Taylor & Francis
Taylor & Francis Group

Baylor University Medical Center Proceedings
The peer-reviewed journal of Baylor Scott & White Health

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ubmc20

Changes in ionized calcium in ethylene glycol poisoning

Roberts Stašinskis, Katrīna Stašinska, Maksims Mukāns, Andis Graudiņš, Viesturs Liguts & Aivars Lejnieks

To cite this article: Roberts Stašinskis, Katrīna Stašinska, Maksims Mukāns, Andis Graudiņš, Viesturs Liguts & Aivars Lejnieks (2022): Changes in ionized calcium in ethylene glycol poisoning, Baylor University Medical Center Proceedings, DOI: 10.1080/08998280.2022.2062550

To link to this article: https://doi.org/10.1080/08998280.2022.2062550

PROC (BAYL UNIV MED CENT)
2022;0(0):1–6

https://doi.org/10.1080/08998280.2022.2062550

Taylor & Francis
Taylor & Francis Group

Changes in ionized calcium in ethylene glycol poisoning

Roberts Stašinskis, MD[a,b], Katrīna Stašinska[b], Maksims Mukāns, MD[b], Andis Graudiņš, MBBS, PhD[b,c], Viesturs Liguts, MD, PhD[a,b], and Aivars Lejnieks, MD, PhD[a,b]

[a]Riga East University Hospital, Riga, Latvia; [b]Riga Stradins University, Riga, Latvia; [c]Monash Health at Monash University, Melbourne, Australia

ABSTRACT

Ethylene glycol is a sweet-tasting toxic alcohol contained in a variety of chemical preparations. In patients poisoned with ethylene glycol, diagnosis is often based upon clinical suspicion and nonspecific tests. Hypocalcemia is often present due to calcium oxalate crystals formed by oxalic acid metabolite complexation. This retrospective study involved a review of clinical records of patients with a diagnosis of ethylene glycol poisoning. Results of blood gas samples, lactate, ionized calcium, and serum creatinine were documented and compared between various groups. The ionized calcium concentration was below the normal range in 59% of cases at the time of presentation and more commonly associated with a blood pH of <7.3 in 79% of cases. The number of patients with a low ionized calcium concentration increased over time. A low ionized calcium concentration was a common finding in cases of severe ethylene glycol poisoning and was more commonly associated with patients exhibiting metabolic acidosis or developing acute kidney injury or death. Ionized calcium concentration on presentation may be an additional marker in concert with blood pH that can be used in the risk assessment and stratification of severity and complications of ethylene glycol poisoning.

KEYWORDS Ethylene glycol; hypocalcemia; ionized calcium; toxic alcohol

Intoxication with ethylene glycol (EG) can result in severe metabolic derangement and significant morbidity or death, especially with delayed diagnosis, and commonly requires prolonged intensive care admission and therapy.[1,2] The most accurate method of detection of EG poisoning is by direct quantitative testing, although this is not available in many countries due to the expense and equipment maintenance due to infrequent use.[1–4] The presence of a raised anion gap (AG), metabolic acidosis (MA), unexplained osmolar gap, and lactate gap suggest exposure to this toxic alcohol.[2,5] Hypocalcemia is a feature often seen in severe EG poisoning.[6] This results from the combination of ionized calcium (iCa) with oxalic acid, a metabolite of EG, to form calcium oxalate crystals (COC) that are deposited in various organs, resulting in end-organ damage.[7–9] While the degree of acidosis correlates with severity of poisoning, little is known regarding whether there is an additive correlation between low iCa, severity of poisoning, and development of complications such as acute kidney injury (AKI) and mortality. Hodgman et al reported no association between iCa and blood pH in a retrospective cohort of patients with EG toxicity. However, they did not look at outcomes such as end-organ damage, morbidity, and death with respect to iCa.[10] The purpose of this study was to reevaluate the changes in blood iCa in an independent cohort of confirmed EG poisoning cases and correlate it with changes in arterial blood pH, AG, lactate, bicarbonate, and serum creatinine (sCr) concentrations. In addition, the aim was to assess whether low iCa concentration is a common finding in EG poisoning and how it correlates with severity of disease.

