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Is Serum Lactate Level a Prognostic Factor for the Incidence and Mortality of Ventilator-Associated Pneumonia Among Poisoned ICU-Admitted Patients?

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Abstract

Background: Lactate level is known to increase among the majority of patients with toxicity. This study aimed to determine whether lactate level upon admission is higher among patients with ventilator-associated pneumonia (VAP).
Objectives: We aimed to determine whether serum lactate level is associated with the increased risk of VAP in intensive care unit (ICU)-admitted patients with toxicity.
Methods: This retrospective study was conducted in a training medical poisoning center in Iran, using convenience sampling. A total of 157 poisoned patients, aged $\geq$ 13 years, who were admitted to the ICU over the past seven months, were included in the study. Subjects were categorized into two groups, based on their VAP diagnosis (VAP-positive and non-VAP) and the outcomes (surviving or non-surviving). The VAP-positive patients were compared with others with regard to the mean level of serum lactate level upon admission. Additionally, non-surviving patients were compared with their surviving counterparts.
Results: Overall, 71 (45.2 %) VAS-positive cases were reported, in addition to 36 cases of mortality. Alkaline phosphatase (ALP) was the most common toxic agent (36%), followed by methanol. Significant differences were noted between the groups in terms of Simplified Acute Physiology Score-II (SAPS-II), Glasgow Coma Scale (GCS) score, length of ICU stay, and percentage of ventilation process. The mean levels of lactate at admission were 3.71 $\pm$ 3.35 and 4.19 $\pm$ 4.09 among VAP-positive and non-VAP patients, respectively; the difference was not statistically significant. Also, non-surviving patients had a longer ICU stay (12.20 days), compared to surviving patients (5.39) (P = 0.008). Moreover, admission lactate level was 7.06 $\pm$ 5.29 mmol/L among non-surviving patients and 3.01 $\pm$ 2.53 among surviving cases (P < 0.001).
Conclusions: Based on the findings, the mortality rate was 22.9% among poisoned patients with an elevated serum lactate level. We can conclude that mortality is associated with toxicants, but not the occurrence of VAP; in fact, VAP scenarios do not elevate serum lactate level.

Keywords: VAP, ICU, Lactate, Poisoning

1. Introduction

Lactate is generated by most tissues in the human body, with the maximum level of production found in muscles (1). Lactate is produced by Krebs and Cori cycles under aerobic and anaerobic conditions, respectively (2). Although lactate is quickly eliminated by the liver and kidneys under normal conditions, it can be elevated for various reasons (3). Generally, enhanced lactate level may be due to increased production, decreased clearance, or a combination of both.

The contributing factors for enhanced lactate level include hypoperfusion due to macro/micro circulatory dysfunction, mitochondrial dysfunction (potential absence of key enzymatic cofactors), and presence of a hypermetabolic state (4-6). In general, elevated lactate level is not universally clarified. The majority of conducted studies consider a cut-off range of 2.0 - 2.5 mmol/L, while in a number of studies, high lactate level has been described as > 4 mmol/L (7-10).

Lactate level is commonly assessed in the context of shock evaluation. The clinical prognostic role of serum lactate was suggested in 1964 by Broder and Weil as a risk prediction factor of ventilator-associated pneumonia (VAP) (11). VAP is a nosocomial pneumonia, which develops after 48 hours of mechanical ventilation. Based on the national healthcare safety agenda, VAP had an incidence of 0.0 - 4.4 per 1000 ventilator days in 2012, depending on the patient care location (12). Also, the excess cost associated with VAP was estimated at approximately 40,000 dollars per patient (13).

According to the infectious diseases society of America (IDSA), VAP negatively impacts patient outcomes. Based on two recent studies, VAP prolongs the process of mechanical ventilation by 7.6 to 11.5 days and extends hospitalization by 11.5 to 13.1 days, compared to cases with no VAP (12, 14, 15). In addition, all-cause mortality, associated with VAP, has been reported to range from 20% to 50% (16).

