

## A case of acute kidney injury due to ethylene glycol intoxication

Nefrologo in corsia

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### ABSTRACT

In this article we describe a case of acute kidney injury caused by ethylene glycol intoxication which partially reversed after temporary hemodialysis treatment. The diagnosis was obtained after the patient's clinical history and the finding of ethylene glycol in the blood, numerous intratubular crystals at renal biopsy, and the presence of large amounts of atypical – spindle-like and needle-like – calcium oxalate crystals in the urinary sediment.

**KEYWORDS:** Ethylene glycol, acute kidney injury, urinary sediment, calcium oxalate crystals

## Introduction

Ethylene glycol (EG) is a fluid used in antifreeze solutions, whose ingestion occurs by mistake (especially in children and in work accidents) or intentionally, for suicidal purposes or for its ethanol-like euphoric effect [1]. The ingestion of EG causes a multiorgan involvement including the kidneys due to acute intratubular calcium oxalate precipitation with consequent tubular obstruction and acute kidney injury (AKI) [2, 3].

In this article, we describe a patient who developed AKI after EG ingestion for suicidal purposes, which partially reversed after hemodialysis treatment.

## Case report

On May 3<sup>rd</sup>, 2021, a 57-year-old man was evaluated at the emergency unit of “A. Manzoni” hospital, Lecco, Italy, for drowsiness associated with agitation and purposeless movements of the four limbs, and anuria. An almost empty bottle containing a blue-colored antifreeze solution and a full rat-killing bottle were found in the patient’s backpack. Therefore, a nasogastric feeding-tube was positioned, through which a blue fluid was suctioned, similar to the antifreeze bottle content. Electrocardiogram was normal and a non-contrast CT scan showed normal kidneys. Ultrasound investigation and echocardiogram were not performed.

Laboratory data showed: serum creatinine 6.1 mg/dL (normal value [NV]: 0.6-1.17); BUN not available, acid-base balance: pH 7.15 (NV: 7.34-7.45), lactates 24 mmol/L (NV: 0.5-1.5); HCO<sub>3</sub><sup>-</sup> 15.9 mmol/L (NV: 22-26); Ca<sup>++</sup> 0.93 mmol/L (NV: 1.15-1.30); anionic gap 32 (NV: 8-16); Na<sup>+</sup> 138 mmol/L (NV:135-145); K<sup>+</sup> 4.7 mmol/L (NV: 3.5-5.0); phosphorus was not performed. Blood count and hepatic enzymes were normal.

On the basis of the findings described above, EG poisoning was hypothesized and the Poison Control Center of “San Matteo” Hospital in Pavia was contacted for the measurement of EG in blood and urine and for advice about a targeted treatment, which was fomepizole 1g/day and thiamine 100 mg/day. Endotracheal intubation was performed for airway protection because of severe CNS depression. In addition, a 3-hour hemodialysis, with high blood (300 mL/min) and dialysate (600 mL/min) flow and bicarbonate and high-flux polysulfone filter with a wide surface (2.1 m<sup>2</sup>) was started, which was repeated on the two following days. No dialysate modifications such as those suggested by Peces et al. [4] were used.

On May 4<sup>th</sup>, the toxicology screening showed the presence of EG in the urine (76 mg/dL), while it was absent in the blood. Thus, fomepizole was stopped. On the same day, a slow and partial consciousness recovery was noticed which led to patient extubation with no subsequent respiratory problems.

On May 6<sup>th</sup>, diuresis increased and a second-morning urine sample was collected from a vesical catheter. Dipstick showed: specific gravity 1.000 (NV: 1000-1030), pH 7.5 (NV: 5-8), albumin ± (NV: absent), glucose + (NV: absent), hemoglobin ++++ (NV: absent), leucocyte esterase +++ (NV: absent), nitrites negative, ketones absent. Urinary sediment (Used) examination, performed by one of us (G.L.) with bright-field and polarized light microscopy, after standardized centrifugation [5], showed: isomorphic erythrocytes > 100/high power field at 400x (HPF) (NV: ≤1/ microscopic field), leukocytes 50-60/ HPF (NV: ≤ 1/ microscopic field), crystals > 50/HPF (NV: absent). The latter were spindle-like and needle-like structures of variable size, both individual and in aggregates, which under polarized light showed a strong and polychromatic birefringence (Figures 1 and 2), similar to those described by several authors in EG intoxication [6–11].