METHODS

This was a retrospective descriptive analysis of the clinical records of patients presenting to a national tertiary referral center with a specialist toxicology service and poison information center. Patients were included if they had a diagnosis of EG poisoning (T52.3[11]) from January 1, 2012, to December 31, 2020. The research was approved by the

Corresponding author: Roberts Stašinskis, MD, Riga Eastern University Hospital – RAKUS "Gailezers" Number 2 Hipokrata Street, Riga, LV-1038, Latvia (e-mail: roberts.stasinskis@inbox.lv)

The authors report no funding or conflicts of interests.

Received February 11, 2022; Revised March 21, 2022; Accepted April 1, 2022.

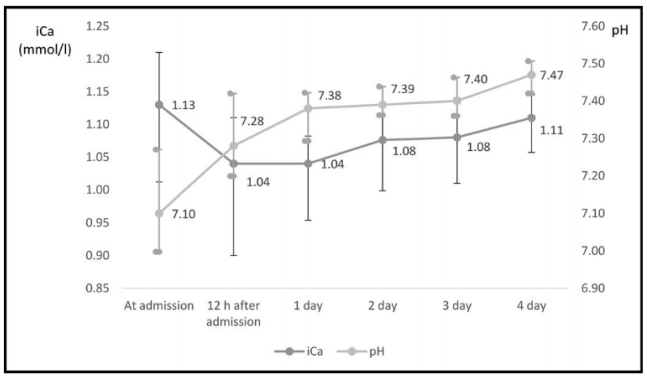

Figure 1. Changing median concentration of ionized calcium (iCa) and pH over time in all patients.

institutional ethics committee. The study included patients with a history of reported exposure to EG confirmed by qualitative blood or urine assay for EG using gas-liquid chromatography and thin-layer chromatography. Quantitative assays are not available in our institution. Patients <18 years of age were excluded from the study. Based on past medical history, none of the patients in the study was known to have chronic kidney disease.

Demographic data collected on each admission included gender, age, disposition, length of stay, and outcome. Clinical data included treatment undertaken, use of ethanol infusion, and requirement for renal replacement therapy (continuous veno-venous hemodialysis [CVVHD]). Patients were stratified by blood pH, as either pH $\geq$ 7.3 or pH < 7.3. Comparisons of other biochemical variables as well as the requirement for CVVHD were made between these two groups. Laboratory data were recorded from the time of admission, 12 hours later, and daily from hospital day 1 to hospital day 4. Data included arterial blood pH, bicarbonate, calculated AG, iCa, lactate, and sCr concentrations.

Statistical analyses were undertaken utilizing SPPS statistical software (IBM SPPS Statistics, v 23.0, Chicago, IL). Data were analyzed for normality utilizing the Shapiro-Wilk test. Normally distributed data are reported as mean with 95% confidence interval and nonparametric data as median and interquartile range (IQR). Comparison of nonparametric continuous data was undertaken using the Mann-Whitney U test and Spearman rho correlation, while categorical data were compared using Pearson chi-square and Fisher's exact tests. The independent variables included outcome of disease, those receiving CVVHD, and blood pH <7.3 and $\geq$7.3. Linear regression analysis was performed comparing blood pH and iCa concentration at admission. Tables and graphs were created in Microsoft Office Excel (365 ProPlus, 2013).

RESULTS

The study included 47 patients, 9 women and 39 men. The median age was 58 years (IQR 48–65). Thirty-seven patients recovered and were discharged from the hospital, and 10 patients died. The median length of hospital stay for all patients was 7 days (IQR 3–11); it was 8 days (IQR 5–13) for patients who were discharged and 1 day (IQR 1–3) for patients who died.

