



## Ethylene Glycol Toxicity and Its Therapy Management: A Literature Review

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### ABSTRACT

**Background:** Ethylene glycol (EG) is an antifreeze substance commonly used as an additive for syrup preparations. One of the detrimental effects caused by EG toxicity is acute renal failure (ARF) and death, assuming therapy and management are delayed. Presently, there are limited studies on toxicity of EG and therapy. Therefore, this study aimed to provide an overview of EG toxicity levels, clinical manifestations, arising reactions, and therapy management methods.

**Objectives:** A narrative review design was employed with data collected from PubMed and Google Scholar. The strategy used keywords such as "ethylene glycol toxicity" and "acute renal" with the assistance of Boolean operators including AND and OR.

**Methods:** The result showed that the minimum EG level for toxicity was at 22 mg/dL, followed by metabolic acidosis with an increased anion gap (>10mmol/L). Based on case reports from one experimental study, the clinical manifestations of patients experiencing EG poisoning included decreased consciousness, tachycardia, and coma, with ARF occurring after 24-72 hours.

**Results:** Write study findings in this section.

**Conclusion:** EG poisoning could cause kidney damage in the form of ARF and lead to death, assuming therapy was delayed. Presently, the most effective therapy for EG poisoning was fomepizole.

**Keywords:** ethylene glycol, renal failure, therapy, toxicity

### INTRODUCTION

The hazards associated with Ethylene Glycol (EG) is widely discussed among stakeholders, including the public, healthcare professionals, pharmaceutical industries, and the Indonesian government.<sup>1</sup> In addition, it is extensively used as radiator fluids and brake oil.<sup>2</sup> World Health Organization (WHO) had officially reported cases of EG poisoning in Gambia, particularly affecting children who experienced toxic effects such as Acute Renal Failure (ARF), leading to death. According to a report dated October 5, 2022, WHO confirmed the deaths of 66 children in Gambia due to the use of contaminated syrup preparations.<sup>3</sup> After analysis, it was discovered that the cause of death, resulting in ARF, was contamination with EG and Diethylene Glycol (DEG) detected in the syrup preparations. The local Drug Regulatory Authority identified 4 syrup preparations suspected of being contaminated with EG and DEG.<sup>3</sup> Based on this case report, pediatric patients suffering from ARF had a history of using syrup preparations containing EG or DEG. Currently, there is no reported evidence ARF related to EG, leading to the need for comprehensive studies on EG.

In theory, EG is not recommended for human consumption due to toxic properties, sweet taste, and antifreeze characteristics. This chemical compound is often used as an additive in household fluids.<sup>4</sup> Syrup preparations suspected to contain EG or DEG may originate from common additives such as propylene, polyethylene glycol, sorbitol, and glycerine or glycerol.<sup>6</sup>

The relationship between EG and ARF can be anticipated based on toxicity mechanism. Preliminary studies stated that direct quantitative testing was the most accurate method for detecting EG poisoning. Due to limited resources and technology, conducting a comprehensive toxicity examination in clinical laboratories.<sup>5</sup> is impractical. In addition, the literature on EG toxicity remains limited. This present literature review addresses

scientific inquiries regarding EG toxicity levels, mechanisms, associated effects, and therapeutic management methods.

### METHODS

#### Study design

This study adopted a narrative review method.

#### Search strategy

Literature was searched from PubMed and Google Scholar using keywords such as EG toxicity and acute renal, with Boolean operators, namely AND and OR. The focus is on studies related to EG toxicity.

#### Eligibility criteria

The inclusion criteria comprised case studies, pharmacological tests, or observational investigations addressing scientific inquiries about EG toxicity levels, mechanisms, clinical symptoms or manifestations, and therapeutic management methods. However, the exclusion criteria included duplicate articles, non-case reports, and experimental studies. The search was not constrained by publication year due to the scarcity of relevant studies meeting these criteria. The selection process included adhering to specific inclusion criteria and mapping studies by sorting and interpreting qualitative and quantitative data while categorizing materials based on issues and titles.

#### Data Extraction

Data was extracted from eligible studies, comprising information such as authorship, study type (observational or experimental), and objectives. The main aim of this scientific study is to provide a comprehensive overview of EG toxicity, clinical conditions, and appropriate therapeutic management methods.

#### Data Analysis

The results from the narrative synthesis are shown in Figure 1, providing an overview of the included studies.