Classic clinical signs of VAP include fever, leukocytosis, purulent secretions, worsening oxygenation, infiltrates, and pathogenic cultures; these signs are neither sensitive nor specific (17). Laboratory tests and markers have been also suggested to promote the risk management of VAP. Procalcitonin, clinical pulmonary infection score, lung biopsy, C-reactive protein (CRP), and soluble triggering receptors expressed on myeloid cells-1 (sTREM-1), have been all suggested to have diagnostic values for VAP (18-21).

Despite the large number of studies on VAP, no research has focused on the efficacy of serum lactate level at admission in the prognosis of VAP occurrence and its subsequent outcomes. Accordingly, in this study, we aimed to explore the association between serum lactate level upon admission and subsequent development and mortality of VAP among patients in a toxicological intensive care unit (ICU).

2. Methods

2.1. Study Design and Sample Collection

The present retrospective, cross-sectional study was conducted among poisoned ICU-admitted patients with VAP diagnosis during seven months in 2015. The non-probability sampling method (convenience sampling) was used to recruit the subjects (power of 80%). All poisoned patients (aged 13-84 years), who were admitted to the ICU of Loghman-Hakim hospital (Tehran, Iran) and were evaluated in terms of lactate level, were considered eligible for the study. The inclusion criteria were as follows: 1) age of $\geq$ 13 years; 2) measurement of serum lactate level; and 3) hospitalization for poisoning. On the other hand, patients, in whom the lactate level was not assessed or were diagnosed with sepsis, were excluded from the study. The study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (95.04.16-117).

Loghman-Hakim educational hospital was constructed in 1971. This hospital is specialized in the management of patients suffering from chemical and drug intoxications; as a result, it is a unique referral center for poisoning cases. The specialized services of this hospital were promoted, following the quantitative and qualitative physical developments in the hospital area. So far, the hospital consists of 20 sections with 15,000 - 25,000 visits annually. This educational hospital is affiliated to Shahid Beheshti University of Medical Sciences. With 420 licensed and 362 active beds, Loghman-Hakim Educational Hospital is ranked first in all hospital evaluations.

Lactate analysis was performed, using 0.5 mL of the plasma sample and Biorex diagnostic reagents, according to the manufacturer's instructions at the time of admission. Other evaluated covariates consisted of the patient's age, gender, application of mechanical ventilation, acute physiology score-II (SAPS-II), Glasgow coma scale (GCS) score, toxicant agent (aluminum phosphide, methanol, opium, amphetamine, MDT, benzodiazepine, anticonvulsants, and tramadol), pH, and length of ICU stay.

VAP diagnosis was based on new or progressive chest radiography infiltrations with at least two of the following criteria: 1) fever (body temperature $\geq$ 38°C) or hypothermia ($<$ 36°C); 2) leukocytosis ($>$ 12 $\times$ 10^9/L leukocytes) or leukopenia ($<$ 3.5 $\times$ 10^9/L); and 3) purulent respiratory secretions. Microbiological confirmation was required in all patients, i.e., positive bronchoalveolar lavage $\geq$ 10^4 colony-forming units (cfu)/mL or positive tracheal aspirate $\geq$ 10^5 cfu/mL (13, 22).

As mentioned in the criteria, the clinical and paraclinical findings were as follows: 1) Mechanical ventilation for at least 48 hours; 2) radiographic changes (new infiltration or extended radiographic findings), leukocytosis, or leukopenia; 3) pathognomonic signs of isolated microorganisms from the specimen culture (tracheal-blood-urine); 4) fever; and 5) increased tracheal secretion. Three outcomes were followed-up and recorded among VAP-positive patients, including in-hospital mortality, vegetative state, and recovery. All the measurements were performed by a trained general physician.

2.2. Statistical Analysis

Descriptive statistics, including number and percentage, were calculated for categorical variables, while mean ($\pm$ SD) values were measured for the continuous ones. VAP-positive cases were compared to non-VAP patients with respect to the mean level of lactate and other covariates at admission. A similar comparison was performed between surviving and non-surviving patients. Comparisons were made, using t-test and Chi-square test. We explored the normality assumption both graphically and numerically. Kolmogorov-Smirnov or Shapiro-Wilk test indicated non-parametric distribution of all variables, except SAPS-II scores. However, as the sample size for each group was greater than 30, based on the central limit theorem of the statistics, we applied parametric analytical methods. Statistical analysis was performed, using SPSS version 20.1.

