperlactatemia in critically ill-patients may reflect the imbalance between local or systemic oxygen supply and oxygen consumption[17].

Previous studies which had similar results as described above include a study by Pasha et al[18] who concluded that non-survivors ($n = 32$, 25%) had significantly higher lactate levels than survivors at the time of admission (137.5 mg/dl vs. 37.7 mg/dl). Fatal outcome rate was significantly higher in patients with lactate levels 100 mg/dl or higher when compared with lactate levels below 100 mg/dl. Young A Kim et al[19], in their study concluded that the initial lactate levels presented significant differences between survivors and non-survivors, and the patients with an initial lactate level ≥ 5 mmol/l (45 mg/dl) showed higher mortality, which is similar to the results of the present study. Shapiro et al[20] demonstrated a 27% mortality rate for septic patients with a lactate value > 4 mmol/L (36 mg/dl) compared with < 5% for septic patients with lactate values < 2.5 mmol/L (22.5 mg/dl). Broder & Weil[21] noted that only 11% of those with serum lactate level greater than 36 mg/dl survived. Varpula et al[22] analyzed hemodynamic parameters in septic shock patients and concluded that initial lactate concentrations were higher in non survivors compared to survivors [3.4 vs. 2.1 mmol/l (30.6 vs. 18.9 mg/dl) respectively, $p < 0.005$].

These observations suggest that a single serum lactate measurement provides useful information in patients with severe sepsis and support the notion that an initial serum lactate measurement could potentially be used to inform medical decision making to improve patient outcomes.

Studies with similar results related to base deficit were those of Palma et al[23] who concluded that any improvement of SBE in severe sepsis and septic shock patients on the third day of ICU stay was a strong predictor of better outcome. Rivers et al[24] concluded that a faster decrement of base deficit in the early goal-directed therapy group in relation to the control group was observed, with normal base deficit values being achieved by the third day. In a study by Park et al[25] who studied the evolution of SBE in patients with sepsis and septic shock resuscitated by EGDT concluded that a faster improvement of SBE occurred in the survivor group and the non survivor group had a worsening of SBE on the second day with a subsequent slow recovery.
In the present study, there is an inverse correlation between plasma lactate and base excess levels i.e., higher the plasma lactate levels, more negative or lesser the base excess levels. There was an increased morbidity and mortality rate with increasing trend in lactate or corresponding decreasing (more negative) base excess levels ($p < 0.01$). The Receiver Operating Characteristic curves indicated a strong predictive power for the initial lactate value (AUC = 0.821), which demonstrated a larger AUC in comparison with the AUC of the initial venous base excess level (0.742). Using multivariate logistic regression analysis, the initial lactate level was a better predictor of outcome – both morbidity and mortality ($p < 0.01$) when compared to the initial base excess levels ($p = 0.633$).

These results indicate that the initial lactate may be useful in the early recognition of patients with a high risk of mortality resulting from septic shock. Hence aggressive management is needed in order to reduce the lactate concentration and to prevent long-lasting hyperlactatemia during the early period of septic shock. The limitations of our study are the number of patients analyzed and the various diagnoses, making the sample heterogeneous. Only the initial plasma lactate levels and base excess were measured. Various studies as cited above emphasize that early lactate clearance has a better chance of survival with decreased morbidity as well. Therefore, serial monitoring of lactate levels and correction of the base deficit following resuscitation forms an important part of monitoring the patient in ICU.

CONCLUSIONS:

The plasma lactate and base excess levels were significant predictors of mortality with a statistically significant difference between their levels among survivors and non survivors with plasma lactate being a better mortality indicator compared to venous base excess levels. The plasma lactate was a better predictor of morbidity with statistically significant correlation between lactate and the morbidity indicators compared to venous base excess levels. Patients with plasma lactate > 15 mg/dl and base excess < -8 meq/l have higher chances of death. We conclude that hyperlactatemia (plasma lactate > 15 mg/dl) and venous base excess levels (< - 8 meq/l) are predictors of outcome in critically ill children at presentation with initial plasma lactate being a better predictor comparison with initial base excess levels.