Ethanol was the primary antidote administered in 45 cases. Fomepizole is not available in our health care setting. CVVHD was utilized in 29 cases. Median length of stay for patients was 9 days (IQR 6–14) for those receiving CVVHD and 4 days (IQR 2–8) for those not receiving CVVHD. Overall, median iCa concentration was low on admission at 1.13 mmol/L (IQR 1.01–1.21) and continued to fall significantly 12 hours after admission (1.04 mmol/L, IQR 0.90–1.11). iCa concentration started to recover on hospital day 2 *(Figure 1)*. Median blood pH significantly increased over time from admission (median admission pH = 7.100, IQR 6.998–7.270) to 12 hours postadmission (median pH = 7.289, IQR 7.199–7.420) and increased further at subsequent time points through hospital day 4 *(Figure 1)*. Linear regression analysis of blood pH and iCa was not statistically significant (R^2= 0.083, P = 0.05) *(Figure 2)*. On admission, iCa was <1.18 mmol/L in 28 cases and blood pH was <7.3 in 37 cases. The proportion of patients with low iCa increased over time, while blood pH improved with treatment over the same time period *(Figure 3)*. Admission iCa negatively correlated with blood pH (r = −0.457; P = 0.001) and lactate concentration (r = −0.376; P = 0.01). The presence of a high AG was strongly negatively correlated with low iCa (r = 0.664; P < 0.001). Admission iCa was strongly positively correlated with bicarbonate concentration (r = 0.765; P < 0.001).

Median admission sCr concentration was 109 µmol/L (IQR 77–166). Notably, there was a correlation between worsening of sCr on day 2 after admission and iCa measured on admission (r = 0.452; P = 0.006). Similar correlations at other time points are summarized in *Figure 4*.

A statistically significant correlation was observed between low iCa concentration and blood pH at the time of hospital admission. When presentation blood pH was $\geq$7.3, median iCa concentration on admission was significantly lower than when the presenting pH was <7.3. Data are summarized in *Figure 5*. Similarly, there was a statistically significant association between the admission concentration of iCa and use of CVVHD. Patients receiving CVVHD had higher admission iCa concentrations than those who did not receive CVVHD (median 1.18 mmol/L, IQR 1.07–1.22, vs 1.06 mmol/L, IQR 1.00–1.19, respectively; P = 0.045). The change in iCa over time for the two treatment groups is summarized in *Figure 6*.

There was a significant difference in iCa 12 hours after admission when comparing discharged patients to those who died. Discharged patients had both significantly higher blood pH and recovery of iCa concentration by this time point than those who died. Data are summarized in *Table 1*. A more detailed description of the changes in iCa concentration, its relationship with presenting blood pH (< or $\geq$7.3),

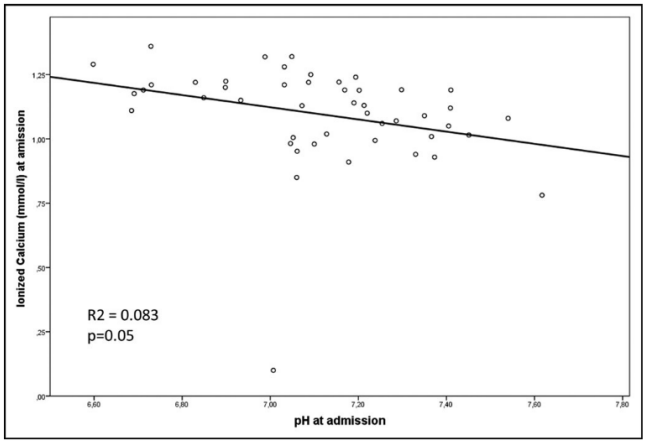

Figure 2. Linear regression analysis comparing blood pH and ionized calcium concentration at the time of hospital presentation.

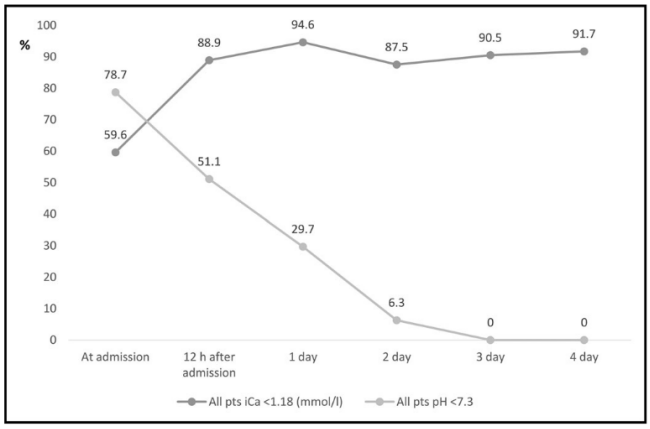

Figure 3. Time course of the percentage of patients with abnormal ionized calcium (iCa) (<1.18 mmol/L) and acidosis (pH < 7.3) during their hospital stay.