3. Results

A total of 157 patients were included in the final analysis. The mean age of the samples was 36.75 ± 16.21 years. Males were dominant in the study sample (73.09 %). Almost half of the participants had undergone mechanical ventilation. Overall, 71 (45.2 %) cases of VAP, as well as 36 cases of mortality, were reported. Alkaline phosphatase (ALP) was the most common toxic agent (36%), followed by methanol. Demographic and baseline characteristics of the study population are presented in Table 1.

Table 2 demonstrates the comparison between VAP-positive and non-VAP patients. There was no significant difference between the groups with respect to age or gender. However, significant differences were noted between the groups regarding SAPS-II and GCS scores, length of ICU stay, and percentage of ventilation. The mean levels of lactate at admission were 3.71 ± 3.35 and 4.19 ± 4.09 among VAP-positive and non-VAP patients, respectively; however, the difference was not statistically significant.

Based on the findings, the mean age of non-surviving patients was higher than surviving patients (43.11 vs. 34.61) (P = 0.028). Also, non-surviving cases had a longer ICU stay (12.20 days), compared to survivors (5.39) (P = 0.008). In addition, admission lactate level was 7.06 ± 5.29 mmol/L among non-surviving cases and 3.01 ± 2.53 mmol/L among surviving patients (P < 0.001); in fact, non-surviving patients had deteriorated clinical conditions (Table 3).

4. Discussion

In this study on hospitalized poisoned patients, we demonstrated that a single measurement of arterial/venous lactate level can provide prognostic information about the increased risk of mortality. To the best of our knowledge, this study is the first research to evaluate the relationship between lactate level at admission and VAP occurrence. Previous studies on prognostic application of lactate level have assessed ICU patients. In this regard, Broder and Weil, who were the first researchers suggesting the risk stratification of serum lactate level, studied 56 cases in shock from a variety of patients and discovered a mortality rate of 89% for lactate level > 4 mmol/L (11).

In this study, a higher admission lactate level was seen in non-surviving patients (P < 0.001), with a mortality rate of 22.90%. This finding indicates that the measurment of lactate biomarker could be helpful in recognizing the mortality rate among ICU patients. This association has been confirmed in various studies. In this regard, Aduen et al. also found that lactate level was significantly higher in non-survivors, regardless of blood pressure (23). Similarly, Vincent et al. (24), Bakker et al. (25), Falk et al. (26), and many other researchers found the same significant results in patients with septic shock.

Moreover, Shapiro et al. (lactate level > 4; 28.4%) (9) and Howell et al. (lactate level > 4; 14%) (7) discovered that lactate level could correctly determine patients with respect to mortality. The present study indicated that mortality due to high lactate level occurred due to toxicants, but not VAS. Generally, assessment of lactate clearance through serial evaluations has been revealed to be a practical predictor of morbidity and mortality. Also, serial lactate measurements may be useful in documenting treatment reactions to various therapeutic interventions (27).

In this study, ALP was more commonly observed among other toxicants; in fact, these patients had a significant enhanced lactate level (lactate > 4 mmol/L; n = 38, 24 %). According to a study by Mehrpour et al. arrested oxidative phosphorylation and poor tissue perfusion may lead to lactic acidosis in aluminium phosphide poisoning (28-30). On the other hand, methanol was the second rampant toxicant among patients in the present study. Also, alcohols (propylene glycol and methanol) have been implicated in enhanced lactate level, and lactate can be falsely increased in such cases (30-34).

Although other researchers have focused on patients, specifically with septic shock and trauma, we focused on 157 poisoned ICU-admitted patients with the development of VAP after 48 hours of mechanical ventilation. VAP may occur in 28% of patients who receive mechanical ventilation, and its incidence enhances with ventilator days (35). The prevalence of VAP was 45.22% in the present study. It should be noted that this survey was performed in winter and spring, which might be the reason for the high prevalence of VAP, compared to the study by Aziz Japoni in Shiraz, Iran (10.2%, n = 42) (36).