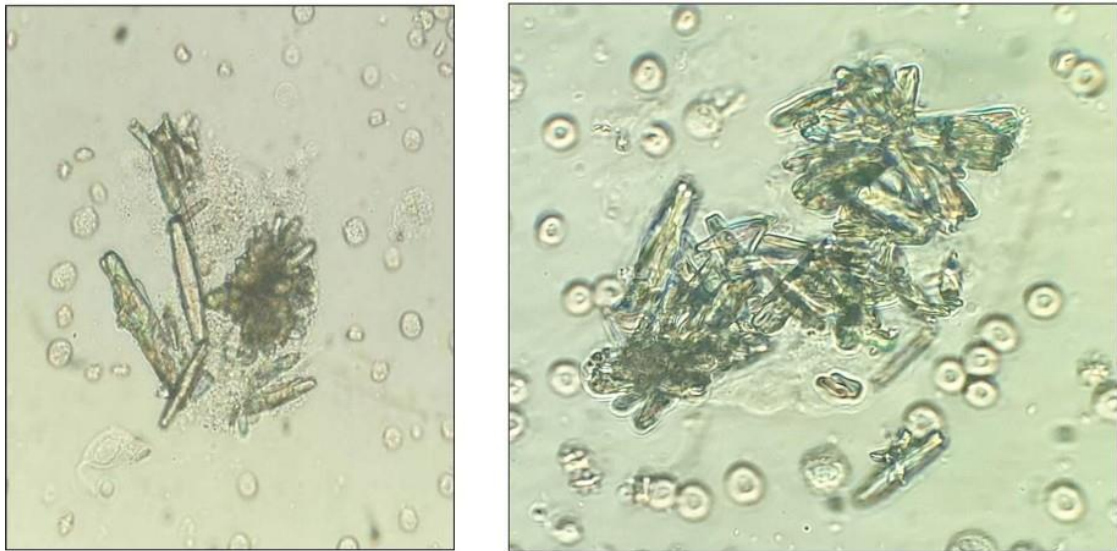


Figure 1: Large aggregates of spindle-like and needle-like calcium oxalate crystals found in the patient's urinary sediment (bright field microscopy, original magnification 400x).