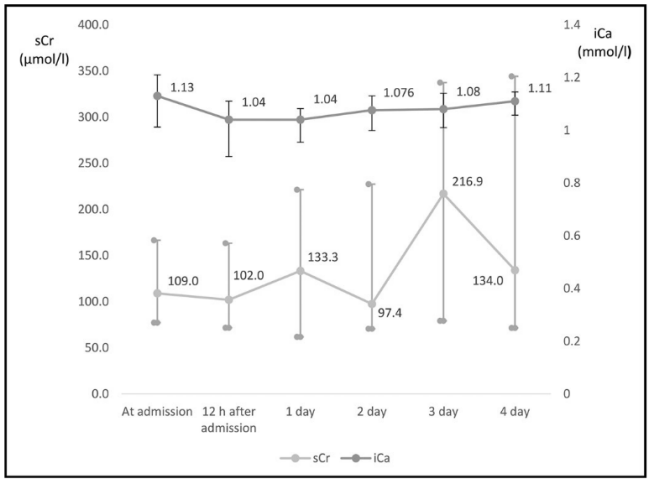

Figure 4. Mean change in median serum creatinine (sCr) and ionized calcium (iCa) for all patients over the course of their hospital stay.

and changes with and without therapy with CVVHD is shown in *Table 2*.

DISCUSSION

EG is a toxic alcohol widely used as a radiator coolant/antifreeze and as an additive in many common household chemicals. It is sweet to taste and may result in accidental exposures in children or be used for intentional ingestion as an ethanol replacement by alcohol-dependent individuals, as well as for deliberate self-poisoning. As little as one mouthful of concentrated EG can result in significant toxicity. Oxalic acid is one of the primary metabolites of EG metabolism that contributes to the development of high AG MA. It binds to iCa in the blood to form calcium oxalate, which precipitates as crystals in various organs in the body, with resultant hypocalcemia and end-organ tissue damage. In particular, AKI with deposition of COC in the renal tubules

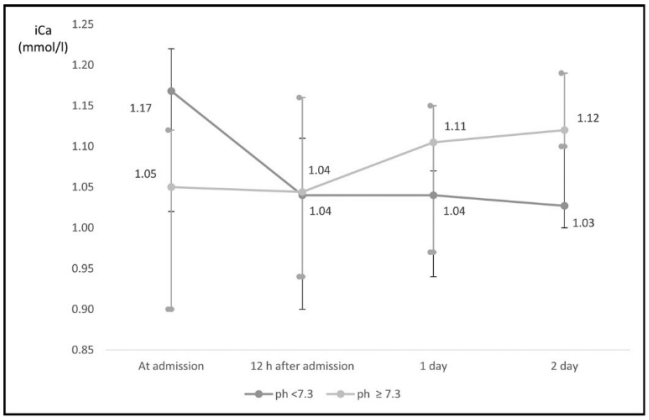

Figure 5. Time course of median ionized calcium (iCa) concentrations for patients with blood pH <7.3 or ≥7.3.

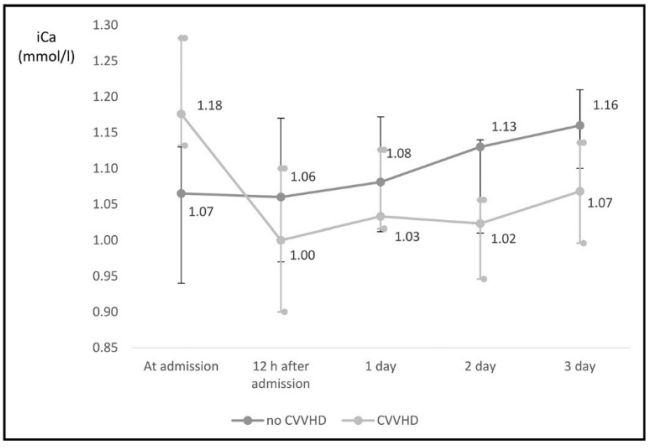

Figure 6. Time course of changes in median ionized calcium (iCa) concentration for patients treated and not treated with continuous veno-venous hemodialysis (CVVHD).