Generally, a higher rate of VAP has been reported in Iran (29, 37-40). Notably, similar rates have been revealed in Latin America, Asia, Africa, and the United States (41, 42). The pathogenic mechanism of VAP is mainly applied through aspiration of secretion with bacteria, colonizing the upper respiratory tract and passing into the lower respiratory tract via leakage between the tracheal wall and the cuff of the endotracheal tube. Therefore, development of strategies to decrease the incidence of nosocomial infections could be more cost-effective and warranted.

In this study, VAP was associated with a high mortality rate, while only a few predisposing risk factors could be modified. Based on the current survey, VAP-positive cases had a lower lactate level compared to non-VAP patients, and no significant correlation was observed. Therefore, VAP incidence might be a result of infection, and the reported mortality rate could be attributed to toxicity.

Table 1. Demographic and Baseline Characteristics of the Study Population

Characteristics	Values[a]
Age, y	36.75 ± 16.21
Range	13 - 84
Median	32
IQR	19
SAPS-II score	33.13 ± 32.00
Range	14 - 59
Median	32
IQR	15
GCS score	10.26 ± 3.87
Range	3 - 15
Median	11
IQR	7
pH	7.28 ± 0.11
Range	6.87 - 7.61
Median	7.30
IQR	0.13
Length of ICU stay	7.01 ± 8.31
Range	1 - 51
Median	5
IQR	7
Admission lactate level, mmol/L	3.95 ± 3.76
Range	0.30 - 17.30
Median	2.30
IQR	3.95
Male	116 (73.09)
Mechanical ventilation	86 (54.80)
VAP	71 (45.20)
Total mortality	36 (22.90)
Toxicant	
ALP	58 (36)
Methanol	15 (9)
Opium	12 (7)
Amphetamine	11(7)
MDT	10 (6)
BZD	8 (5.1)
Anticonvulsant	7 (4)
Tramadol	7 (4)
Others (Op, Co, cardiovascular drugs, antidepressants, and alcohol)	29 (18.47)

[a]Values are expressed as mean ± SD or No. (%).

Table 2. Comparison of VAP-Positive and Non-VAP Patients with Respect to Clinical Parameters[a]

Characteristics	VAP (N = 71)	Non-VAP (N = 86)	P Value
Age, ye	37.88 ± 17.65	35.65 ± 14.96	0.395
SAPS II score	35.11 ± 9.09	30.96 ± 10.56	0.024
GCS score	9.30 ± 3.60	11.11 ± 3.90	0.003
pH	7.28 ± 0.11	7.27 ± 0.10	0.148
Length of ICU stay, d	11.09 ± 10.28	3.29 ± 2.84	< 0.001
Admission lactate level, mmol/L	3.71 ± 3.35	4.19 ± 4.09	0.430
Male	53 (46.10)	62 (53.90)	0.856
Mechanical ventilation	50 (58.80)	35 (41.20)	< 0.001
Mortality	17 (47.20)	19 (52.80)	0.629

[a]Values are expressed as mean ± SD or No. (%).

Table 3. Comparison of Surviving and Non-Surviving Patients with Respect to Clinical Parameters[a]

Characteristics	Non-Surviving (N = 36)	Surviving (N = 120)	P Value
Age, y	43.11 ± 21.04	34.61 ± 13.81	0.028
SAPS II score	40.76 ± 6.41	31.48 ± 9.91	< 0.001
GCS score	9.52 ± 3.77	10.49 ± 3.90	0.192
pH	7.23 ± 0.13	7.29 ± 0.10	0.003
ICU stay, d	12.20 ± 12.68	5.39 ± 4.82	0.008
Admission lactate level, mmol/L	7.06 ± 5.29	3.01 ± 2.53	< 0.001
Male	26 (22.60)	89 (77.39)	0.875
Mechanical ventilation	17 (19.76)	69 (80.23)	0.292

[a]Values are expressed as mean ± SD or No. (%).

Among ICU-admitted patients, a significant relationship was seen between the occurrence of VAP and GCS score, SAPS-II score, and length of ICU stay. These findings were notably similar to studies by Six et al. Froon et al. and Behnia et al. (43-45).