### RESULTS AND DISCUSSION

EG affects individuals differently, potentially leading to central nervous system depression, cardiorespiratory instability, and renal failure, all of which can be fatal without proper management.<sup>4-6</sup> EG poisoning can result in severe consequences such as metabolic disturbances, morbidity, or death, particularly when diagnosis is delayed. In general, patients require hospitalization and prolonged intensive therapy.<sup>7,8</sup>

EG metabolites, including metabolic disturbances and acidosis characterized by an increased anion gap, induce toxic effects. The formation and deposition of Calcium Oxalate Crystals (COC) causes tubular necrosis, resulting in ARF.<sup>9</sup> Emergency conditions such as ARF typically occur in 24 to 72 hours after EG ingestion. Surviving patients may experience the following symptoms: pelvic pain, haematuria, proteinuria, and oliguria. Recovery usually occurs in several weeks.<sup>10</sup> as observed in reported cases of EG poisoning in children from Gambia.

Toxicity mechanism of EG includes the binding of ionized calcium (iCa) with oxalic acid, resulting in the formation of COC stored in various organs, causing damage to body parts.<sup>11</sup> While the severity of acidosis is closely associated with EG toxicity, it remains unclear whether there is an additive correlation between low iCa levels, the severity of poisoning, and the development of complications such as ARF and death. A previous study reported no correlation between iCa and patients' blood pH. There is no relationship between iCa and subsequent consequences such as organ damage, morbidity, and mortality.<sup>12</sup>

#### EG Toxicity Levels

When EG levels exceed a certain threshold value, it induces harmful effects. Literature reviews from 2004 onwards have documented EG toxicity levels ranging from 22 to 706 mg/dL, as shown in Table I. The tolerance level or safe threshold for EG in syrup preparations was established at 0.5 mg/kgBW per day.<sup>13</sup> The lowest EG level causing toxic effects is reportedly 22 mg/dL.<sup>14</sup> Meanwhile, another source stated that toxic dose of EG was 0.1 ml/kg (with solution purity of 95%) or 1 to 2 ml/kg (~1500 mg/kg), with severe toxicity occurring at levels >0.5 g/L.<sup>6</sup>

Based on the 4 referenced case studies, EG levels in the blood and anion gap are the main parameters to assess the severity of EG toxicity. Toxic EG level, estimated at approximately 1 L/kg, equals twice EG distribution