Table 1. Differences in median blood pH values and ionized calcium concentration in patients who were discharged and patients who died after ethylene glycol poisoning

Variable	Died (n = 10)	IQR	Discharged (n = 37)	IQR	*P* value
At admission					
pH	7.07	7.21–6.73	7.13	7.29–7.01	0.362
iCa (mmol/L)	1.06	1.19–0.98	1.15	1.22–1.05	0.231
12 h after admission					
pH	7.23	7.40–6.98	7.33	7.43–7.22	0.078
iCa (mmol/L)	0.88	0.90–0.81	1.06	1.14–0.97	0.001
Hospital stay (days)	1	3–1	8	12–5	0.001

iCa indicates ionized calcium; IQR, interquartile range.

Table 2. Time course of changes in ionized calcium concentration during hospital stay compared to blood pH on presentation and whether patients underwent CVVHD therapy

	At admission		12 h after admission		Day 1		Day 2		Day 3		Day 4	
Variable	Mean	IQR	Mean	IQR	Mean	IQR	Mean	IQR	Mean	IQR	Mean	IQR
iCa (mmol/L)	1.13	1.01–1.21	1.04	0.90–1.11	1.04	0.95–1.08	1.08	1.00–1.13	1.1	1.01–1.14	1.1	1.06–1.15
pH												
<7.3	1.17	1.02–1.22	1.04	0.90–1.11	1.04	0.94–1.07	1.03	1.00–1.12	1.1	1.01–1.16	1.1	1.09–1.15
pH ≥7.3	1.05	0.90–1.12	1.04	0.94–1.16	1.11	0.97–1.15	1.12	1.09–1.19				
P value	0.03		0.56		0.16		0.1		—		—	
CVVHD												
No	1.07	0.99–1.19	1.06	0.95–1.15	1.08	0.99–1.15	1.13	1.12–1.25	1.2	1.11–1.22		
Yes	1.18	1.07–1.22	1	0.90–1.10	1.03	0.94–1.05	1.02	0.99–1.10	1.1	1.00–1.14	1.1	1.06–1.15
P value	0.05		0.58		0.08		0		—		—	

CVVHD indicates continuous veno-venous hemodialysis; IQR, interquartile range.

and parenchyma is a common feature of EG poisoning with established MA.

In patients presenting to the hospital with an unexplained high-AG MA and hypocalcemia, toxic alcohol exposure such as EG poisoning should be considered in the differential diagnosis.[2,7–9] Lack of MA may occur in patients presenting to the hospital in the early stages of EG poisoning or in those who have co-ingested ethanol, a competitive inhibitor of alcohol dehydrogenase in the liver, which preferentially blocks EG metabolism to its acid metabolites.[8,10] While definitive confirmation of exposure can be made using specific quantitative EG blood assays, these are often not available in a clinically relevant timeframe in many jurisdictions. As a result, diagnosis of poisoning must be based upon history of exposure, clinical suspicion, and various nonspecific tests.[12] These include serum electrolytes and sCr, presence of a high AG MA, a high serum osmolality and associated calculated osmolar gap, and the presence of a lactate gap when comparing blood gas and laboratory measured Lac and COC in urine microscopy. Hypocalcemia can also be seen, especially in the presence of AKI resulting from renal tubular COC deposition.