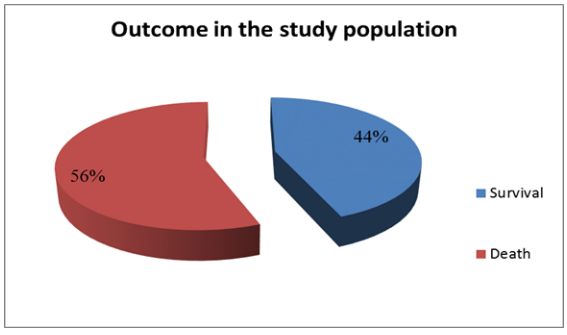

Figure 1. Outcome in the study population.

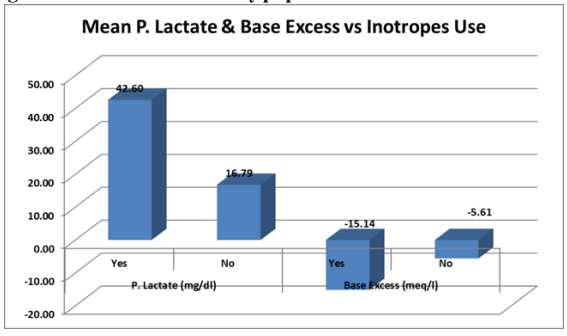

Figure 2. Mean Plasma lactate and Base Excess level in patients with or without ionotropic support.

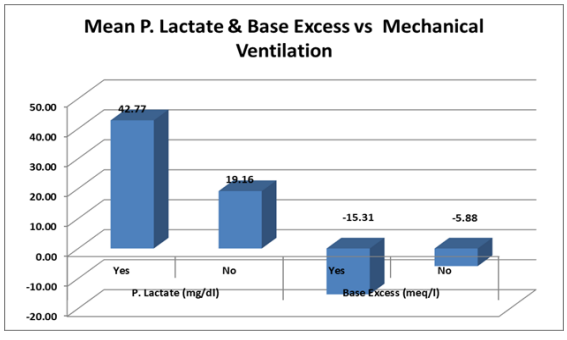

Figure 3. Mean Plasma lactate and Base Excess level in patients with or without ventilator support.

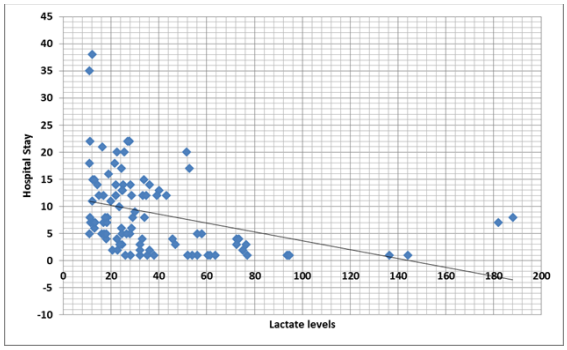

Figure 4. Scatter plot showing correlation of Plasma Lactate with number of days of hospital stay.

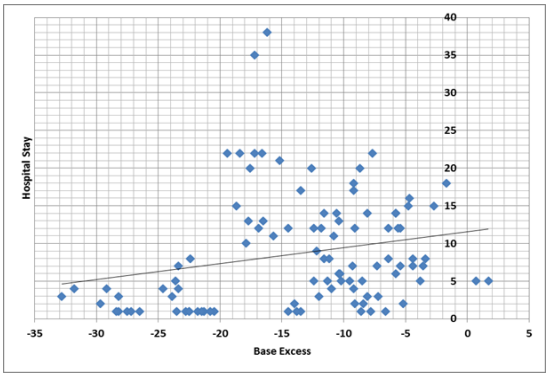

Figure 5. Scatter plot showing correlation of Base Excess with number of days of hospital stay.

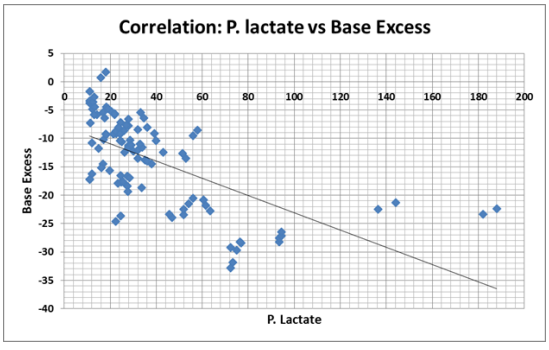

Figure 6. Scatter plot showing correlation between Plasma Lactate and Base Excess levels in patents.