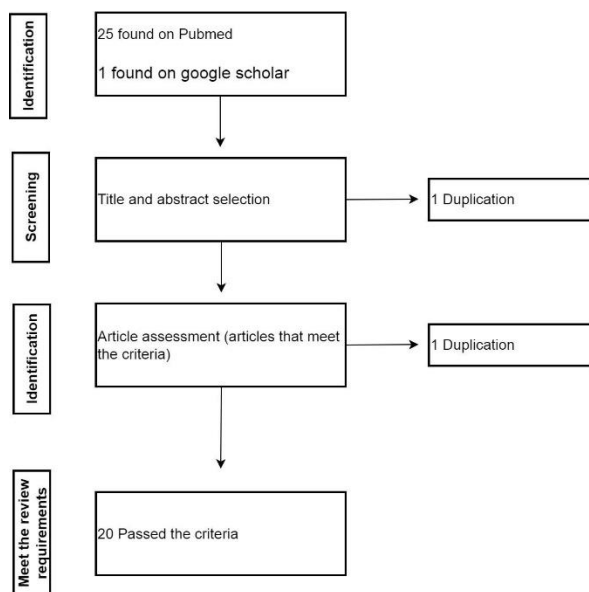


Figure 1. Flow diagram and narrative review

Table I. EG Toxicity Levels Based on Literature Review

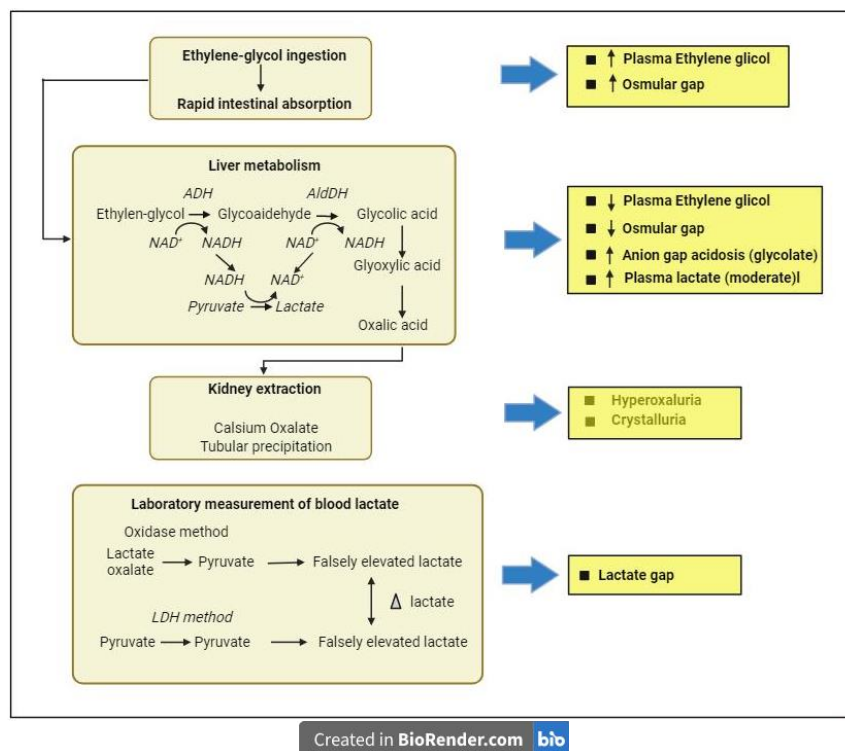
No.	Authors (Year)	Study Method/Subject	EG levels and anion gap in cases
1	Rosen (2021)	Case report of a 52-year-old female patient.	EG level in blood: 22 mg/dL Anion gap: >43 mmol/L
2	Ahmad (2021)	Case presentation of a 50-year-old female patient.	EG level in blood: 64 mg/L Anion gap: 21 mmol/L
3	Cox and Phillips (2004)	Case report of a 16 and 59-year-old boy and woman, respectively.	EG level in blood Case 1: 163 mg/dL Case 2: 511 mg/dL Anion gap Case 1: 35 mmol/L Case 2: 32 mmol/L
4	Velez (2007)	Case report of a 33-year-old man.	EG level in blood: 706 mg/dL Anion gap: 10 mmol/L

volume, ranging from 0.5 to 0.8 L/kg. The anion gap measurements ranged from 10 to 43 mmol/L in these cases. Although the normal anion gap ranges from 12 to 16 mmol/L, instances of EG toxicity with an anion gap of 10 mmol/L have been observed. This implied that high EG levels or anion gap exceeding the normal limit served as parameters for EG toxicity requiring therapeutic intervention.

The American Clinical Toxicology Practice Guidelines state that the threshold for EG level causing toxic effects is 20 mg/dL, or it can also be measured in osmol units at 10 mOsm/L.<sup>15</sup> These levels are usually determined after confirming EG poisoning in the patient.<sup>15,16</sup> The extent of EG consumption directly influences the observed toxicity levels.<sup>17</sup> Furthermore, the time since ingestion, specific EG formulations, and individual patient factors such as body distribution and metabolism can also affect EG level examinations.

### Mechanism of EG Toxicity

The literature review stated that EG do not directly cause toxicity, rather the metabolites induce fatal effects ranging from ARF to death.<sup>9</sup> EG metabolism mainly occurs in the liver, where alcohol dehydrogenase (ADH) converts it to glycolaldehyde. Subsequently, aldehyde dehydrogenase (ALDH) transforms glycolaldehyde into glycolate. The glycolate is further converted into glyoxylic acid, which, is metabolized by lactate dehydrogenase (LDH-5) into oxalate, the main compound responsible for EG toxicity.<sup>14,9</sup>



**Figure 2. Mechanism of EG Toxicity**

EG is rapidly absorbed in the digestive system and is further subjected to liver metabolism through ALDH, producing glycolic acid. This process affects the anion gap due to the presence of the glycolate anion, thereby reducing  $NAD^+$  to  $NADH$ . Furthermore,  $NADH$  is re-oxidized to  $NAD^+$ , generating lactic acid.<sup>6,15</sup> ADH metabolizes EG absorbed by the digestive system into 4 toxic substances, namely glycoaldehyde, glycolate, glyoxylate, and oxalate.<sup>18,8</sup> Finally, EG metabolism in the liver produces oxalic acid, which contributes to the formation of COC in the kidneys.<sup>12</sup> These COC deposits tend to affect various systems, as follows:

#### Digestive system

EG causes gastric irritation due to calcium oxalate deposition on the intestinal mucosa.<sup>15</sup>

#### Central nervous system

EG induces central nervous system depression, which can increase from unresponsive sleep to coma.<sup>15,10</sup>