Symptoms and signs of untreated EG toxicity are divided into three stages. Initially, EG acts as an intoxicant and results in inebriation, similar to ethanol. As EG is metabolized in the liver in the first 6 to 12 hours after ingestion, acid metabolites are produced and there is a gradually developing progressive high AG MA that precedes multiorgan dysfunction. Stage 3 toxicity is the result of COC deposition in various end organs, particularly the kidney and brain. Renal tubular necrosis and AKI develop in the 48 to 72 hours after ingestion. Delayed central nervous toxicity may become evident up to 7 days after exposure.[13] The highest mortality occurs in the first 48 hours after ingestion due to the severe metabolic derangement associated with acidosis.

iCa is the most physiologically important indicator of calcium homeostasis in humans.[14–16] Studies have indicated that the determination of total calcium or albumin-bound

calcium misclassifies a large proportion of patients with impaired calcium homeostasis, thus recognizing iCa as "the gold standard" for detection of hypocalcemia.[15] In patients admitted to the intensive care unit, abnormalities in iCa may serve as a surrogate marker of disease severity, usually returning to normal during recovery from various disease states.[17,18] The negative correlation between iCa and blood pH observed at the time of presentation is most likely the result of pH-sensitive albumin-calcium buffer[19] reactions as well as the subsequent production of COC which resulted in AKI.

In this study, patients were divided into two groups based upon their admission blood pH, either $\geq$7.3 or <7.3. This division was selected based upon the need to initiate empiric treatment for suspected EG poisoning, particularly in those with pH < 7.3.[8] In patients with blood pH $\geq$ 7.3, the level of iCa at presentation was lower than in those with a blood pH < 7.3. In the group with blood pH < 7.3, iCa concentration continued to fall until 2 days after admission, while in the group with pH $\geq$ 7.3, iCa increased earlier, 12 hours after admission. This may be explained by the fact that the time from exposure to presentation may have been shorter for those with initial pH < 7.3 and their clinical course could have been more rapid and severe. As a result, these patients presented to the hospital earlier, given their more critical clinical condition. A sharp drop in iCa was seen in the first 12 hours of hospital stay and remained persistently below the reference range for the next 2 days, most likely due to the formation and deposition of COC. In those patients with blood pH $\geq$ 7.3, the iCa concentration was initially lower but began to increase in the first 12 hours of hospital stay. Patients in this group may have drunk smaller quantities of EG, co-ingested ethanol, had a longer exposure time, or presented in the latter stages of EG poisoning with established AKI.

Hodgman et al reported that there was little correlation between blood pH and iCa in EG-poisoned patients. However, their study aimed to specifically assess whether changes in iCa could be used to detect or diagnose EG poisoning. As with other surrogate markers used to detect this poisoning, these cannot be used in isolation to rule in or rule out EG poisoning. However, when used together with clinical suspicion of EG poisoning, the diagnostic accuracy of the combination of low pH, elevated AG, osmolar gap, and low iCa is likely to be greater. Our study did not aim to test whether iCa is a useful test in diagnosis of EG poisoning. We described the dynamic changes in iCa over time in patients with confirmed EG toxicity. The results suggest that there may be a number of associations between changes in iCa over time and clinical outcomes. In particular, patients with an initial fall in iCa concentration were noted to have increases in sCr concentrations on the first and second days of hospital admission. This observation is most likely also related to the formation of COC and the subsequent deposition in the renal tubules resulting in AKI. Finally, evidence of recovery iCa concentration at the 12-hour time point after admission may be useful to assist in patient prognosis. We noted that discharged patients had higher blood pH and iCa at this time point compared to patients who died.

In conclusion, a low iCa concentration is a common finding in EG poisoning. In our cohort, 59% of patients presented with a low iCa concentration. Mortality was associated with both significantly lower blood pH and iCa concentrations 12 hours after admission when compared to discharged patients. As a result, a combination of both iCa concentration and low blood pH at the 12-hour mark post-admission may provide an early indication of increased risk of outcomes such as AKI and death. These indices may be useful in the overall risk assessment of patients with EG poisoning.

ORCID

Viesturs Liguts http://orcid.org/0000-0002-6885-9239
Aivars Lejnieks http://orcid.org/0000-0002-2097-6698