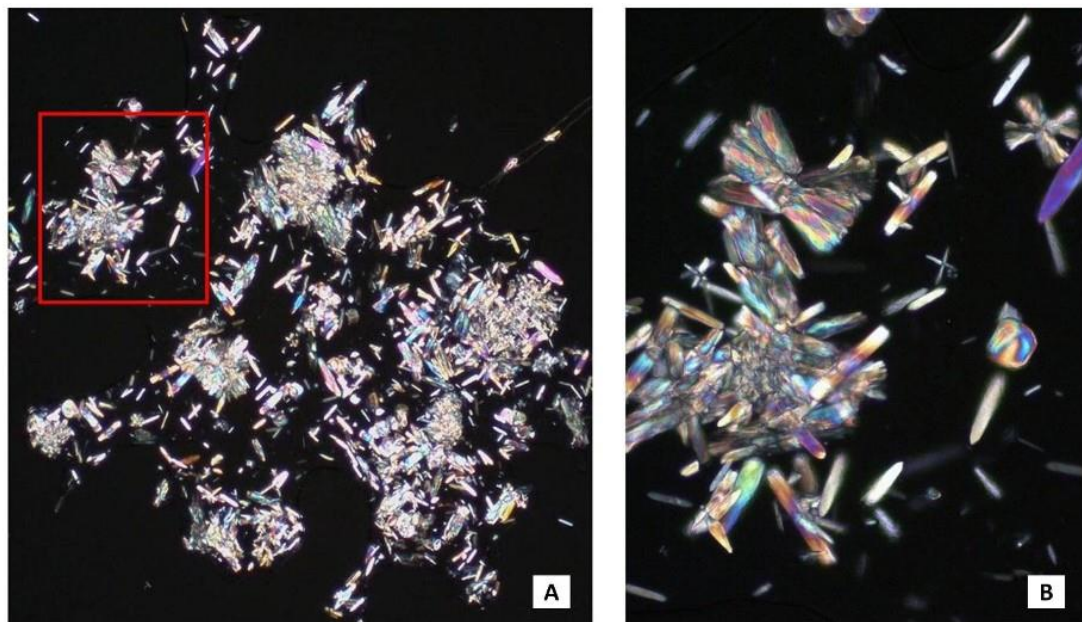


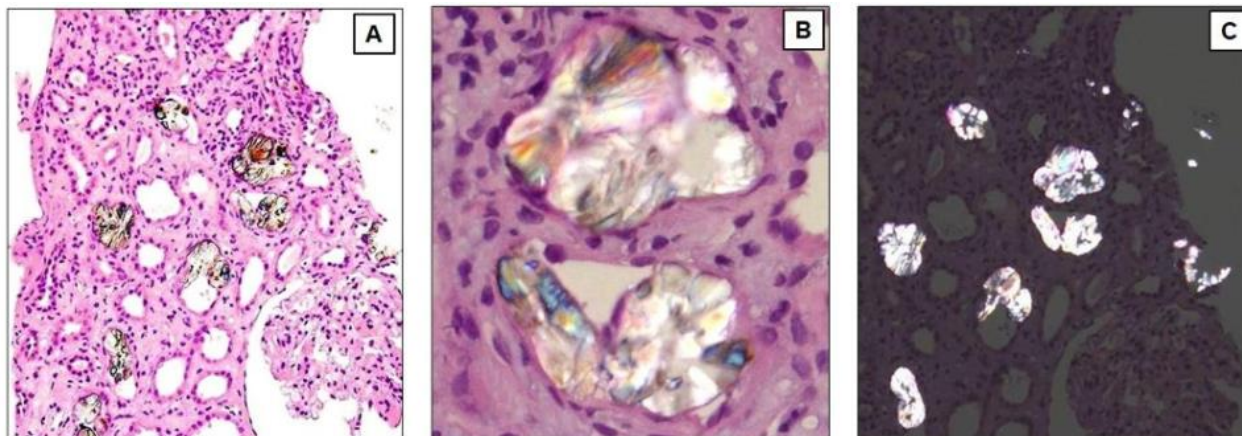
Figure 2: A. Aggregates of calcium oxalate crystals found in the patient's urinary sediment strongly birefringent and polychromatic under polarized light. B. The inset of figure A as seen at higher magnification (original magnification 400x).

On May 12<sup>th</sup>, after normalization of electrolytes and acid-base imbalances and crystalluria reduction, the dialysis was temporarily withdrawn, even though serum creatinine was still high (11.3 mg/dL) (Table 1).

	03/05	04/05	05/05	06/05	12/05	24/05	25/05	04/06
<b>Serum creatinine (mg/dL)</b>	6.1	4.2	5.37	5.3	11.3	7.3	/	5.9
<b>Diuresis (mL/24h)</b>	anuria	anuria	anuria	200	3000	1100	/	1050
<b>Crystalluria</b>	/	/	/	++++	++	absent	/	absent
<b>Fomepizole</b>	x	x	/	/	/	/	/	/
<b>Dialysis</b>	x	x	x	—	—	x	—	—
<b>Renal Biopsy</b>							x	

Table 1: The clinical course during the hospitalization period.

On May 24<sup>th</sup>, hemodialysis was carried out and the next day renal biopsy was performed. This showed 13 normal glomeruli and numerous intra-tubular crystals, which were colorless under bright-field microscopy and strongly birefringent and polychromatic under polarized light (Figure 3). Furthermore, multifocal acute tubular injury was present together with rare lymphocytes and eosinophil aggregates in the interstitium, while vessels were normal. The immunofluorescence staining for immunoglobulins, C1q, C3, fibrinogen, and kappa and lambda light chains was negative.



**Figure 3: Renal biopsy. A. Calcium oxalate crystals within the tubules (hematoxylin-eosin stain, original magnification 200x). B. Detail at high magnification of image A. C. Intratubular crystals as seen under polarized light (original magnification 400x).**

In the same day, Urinalysis examination showed no crystalluria, which was confirmed in the following days (Table 1).