#### Renal system

EG metabolites contribute to reversible renal failure, characterized by oliguria or even anuria. The deposition of COC in the proximal tubular epithelium causes renal failure.<sup>15,10</sup> This phenomenon has also been observed in cattle, where kidney surgery showed crystal deposits.<sup>19</sup>

#### Cardiovascular system

The autopsy results showed the presence of calcium oxalate deposits in the heart.<sup>15,10</sup>

#### Clinical Manifestations of EG Toxicity

EG can lead to various symptoms and prognoses, as shown in Table II. Literature searches showed significant blood chemistry results in EG-poisoned patients, namely (1) heightened blood potassium, (2) decreased blood  $CO_2$ , (3) increased creatinine levels, elevated anion gap, and (4) acidic pH (<7.3). Patients may also show symptoms such as decreased consciousness level, metabolic acidosis, and tachycardia. Laboratory tests often show increased serum osmolality, acidic arterial pH (<7.3), anion gap >17, and bicarbonate value <20.

EG affects the central nervous system, and this is detected by the following symptoms, namely confusion, ataxia, hallucinations, slurred speech, and coma. The most severe effects occurred 6 to 12 hours after EG

**Table II. Symptoms and Prognoses of EG Poisoning Based on Literature Review**

Authors	Symptoms	Prognoses
Song (2017)	Reduced consciousness, pulse and respiratory rates of 98 beats and 30 breaths per minute, respectively, proteinuria, microscopic hematuria. Tachycardia with a heart rate of 134 beats per minute.	The patient experienced a fainting episode, and ARF improved after 23 days.
Silva (2018)	Feeling drowsy, headache, unconsciousness, heart rate 100 beats per minute, blood pressure 130/70 mmHg, reduced urine output, pH 7.08, lactate level 13.9 mmol/L.	The patient gradually improved after 4 days of therapy with normal creatinine levels.
Velez (2007)	Depression and anxiety, blood pressure 132/87 mmHg, heart and respiratory rates 95 beats, and 18 breaths per minute, respectively, oxygen level 96%, still responsive.	The patient did not experience ARF and was discharged on day 4.
Cox (2004) Case I	Reduced consciousness, agonal breathing, heart rate 114 beats per minute, blood pressure 146/76 mmHg, tachycardic heart.	The patient improved.
Case II	Drowsy, responsive to stimuli, heart rate 87 beats per minute, blood pressure 127/88 mmHg, respiratory rate 24 breaths per minute.	
Scaalley (2002)	Decreased consciousness, but still responsive to stimuli, heart and respiratory rates 116 beats, and 28 breaths per minute, blood pressure 158/80 mmHg, oxygen level 99%.	N/A
Rosen (2021)	Decreased consciousness, unresponsive to stimuli.  Bradycardia and cessation of pulse, CPR was performed, followed by renal function replacement (CRRT).  Severe liver shock, renal failure, and respiratory injury.	The patient was discharged after therapy for 85 days.

poisoning.<sup>8</sup> Preliminary studies also stated that calves exposed to EG poisoning showed central nervous system disturbances such as stereotyped behavior, depression, paralysis, and seizures. Chemical laboratory tests commonly detected signs of azotemia or kidney function decline, observed through microscopic evidence of tubular necrosis.<sup>19</sup> Another study focused on the brain stated that EG poisoning caused bilateral symmetric hyperintensity in the basal ganglia, thalamus, and brainstem.<sup>20</sup>

### Management of EG Toxicity

Based on the literature review, the recommended initial therapy for EG toxicity included the administration of fomepizole and sodium bicarbonate, as shown in Table III. This method was designed to address the mechanism of toxicity and prognoses resulting from the rapid absorption of EG in the digestive tract. Peak EG levels were observed in the first 1 to 4 hours after ingestion, leading to the onset of ARF in 24 to 72 hours.

Several studies stated the critical need for rapid-action therapy through intravenous injection in cases of EG toxicity. Therapy protocols commonly included administering antidotes to expedite elimination as well as bicarbonate therapy aimed at normalizing pH and anion gap levels. Patients with severe toxicity are diagnosed with significant EG and lactate levels or anion gap values.