1. McQuade DJ, Dargan PI, Wood DM. Challenges in the diagnosis of ethylene glycol poisoning. *Ann Clin Biochem*. 2014;51(Pt 2):167–178. doi:10.1177/0004563213506697.
2. Scalley RD, Ferguson DR, Piccaro JC, Smart ML, Archie TE. Treatment of ethylene glycol poisoning. *Am Fam Physician*. 2002; 66(5):807–812. http://www.ncbi.nlm.nih.gov/pubmed/12322772.
3. Eder AF, McGrath CM, Dowdy YG, et al. Ethylene glycol poisoning: toxicokinetic and analytical factors affecting laboratory diagnosis. *Clin Chem*. 1998;44(1):168–177. http://www.ncbi.nlm.nih.gov/pubmed/9550575. doi:10.1093/clinchem/44.1.168.
4. Wu AHB, McKay C, Broussard LA, et al; National Academy of Clinical Biochemistry Laboratory Medicine. National Academy of Clinical Biochemistry Laboratory Medicine practice guidelines: recommendations for the use of laboratory tests to support poisoned patients who present to the emergency department. *Clin Chem*. 2003;49(3): 357–379. doi:10.1373/49.3.357.
5. Weiner S. Toxic alcohols. In *Goldfrank's Toxicologic Emergencies*. 10th ed. New York: McGraw-Hill Education; 2015:1346–1357.
6. Morfin J, Chin A. Images in clinical medicine. Urinary calcium oxalate crystals in ethylene glycol intoxication. *N Engl J Med*. 2005; 353(24):e21. doi:10.1056/NEJMicm050183.
7. Takayesu JK, Bazari H, Linshaw M. Case records of the Massachusetts General Hospital. Case 7-2006. A 47-year-old man with altered mental status and acute renal failure. *N Engl J Med*. 2006;354(10):1065–1072. doi:10.1056/NEJMcpc059043.
8. Davis DP, Bramwell KJ, Hamilton RS, Williams SR. Ethylene glycol poisoning: case report of a record-high level and a review. *J Emerg Med*. 1997;15(5):653–667. doi:10.1016/S0736-4679(97)00145-5.
9. Megarbane B, Borron S. Methanol, ethylene glycol and other toxic alcohols. In: *Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose*. 4th ed. Philadelphia: Saunders Elsevier; 2007:611–622.
10. Hodgman M, Marraffa JM, Wojcik S, Grant W. Serum calcium concentration in ethylene glycol poisoning. *J Med Toxicol*. 2017;13(2): 153–157. doi:10.1007/s13181-017-0598-4.
11. International Statistical Classification of Diseases and Related Health Problems (ICD-10). https://www.who.int/standards/classifications/classification-of-diseases.
12. Manini AF, Hoffman RS, McMartin KE, Nelson LS. Relationship between serum glycolate and falsely elevated lactate in severe ethylene

glycol poisoning. *J Anal Toxicol*. 2009;33(3):174–176. doi:10.1093/jat/33.3.174.
13. Kruse JA. Methanol and ethylene glycol intoxication. *Crit Care Clin*. 2012;28(4):661–711. doi:10.1016/j.ccc.2012.07.002.
14. Byrnes MC, Huynh K, Helmer SD, Stevens C, Dort JM, Smith RS. A comparison of corrected serum calcium levels to ionized calcium levels among critically ill surgical patients. *Am J Surg*. 2005;189(3):310–314. doi:10.1016/j.amjsurg.2004.11.017.
15. Li M, Wang C, Zhou E-W, Liu Y-P. Time to stop debating about the everlasting story: some issues concerning serum total calcium and ionized calcium. *Chin Med J (Engl)*. 2020;133(10):1251–1252. doi:10.1097/CM9.0000000000000803.
16. Thode J, Juul-Jørgensen B, Bhatia HM, et al. Comparison of serum total calcium, albumin-corrected total calcium, and ionized calcium in 1213 patients with suspected calcium disorders. *Scand J Clin Lab Invest*. 1989;49(3):217–223. http://www.ncbi.nlm.nih.gov/pubmed/2662382. doi:10.3109/00365518909089086.
17. Aberegg SK. Ionized calcium in the ICU: Should it be measured and corrected?. *Chest*. 2016;149(3):846–855. doi:10.1016/j.chest.2015.12.001.
18. Kelly A, Levine MA. Hypocalcemia in the critically ill patient. *J Intens Care Med*. 2013;28(3):166–177. doi:10.1177/0885066611411543.
19. Baird GS. Ionized calcium. *Clin Chim Acta*. 2011;412(9-10):696–701. doi:10.1016/j.cca.2011.01.004.