On June 4<sup>th</sup>, as renal function (serum creatinine 5.9 mg/dL; eGFR 15 mL/min) and general conditions had slowly improved, the patient was discharged. No respiratory, neurological, or cardiological symptoms were present. Subsequently, the patient was lost at follow-up.

## Discussion

In this paper, we describe a case of EG poisoning, whose clues for diagnosis were the patient's clinical history and the finding of: EG in the blood, numerous intratubular crystals at renal biopsy, and severe crystalluria at targeted urinary sediment examination performed with phase contrast and polarized light microscopy.

EG nephropathy is a rare condition, known since the late seventies [2, 3, 6].

EG is a fluid used in antifreeze solutions, whose ingestion occurs by mistake (children, work accidents) or intentionally, for suicidal purposes (as in our patient), or for its ethanol-like euphoric effect [1].

Shortly after ingestion, EG is oxidized in the liver, by alcohol dehydrogenase and aldehyde dehydrogenase, into glycolic acid, glyoxylic acid, and oxalic acid, all of which are highly toxic. Furthermore, oxalic acid binds to serum calcium, causing hypocalcemia and calcium oxalate crystal precipitation in the kidneys, central nervous system, heart, and lungs [1].

Several mechanisms lead to kidney injury. The first and principal one is the intratubular calcium oxalate crystals precipitation, with subsequent tubular obstruction. This is followed by crystal phagocytosis by tubular cells, which causes damage up to necrosis by apoptosis. Then, as a consequence of tubular membrane damage, crystals pass into the interstitium with subsequent inflammation and final "crystal granuloma" formation [12].



Definitive diagnosis of EG poisoning is based on serum and urinary EG levels measurement, which however is available only in highly specialized laboratories.

In the absence of EG levels, a presumptive diagnosis can be made if there is a strong suspicion of EG ingestion (as it was in our patient) associated with one or more of the following criteria [13]:

- arterial pH < 7.3
- serum bicarbonate levels < 20 mEq/L
- osmolal serum gap > 10 mOsm/L
- presence of spindle-like and needle-like crystals in the urine

A presumptive diagnosis can also be made if the ingestion of a toxic dose of EG is known (>100 mL) [14], associated with osmolal serum gap (OSG) > 10. Noteworthy, OSG is increased in the presence of EG, while anion gap increases only in the presence of EG metabolites [15].

Used examination is a simple, reliable, fast, and inexpensive tool to diagnose this severe clinical condition. This is characterized by the presence, usually in high amounts, of spindle- and needle-like mono- and bi-hydrate calcium oxalate crystals, strongly birefringent and polychromatic under polarized light (Figures 1 and 2) [6–11]. These are totally different from common mono- and bi-hydrate calcium oxalate crystals, as described by several authors (Figure 4).