Fomepizole is the main antidote therapy for EG poisoning, and it functions by inhibiting ADH enzymes secreted in the liver during EG metabolism. The inhibition of EG metabolism prevents the formation of toxic metabolites. Fomepizole antidote therapy should start when EG levels exceed 20 to 25 mg/dL or metabolic acidosis is present (plasma bicarbonate <15 mmol/L). The initial dose of fomepizole is 15 mg/kgBW, followed by maintenance therapy of 10 mg/kgBW every 12 hours for a minimum of 4 times for patients without hemodialysis or every 6 hours for those with hemodialysis until normal pH is reached.<sup>6</sup> According to EG toxicity management guidelines, when the standard therapy fails, fomepizole may be continued at 15 mg/kg every 12 hours until acidosis is resolved, symptoms disappear, and EG levels are normalized.<sup>21</sup> Additional therapy includes intravenous thiamine and pyridoxine 100 mg and 50 mg every 12 hours and 6 hours. In cases where fomepizole is unavailable, ethanol may be administered to prevent EG metabolism into oxalic acid.<sup>6</sup> However, due to the significant side effects of ethanol, it should be considered as a last resort in therapy.

**Table III. Management of EG Toxicity Based on Literature Review**

<b>Authors</b>	<b>Management</b>	<b>Therapy</b>	<b>Prognoses</b>
Song (2017)	Fluid replacement (NaCl)	Sodium bicarbonate, thiamine (initial therapy). Fomepizole was administered at 15 mg/kg i.v, then 10 mg/kg, 4 doses every 12 hours.	The condition of the patient deteriorated, and this eventually led to a coma.
	Renal replacement therapy (RRT) Hemodialysis		The patient still experienced ARF. On day 23, the patient started to improve and was discharged.
Moore (2008)	Fluid replacement  Hemodialysis Respiratory assistance		The patient returned to normal after 36 hours of management.
Velez (2007)	Hemodialysis	Given fomepizole at 15 mg/kg i.v. after 4 hours of EG ingestion. Continued with 10 mg/kg, for a total of 8 doses every 12 hours (4 doses at 15 mg/kg, and 10 mg/kg).	The patient did not experience ARF and was discharged on day 4.
Cox (2004) Case I	Hemodialysis for 6 hours	Administered 80g of activated charcoal sodium bicarbonate i.v. and 800 mg of fomepizole i.v. Fomepizole was administered at 15 mg/kg i.v, then 10 mg/kg every 12 hour interval for 4 doses during dialysis. For 2 days, thiamine 100 mg i.v, and pyridoxine 100 mg and 50 mg, respectively i.v every 6 hours.	The patient improved.
Case II	Administration of NaCl fluid  Hemodialysis for 6 hours	Sodium bicarbonate i.v.  Fomepizole was administered at 15 mg/kg i.v, then 10 mg/kg every 12 hour interval for 4 doses during dialysis. Thiamine and pyridoxine 100 mg and 50 mg i.v every 12 hours, and 6 hours.	The patient improved on day 8 and was discharged.
Scalley (2002)	In the first hour, administration of activated charcoal	Fomepizole for standard therapy: First dose at 15 mg/kg, administered every 6 hour Subsequent doses 10 mg/kg every 12 hour interval for 4 doses.	
Rosen (2021)	Clinical suspicion of alcohol poisoning, the patient received resuscitation fluid Hemodialysis	Start with administration of sodium bicarbonate, fomepizole, thiamine, and pyridoxine.	

because EG entering the bloodstream with hepatic metabolism into oxalic acid. The metabolism of oxalic acid in the liver then led to the formation of COC in the kidneys, contributing to ARF. Increased oxalic acid levels trigger metabolic acidosis in patients, leading to compensatory respiratory alkalosis characterized by hyperventilation and tachycardia, which progresses to decreased consciousness. Acidic pH and an increased anion gap are important parameters for initial management, including using sodium bicarbonate, an alkaline solution. Additionally, patients diagnosed or identified with severe EG poisoning require fluid replacement and hemodialysis. Renal replacement therapy (RRT) may be recommended when patients with more severe conditions fail to respond to standard therapy.

## CONCLUSION

In conclusion, EG metabolites caused toxic effects and symptoms, including disturbances in the central nervous system, metabolic acidosis, anion gap, and COC formation. Based on the literature review, the minimum EG level that caused toxic symptoms was 22 mg/dL with an anion gap value > 10 mmol/L. EG poisoning could lead to kidney damage (ARF) and eventually death, assuming not promptly and correctly treated. The most effective management of EG poisoning was fomepizole antidote therapy, which could be combined with palliative measures such as sodium bicarbonate, normal saline, and hemodialysis adjusted to the existing clinical manifestations.