The limitations of this study were the retrospective design and implementation at a unique referral center. Therefore, further prospective, multicenter studies are required to confirm the findings.

Based on the findings, the mortality rate was 22.9% among poisoned patients with an elevated serum lactate level. We can conclude that mortality was caused by toxicants, but not the occurrence of VAP; in fact, VAP scenarios did not elevate the serum lactate level.

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Footnote

Conflicts of Interest: The authors declare no conflicts of interest regarding the publication of this paper.

References

1. van Hall G. Lactate kinetics in human tissues at rest and during exercise. *Acta Physiol (Oxf).* 2010;**199**(4):499–508. doi: 10.1111/j.1748-1716.2010.02122.x. [PubMed: 20345411].
2. Petersen C. D-lactic acidosis. *Nutr Clin Pract.* 2005;**20**(6):634–45. [PubMed: 16306301].
3. Levraut J, Ichai C, Petit I, Ciebiera JP, Perus O, Grimaud D. Low exogenous lactate clearance as an early predictor of mortality in normolactatemic critically ill septic patients. *Crit Care Med.* 2003;**31**(3):705–10. doi: 10.1097/01.CCM.0000045561.85810.45. [PubMed: 12626973].
4. Jones AE, Puskarich MA. Sepsis-induced tissue hypoperfusion. *Crit Care Nurs Clin North Am.* 2011;**23**(1):115–25. doi: 10.1016/j.ccell.2010.12.007. [PubMed: 21316571].
5. Trzeciak S, Dellinger RP, Parrillo JE, Guglielmi M, Bajaj J, Abate NL, et al. Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival. *Ann Emerg Med.* 2007;**49**(1):88–98. doi: 10.1016/j.annemergmed.2006.08.021. [PubMed: 17095120] 98 e1-2.
6. Donnino MW, Carney E, Cocchi MN, Barbash I, Chase M, Joyce N, et al. Thiamine deficiency in critically ill patients with sepsis. *J Crit Care.* 2010;**25**(4):576–81. doi: 10.1016/j.jcrc.2010.03.003. [PubMed: 20646908].
7. Howell MD, Donnino M, Clardy P, Talmor D, Shapiro NI. Occult hypoperfusion and mortality in patients with suspected infection. *Intensive Care Med.* 2007;**33**(11):1892–9. doi: 10.1007/s00134-007-0680-5. [PubMed: 17618418].
8. Hurst T, Doty C. FOAM EM RSS 2015. Available from: http://www.foamem.com/category/italian/page/151/.
9. Shapiro NI, Howell MD, Talmor D, Nathanson LA, Lisbon A, Wolfe RE, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med.* 2005;**45**(5):524–8. doi: 10.1016/j.annemergmed.2004.12.006. [PubMed: 15855951].
10. Callaway DW, Shapiro NI, Donnino MW, Baker C, Rosen CL. Serum lactate and base deficit as predictors of mortality in normotensive elderly blunt trauma patients. *J Trauma.* 2009;**66**(4):1040–4. doi: 10.1097/TA.0b013e3181895e9e. [PubMed: 19359912].
11. Broder G, Weil MH. Excess Lactate: An Index of Reversibility of Shock in Human Patients. *Science.* 1964;**143**(3613):1457–9. [PubMed: 14107454].
12. Melsen WG, Rovers MM, Groenwold RH, Bergmans DC, Camus C, Bauer TT, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. *Lancet Infect Dis.* 2013;**13**(8):665–71. doi: 10.1016/S1473-3099(13)70081-1. [PubMed: 23622939].