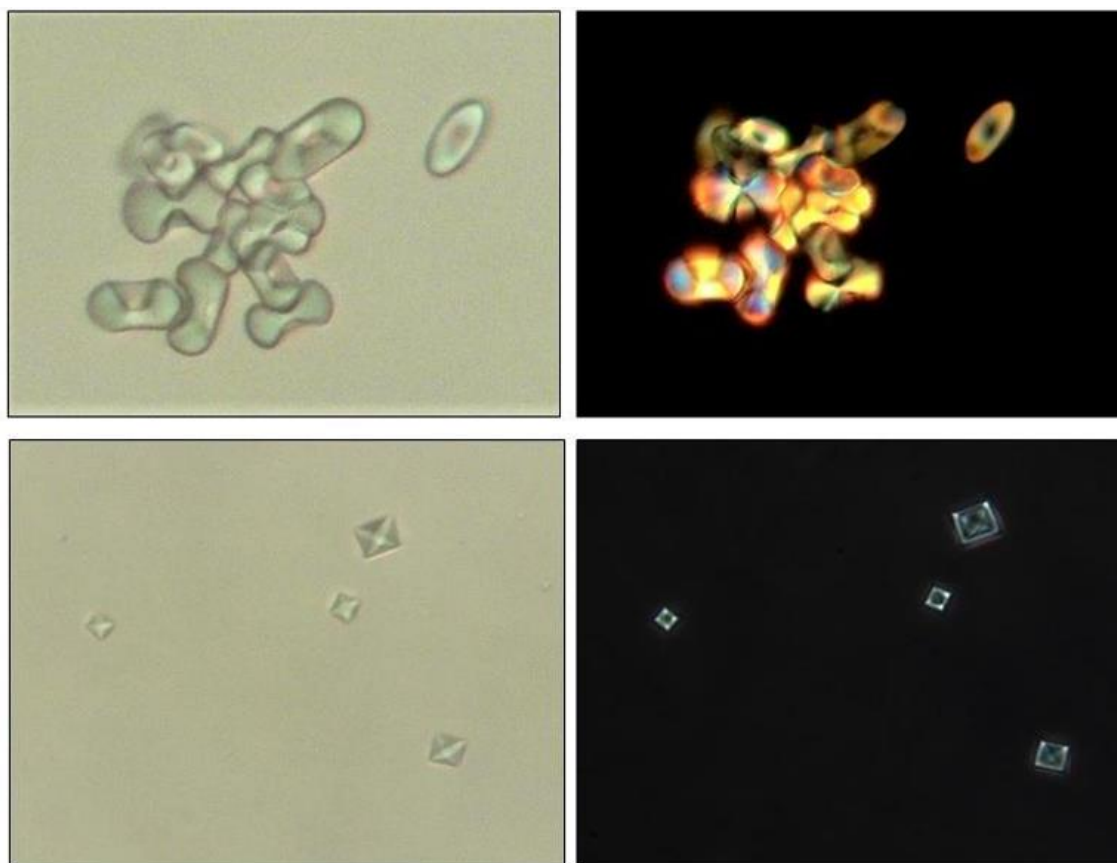


Figure 4: Common mono-hydrate calcium oxalate crystals, as seen with bright-field (A) and polarized light microscopy (B). Common bi-hydrate calcium oxalate crystals, as seen with bright field (C) and polarized light microscopy (D) (original magnification 400x).

As a treatment, fomepizole (or, if unavailable, ethanol) is used in patients with blood EG levels > 20 mg/dL, since it blocks alcohol dehydrogenase and the subsequent production of EG toxic metabolites [11]. Thiamine and pyridoxine can be used as alternative drugs for EG elimination [16].

Hemodialysis is an effective tool for the elimination of toxic metabolites from blood and electrolyte imbalance correction. It must be started in the presence of severe metabolic acidosis, high EG blood levels, and/or acute kidney injury [1].

According to Iliuta et al., dialysis should be performed with a large surface filter (>1.5 mq) and a high blood flow (300 mL/min) associated with fomepizole administration [17]. In addition, in patients with normal renal function and normal serum levels of phosphorus and potassium, Peces suggests the use of an HD solution of bicarbonate enriched with phosphorus and potassium [4]. An alternative dialytic approach is represented by sustained low-efficiency dialysis (SLED), which consists of a long procedure (up to 16 hours) that allows a slow removal from the blood of toxic substances with the prevention of their fast post-dialysis increase. SLED is primarily used for hemodynamically unstable patients [11].

Besides kidneys, EG poisoning involves other organs, as a consequence of calcium oxalate tissue deposition and/or metabolic alterations.

Neurologic involvement is characterized by drowsiness, euphoria, seizures, or coma in early stages. Later it can lead to nervous system depression [1].

Heart disease is characterized by arrhythmias and myocardial contractility reduction, also favored by metabolic acidosis and hypocalcemia [3].

Respiratory system damage is caused by two mechanisms: inhalation, with upper tract airways irritation after exposure to EG for four weeks or more [2]; ingestion, with pulmonary effects which occur in 12-72 hours: acute dyspnea, tachypnea, hyperventilation, pulmonary edema [3,18].

## Conclusions

Our case describes a rare clinical condition characterized by severe AKI, whose diagnosis requires an articulated approach, which includes Used examination, a fast and inexpensive diagnostic tool, often neglected by nephrologists.