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## CONFLICT OF INTEREST

We don't have conflicts of interest or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers' bureaus, membership, employment, consultancies, stock ownership, or other equity interests and expert testimony or patent licensing arrangements), or non-financial interests such as personal or professional relationships, affiliations, knowledge or beliefs in the subject matter or materials discussed in this manuscript

## STATEMENT OF ETHICS

None

## REFERENCES

1. Mumpuni RY. Tata Laksana Keracunan Minuman Keras Opolosan (Metanol dan ethylene Glycol) Dengan Fomefazole, Etanol, dan Hemodialisis. *Journal Nursing Care and Biomolecular*. 2017;1(1):1. doi:10.32700/jnc.v1i1.3
2. Silva RFD, Sumanadasa HS, Wijekoon S, Kamani J, Wanigasuriya P. Two Cases of Ethylene Glycol Poisoning Treated Successfully with Haemodialysis.
3. Medical Product Alert N°6\_2022\_Substandard (contaminated) paediatric medicines.html.
4. Stašinskis R, Stašinska K, Mukāns M, Graudiņš A, Liguts V, Lejnieks A. Changes in ionized calcium in ethylene glycol poisoning. *Baylor University Medical Center Proceedings*. 2022;35(4):460-465. doi:10.1080/08998280.2022.2062550
5. Bhalla A. Bedside point of care toxicology screens in the ED: Utility and pitfalls. *Int J Crit Illn Inj Sci*. 2014;4(3):257. doi:10.4103/2229-5151.141476
6. Ahmad Y, Kissling S, Torrent C. The three biological gaps and hyperoxaluria in ethylene glycol poisoning: case presentation and review. Published online 2021.
7. McQuade DJ, Dargan PI, Wood DM. Challenges in the diagnosis of ethylene glycol poisoning. *Ann Clin Biochem*. 2014;51(2):167-178. doi:10.1177/0004563213506697
8. Scalley RD, Ferguson DR, Smart ML, Archie TE. Treatment of Ethylene Glycol Poisoning. 2002;66(5):6.
9. Cox RD, Phillips WJ. Ethylene Glycol Toxicity. *Military Medicine*. 2004;169(8):660-663. doi:10.7205/MILMED.169.8.660
10. Leth PM, Gregersen M. Ethylene glycol poisoning. *Forensic Science International*. 2005;155(2-3):179-184. doi:10.1016/j.forsciint.2004.11.012



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11. Gallagher N, Edwards FJ. The Diagnosis and Management of Toxic Alcohol Poisoning in the Emergency Department: A Review Article. *Advanced Journal of Emergency Medicine*. 2019;3(3):e28. doi:10.22114/ajem.v0i0.153
12. 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
13. Badan Pengawas Obat dan Makanan - Republik Indonesia.html.
14. Rosen R, Robbins-Juarez S, Stevens J. Ethylene Glycol Intoxication Requiring ECMO Support. Yegneswaran B, ed. *Case Reports in Critical Care*. 2021;2021:1-5. doi:10.1155/2021/5545351
15. Miller H, Barceloux DG, Krenzelok EP, Olson K, Watson W. American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning. *Journal of Toxicology: Clinical Toxicology*. 1999;37(5):537-560. doi:10.1081/CLT-100102445
16. Brent J. Fomepizole for Ethylene Glycol and Methanol Poisoning. *N Engl J Med*. 2009;360(21):2216-2223. doi:10.1056/NEJMct0806112
17. Velez LI, Shepherd G, Lee YC, Keyes DC. Ethylene glycol ingestion treated only with fomepizole. *J Med Toxicol*. 2007;3(3):125-128. doi:10.1007/BF03160922
18. Gardner TB, Manning HL, Beelen AP, Cimis RJ, Cates JMM, Lewis LD. Ethylene Glycol Toxicity Associated With Ischemia, Perforation, and Colonic Oxalate Crystal Deposition. *J Clin Gastroenterol*. 2004;38(5).
19. Agerholm JS, Hansen KS, Voogd HL, Krogh AKH. Ethylene glycol toxicosis in milk-fed dairy calves. *Acta Vet Scand*. 2022;64(1):7. doi:10.1186/s13028-022-00626-1
20. Moore MM, Kanekar SG, Dhamija R. Ethylene Glycol Toxicity: Chemistry, Pathogenesis, and Imaging. *Radiology Case Reports*. 2008;3(1):122. doi:10.2484/rcr.v3i1.122
21. A Systematic Review of Ethanol and Fomepizole Use in Toxic Alcohol Ingestions - PMC.html.