13. Kalil AC, Metersky ML, Klompas M, Muscedere JG, Sweeney DA, Palmer LB, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis.* 2016;**63**(5):e61–e111. doi: 10.1093/cid/ciw353.
14. Muscedere JG, Day A, Heyland DK. Mortality, attributable mortality, and clinical events as end points for clinical trials of ventilator-associated pneumonia and hospital-acquired pneumonia. *Clin Infect Dis.* 2010;**51 Suppl 1**:S120–5. doi: 10.1086/653060. [PubMed: 20597661].
15. Kollef MH, Hamilton CW, Ernst FR. Economic impact of ventilator-associated pneumonia in a large matched cohort. *Infect Control Hosp Epidemiol.* 2012;**33**(3):250–6. doi: 10.1086/664049. [PubMed: 22314062].
16. Koenig SM, Truwit JD. Ventilator-associated pneumonia: diagnosis, treatment, and prevention. *Clin Microbiol Rev.* 2006;**19**(4):637–57. doi: 10.1128/CMR.00051-05. [PubMed: 17041138].
17. Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas and Bennett's Infectious Disease Essentials. Elsevier Health Sciences; 2016.
18. Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet.* 2004;**363**(9409):600–7. doi: 10.1016/S0140-6736(04)15591-8. [PubMed: 14987884].
19. Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA.* 2009;**302**(10):1059–66. doi: 10.1001/jama.2009.1297. [PubMed: 19738090].
20. Seligman R, Meisner M, Lisboa TC, Hertz FT, Filippin TB, Fachel JM, et al. Decreases in procalcitonin and C-reactive protein are strong predictors of survival in ventilator-associated pneumonia. *Crit Care.* 2006;**10**(5):R125. doi: 10.1186/cc5036. [PubMed: 16956405].
21. Fagon JY. Biological markers and diagnosis of ventilator-associated pneumonia. *Crit Care.* 2011;**15**(2):130. doi: 10.1186/cc10050. [PubMed: 21418551].
22. American Thoracic S, Infectious Diseases Society of A. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med.* 2005;**171**(4):388–416. doi: 10.1164/rccm.200405-644ST. [PubMed: 15699079].
23. Aduen J, Bernstein WK, Khastgir T, Miller J, Kerzner R, Bhatiani A, et al. The use and clinical importance of a substrate-specific electrode for rapid determination of blood lactate concentrations. *JAMA.* 1994;**272**(21):1678–85. [PubMed: 7966896].
24. Vincent JL, Dufaye P, Berre J, Leeman M, Degaute JP, Kahn RJ. Serial lactate determinations during circulatory shock. *Crit Care Med.* 1983;**11**(6):449–51. [PubMed: 6406145].
25. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg.* 1996;**171**(2):221–6. doi: 10.1016/S0002-9610(97)89552-9. [PubMed: 8619454].
26. Falk JL, Rackow EC, Leavy JA, Weil MH. Delayed lactate clearance in patients with shock. New York: Wiley-Liss Div John Wiley & Sons Inc; 1985.
27. Regnier MA, Raux M, Le Manach Y, Asencio Y, Gaillard J, Devilliers C, et al. Prognostic significance of blood lactate and lactate clearance in trauma patients. *Anesthesiology.* 2012;**117**(6):1276–88. doi: 10.1097/ALN.0b013e318273349d. [PubMed: 23168430].
28. Mehrpour O, Jafarzadeh M, Abdollahi M. A systematic review of aluminium phosphide poisoning. *Arh Hig Rada Toksikol.* 2012;**63**(1):61–73. doi: 10.2478/10004-1254-63-2012-2182. [PubMed: 22450207].