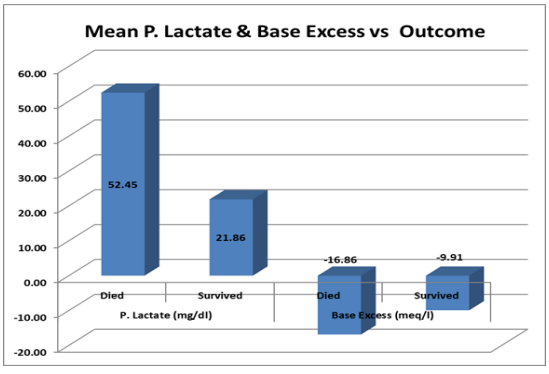

Figure 7. Mean Plasma Lactate and Base Excess with the outcome

REFERENCES:

1) Delinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004; 32: 858-73.
2) Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001; 29: 1303-1310.
3) McCaig LF, Nawar EW. National Hospital Ambulatory Medical Care Survey: 2004 emergency department summary. Adv Data. 2006: 1-29.
4) Carcillo JA, Fields AI (2002) Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. Crit Care Med 30:1365–1378.
5) Brierley J, Carcillo JA, Zimmerman J, Zuckerberg A et al (2009) Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American college of critical care medicine. Crit Care Med 37:666–688.
6) Dellinger RP, Levy MM, Carlet JM, Vincent JL (2008) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 36:296–327.
7) De Backer D, Creteur J, Dubois MJ, et al., The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects. Crit Care Med. 2006; 34:403-408.
8) Englehart MS, Schreiber MA. Measurement of acid-base resuscitation endpoints: lactate, base deficit, bicarbonate or what? Curr Opin Crit Care. 2006; 12:569- 574.
9) Howell MD, Donnino M, Clardy P, Talmor D, Shapiro NI (2007) Occult hypoperfusion and mortality in patients with suspected infection. Intensive Care Med 33:1892–1899.
10) Handy J. Lactate – The bad boy of metabolism, or simply misunderstood? Curr Anaesth Crit Care 2006; 17:71-6.
11) Nguyen HB, Rivers EP, Abrahamian FM, et al. Severe sepsis and septic shock: review of the literature and emergency department management guidelines. Ann Emerg Med. 2006; 48:28-54.
12) Husain FA, Martin MJ, Mullenix PS, Steele SR, Elliott DC. Serum lactate and base deficit as predictors of mortality and morbidity. Am J Surg 2003; 185:485- 91.
13) Kern JW, Shoemaker WC. Meta-analysis of hemodynamic optimization in high-risk patients. Crit Care Med. 2002;30:1686-92

14) Singer M, De S, V, Vitale D, Jeffcoate W. Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. Lancet. 2004; 364:545-8.
15) Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. N Engl J Med. 1995; 333:1025-32.
16) Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002; 360:219-23.
17) Van Beest PA, Brander L, Jansen SP, Rommes JH, Kuiper MA, Spronk PE. Cumulative lactate and hospital mortality in ICU patients. Ann Intensive Care 2013; 3:6.
18) Jat KR, Jhamb U, Gupta VK (2011) Serum lactate levels as the predictor of outcome in pediatric septic shock. Indian J Crit Care Med 15:102–107
19) Kim YA, Ha EJ, Jhang WK, Park SJ. Intensive Care Med. 2013 Oct; 39(10):1818-23.
20) Park M, Azevedo LC, Maciel AT, Pizzo VR, Noritomi DT, da Cruz Neto LM. Evolutive standard base excess and serum lactate level in severe sepsis and septic shock patients resuscitated with early goal-directed therapy: Still outcome markers? Clinics (Sao Paulo) 2006; 61:47-52.
21) Meregalli A, Oliveira RP, Friedman G. Occult hypoperfusion is associated with increase mortality in hemodynamically stable, high-risk, surgical patients. Critical Care. 2004; 8:R60-64.
22) Varpula M, Tallgren M, Saukkonen K, Voipio-Pulkki LM, Pettila V: Hemodynamic variables related to outcome in septic shock. Intensive Care Med 2005, 31 (8):1066-1071.
23) Palma LC, Ferreira GF, Amaral ACKB et al - Acidosis and mortality in severe sepsis and septic shock evaluated by base excess variation. Crit Care, 2003; 7 (Suppl3):P39.
24) Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001, 345(19):1368-1377.
25) Shapiro N, Howell MD, Talmor D, et al. Serum lactate as a predictor of mortality in emergency medicine patients with infection. Ann Emerg Med. 2005; 45:524-528.