## BIBLIOGRAFIA

1. Brent J. Current Management of Ethylene Glycol Poisoning. *Drugs* 2001; 61: 979-988. <https://doi.org/10.2165/00003495-200161070-00006>.
2. Wills JH, Coulston F, Harris ES, et al. Inhalation of aerosolized ethylene glycol by man. *Clin Toxicol* 1974; 7: 463-76. <https://doi.org/10.3109/15563657408988020>.
3. Vale JA. Ethylene glycol poisoning. *Vet Hum Toxicol* 1979; 21(Suppl):118-20. <https://doi.org/10.1136/pgmj.52.611.598>.
4. Peces R, Fernández R, Peces C et al. Effectiveness of pre-emptive hemodialysis with high-flux membranes for the treatment of life-threatening alcohol poisoning. *Nefrología* 2008; 28:413-418. <https://pubmed.ncbi.nlm.nih.gov/18662149/>.
5. Fogazzi GB, Passerini P, Bazzi M et al. Use of high power field in the evaluation of formed elements of urine. *J Nephrol* 1989; 2: 107-112. <https://moh-it.elsevierpure.com/en/publications/use-of-high-power-field-in-the-evaluation-of-formed-elements-of-u>
6. Godolphin W, Meagher EP, Sanders HD, et al. Unusual calcium oxalate crystals in ethylene glycol poisoning. *Clin Toxicol* 1980; 16: 479-486. <https://doi.org/10.3109/15563658008989977>.
7. Terlinsky AS, Grochowski J, Geoly KL, Stauch BS, Hefter L. Identification of atypical calcium oxalate crystalluria following ethylene glycol ingestion. *Am J Clin Pathol*. 1981; 76: 223-226. <https://doi.org/10.1093/ajcp/76.2.223>.
8. Jacobsen D, Hewlett TP, Webb R, Brown ST, Ordinario AT, McMartin KE. Ethylene glycol intoxication: evaluation of kinetics and crystalluria. *Am J Med*. 1988; 84: 145-152. [https://doi.org/10.1016/0002-9343\(88\)90024-1](https://doi.org/10.1016/0002-9343(88)90024-1).
9. Fogazzi GB. Crystalluria: a neglected aspect of urinary sediment analysis. *Nephrol Dial Transplant*. 1996; 11: 379-387. <https://pubmed.ncbi.nlm.nih.gov/8671802/>.
10. Fogazzi GB. The urinary sediment an integrated view, third edition. Milano, Elsevier: 2010, pp. 115-119.
11. Di Mario F, Delsante M, Palladini A, et al. Unexplained life-threatening high anion gap metabolic acidosis: the answer is in the urine! *J Nephrol* 2021; 34:2101–2104 <https://doi.org/10.1007/s40620-021-01051-9>.
12. Mulay SR, Anders HJ. Crystal nephropathies: mechanisms of crystal-induced kidney injury. *Nat Rev Nephrol*. 2017; 13:226-240. <https://doi.org/10.1038/nrneph.2017.10>.
13. Barceloux DG, Krenzelok EP, Olson K, et al. American Academy of Clinical Toxicology Practice Guidelines on the treatment of ethylene glycol poisoning. *J Toxicol Clin Toxicol* 1999; 37: 537-560. <https://doi.org/10.1081/ctt-100102445>.
14. Corley RA, Meek ME, Carney EW. Mode of action: oxalate crystal-induced renal tubule degeneration and glycolic acid-induced dysmorphogenesis – renal and developmental effects of ethylene glycol. *Crit Rev Toxicol* 2005; 35: 691–702. <https://doi.org/10.1080/10408440591007322>.
15. Regolisti G, Fani F, Antoniotti R, et al. Acidosi metabolica. *Giorn Ital Nefrol* 2016; 33: 1-39. <https://giornaleitalianodinefrologia.it/2016/12/acidosi-metabolica/>.
16. Grigorasi GR, Nistor I, Corlade-Andrei M, Voroneanu L, Siroopol D. Outcomes of death and prolonged renal insufficiency in ethylene glycol poisoned patients. *Int Urol Nephrol* 2021. <https://doi.org/10.1007/s11255-021-02837-3>.
17. Iliuta I-A, Lachance P, Ghannoum M, et al. Prediction and validation of the duration of hemodialysis sessions for the treatment of acute ethylene glycol poisoning. *Kidney Int* 2017; 92:453–460. <https://doi.org/10.1016/j.kint.2017.02.018>.
18. Piagnerelli M, Carlier E, Lejeune P. Adult respiratory distress syndrome and medullary toxicity: two unusual complications of ethylene glycol intoxication. *Intensive Care Med* 1999; 25:1200. <https://doi.org/10.1007/s001340051042>.