29. Hashemian M, Talaie H, Akbarpour S, Mahdavinejad A, Mozafari N. Central Nervous System Depressants Poisoning and Ventilator Associated Pneumonia: An Underrated Risk Factor at the Toxicological Intensive Care Unit. *Iran Red Crescent Med J.* 2016;**18**(1):e30989. doi: 10.5812/ircmj.30989. [PubMed: 26889400].
30. Mozafari N, Talaie H, Shoaei SD, Hashemian M, Mahdavinejad A. Survey on Hypothermia and Hyperthermia in Poisoned Patients in a Unique Referral Hospital, Tehran, Iran. *Iran Red Crescent Med J.* 2016;**18**(4):ee35483. doi: 10.5812/ircmj.35483. [PubMed: 27275403].
31. Sandberg Y, Rood PP, Russcher H, Zwaans JJ, Weige JD, van Daele PL. Falsely elevated lactate in severe ethylene glycol intoxication. *Neth J Med.* 2010;**68**(1):320–3. [PubMed: 20739730].
32. Zosel A, Egelhoff E, Heard K. Severe lactic acidosis after an iatrogenic propylene glycol overdose. *Pharmacotherapy.* 2010;**30**(2):219. doi: 10.1592/phco.30.2.219. [PubMed: 20099997].
33. Kruse JA. Methanol poisoning. *Intensive Care Med.* 1992;**18**(7):391–7. [PubMed: 1469176].
34. Shahangian S, Ash KO. Formic and lactic acidosis in a fatal case of methanol intoxication. *Clin Chem.* 1986;**32**(2):395–7. [PubMed: 3943215].
35. Browne E, Hellyer TP, Baudouin SV, Conway Morris A, Linnett V, McAuley DF, et al. A national survey of the diagnosis and management of suspected ventilator-associated pneumonia. *BMJ Open Respir Res.* 2014;**1**(1):e000066. doi: 10.1136/bmjresp-2014-000066. [PubMed: 25553248].
36. Japoni A, Vazin A, Davarpanah MA, Afkhami Ardakani M, Alborzi A, Japoni S, et al. Ventilator-associated pneumonia in Iranian intensive care units. *J Infect Dev Ctries.* 2011;**5**(4):286–93. [PubMed: 21537070].
37. Shariatpanahi ZV, Taleban FA, Mokhtari M, Shahbazi S. Ginger extract reduces delayed gastric emptying and nosocomial pneumonia in adult respiratory distress syndrome patients hospitalized in an intensive care unit. *J Crit Care.* 2010;**25**(4):647–50. doi: 10.1016/j.jcrc.2009.12.008. [PubMed: 20149584].
38. Talaie H, Sabeti S, Mahdavinejad A, Barari B, Kamalbeik S. A survey on microorganisms and their sensitivity by E-test in ventilator-associated pneumonia at Toxicological-Intensive Care Unit of Loghman-Hakim Hospital. *Acta Biomed.* 2010;**81**(3):210–6. [PubMed: 22530459].
39. Hashemian M, Kamalbeik S, Haji Seyed Razi P, Barari B, Salimi A, Talaie H, et al. VAP or poisoning; which one has more effect on patients' outcomes in toxicological ICU?. *Acta Biomed.* 2015;**86**(1):63–8. [PubMed: 25948030].
40. Shoaei SD, Sistanizad M, Mozafari N, Alinia T, Talaie H. The Overestimation of Vancomycin-Associated Nephrotoxicity: The Effect of Rhabdomyolysis and Nephrotoxicants at a Referral Poison Center, Tehran, Iran. *Iran Red Crescent Med J.* 2016;**18**(10).
41. DiCocco JM, Croce MA. Ventilator-associated pneumonia: an overview. *Expert Opin Pharmacother.* 2009;**10**(9):1461–7. doi: 10.1517/14656560903007922. [PubMed: 19505213].
42. Askarian M, Gooran NR. National nosocomial infection surveillance system-based study in Iran: additional hospital stay attributable to nosocomial infections. *Am J Infect Control.* 2003;**31**(8):465–8. [PubMed: 14647108].
43. Six S, Jaffal K, Ledoux G, Jaillette E, Wallet F, Nseir S. Hyperoxemia as a risk factor for ventilator-associated pneumonia. *Crit Care.* 2016;**20**(1):195. doi: 10.1186/s13054-016-1368-4. [PubMed: 27334713].
44. Froon AH, Bonten MJ, Gaillard CA, Greve JW, Dentener MA, de Leeuw PW, et al. Prediction of clinical severity and outcome of ventilator-associated pneumonia. Comparison of simplified acute physiology score with systemic inflammatory mediators. *Am J Respir Crit Care Med.* 1998;**158**(4):1026–31. doi: 10.1164/ajrccm.158.4.9801013. [PubMed: 9769255].
45. Behnia M, Logan SC, Fallen L, Catalano P. Nosocomial and ventilator-associated pneumonia in a community hospital intensive care unit: a retrospective review and analysis. *BMC Res Notes.* 2014;**7**:232. doi: 10.1186/1756-0500-7-232. [PubMed: 24725655].