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NEPHROLOGY - REVIEW

Renal toxicity caused by diethylene glycol: an overview

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Abstract

Diethylene glycol (DEG) is nephrotoxic, potentially resulting in high morbidity and mortality. Its main nephrotoxic by-product is diglycolic acid (DGA). This narrative overview summarizes selected literature with a focus on clinical findings, pathophysiology, diagnosis including morphological features of renal biopsies, and management. The kidney injury in DEG poisoning is secondary to proximal tubular necrosis caused by DGA. Marked vacuolization and edema of epithelial cells obstruct the lumen, reducing urine flow and, consequently, resulting in anuria and uremia. The clinical alterations due to DEG poisoning are dose-dependent. Patients may present with gastrointestinal symptoms and anion gap metabolic acidosis, followed by renal failure, and, later, encephalopathy and neuropathy. Although this three-phase pattern has been described, signs and symptoms may be overlapping. Data about DEG intoxication is scarce. Sometimes the diagnosis is challenging. The management includes supportive care, gastric decontamination, correction of acid–base disorders, and hemodialysis. The understanding of the metabolic processes related to DEG poisoning may contribute to its management, preventing death, serious sequels, or irreversible lesions.

Keywords Diethylene glycol · Intoxication · Nephrotoxicity · Acute kidney injury · Metabolic acidosis

Introduction

Diethylene glycol (DEG) is an odorless and sweet substance that is toxic to humans [1]. As alcohol with peculiar physicochemical characteristics, it has several uses in the industry [2]. DEG is a solvent found in many consumer products, including antifreeze, brake fluids, lubricants, cosmetic creams, and paints [3].

This alcohol is described in the scientific literature as an agent capable of causing renal toxicity, whose intoxication produces severe metabolic acidosis with an increased anion gap and acute kidney injury [1, 2, 4–7]. These changes are associated with high morbidity and mortality. The clinical symptoms of DEG include vomiting, sensory alterations, oliguria, azotemia, and elevated levels of transaminases, which could indicate liver damage [8].

The first report of mass poisoning by DEG occurred in 1937 and, since then, some epidemics have been described [3]. Despite this, the data available in the literature are scarce and with limited analyzes regarding short- and long-term effects. [7]

In this context, we aimed to summarize the selected literature about renal toxicity associated with DEG poisoning in this narrative review.

Methodology

Data were obtained independently by four authors who carried out a non-systematic search in the PubMed database. Search strategies included Medical Subject Heading terms for "diethylene glycol" and "kidney injury''. The selection criteria were: (i) time frame from 2015 to 2021; (ii) observational studies (case series, case–control, cohort, and cross-sectional), clinical trials, recent consensus statements,

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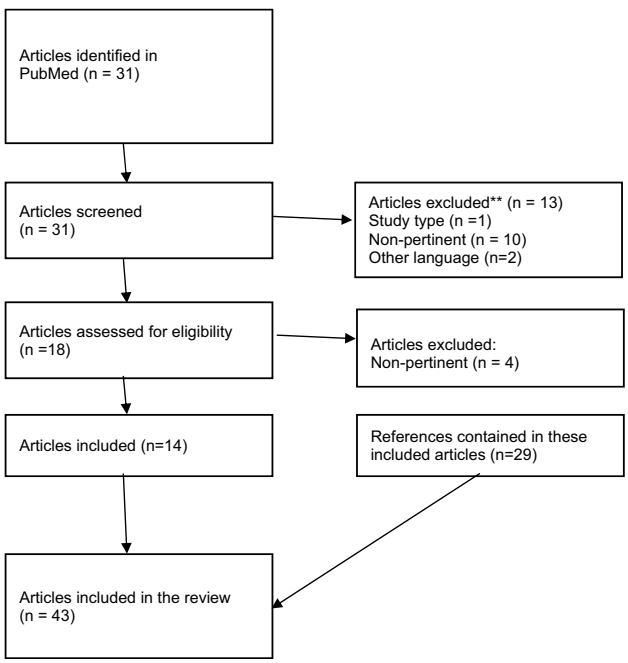
and guidelines; (iii) full text available in electronic format, written in English or Portuguese; (iv) studies with adequate methodological rigor; and (v) studies about any aspect concerning kidney injury associated with DEG intoxication. The exclusion criteria were: (i) studies that did refer to kidney injury associated with DEG; (ii) articles other than the specified inclusion criteria. Adopting the aforementioned search descriptors, 31 articles were obtained and had the title and abstract read by four authors. After this step, 14 articles were selected and completely read. In addition, the bibliographic references of the identified articles were also evaluated. To provide an overview of outcomes from selected case reports and case series, we calculated percentages of total cases reviewed that presented with certain clinical features.

The details of the selection process are displayed in Flowchart 1.

Pathophysiology

Pharmacokinetic data from DEG were not obtained directly from humans, since, in addition to the high toxicity of DEG metabolites, the diagnosis of this intoxication is usually delayed, which can make diagnosis and data collection difficult. In this sense, pre-clinical trials present an important tool for the study of the mechanisms of DEG toxicity [9].

Although DEG consists of two linked ethylene glycol molecules, its metabolism generates different products, which are not ethylene glycol (EG) and its by-products. Calcium oxalate crystals, one of the metabolites of EG



Flowchart 1. Flow diagram of studies selected for inclusion in the review

responsible for renal injury, are not observed in tissues of DEG [2, 9].

After oral ingestion, DEG is rapidly absorbed by the gastrointestinal tract and is subsequently widely distributed to most tissues through blood circulation. According to an experimental study in primates, the peak of serum concentration occurs between 30 and 60 min [10]. Dermal absorption can also occur, although it is less common [11].

Experimental models with rats showed that about 50–70% of DEG is oxidized by alcohol dehydrogenase (ADH) in 2-hydroxyethoxy acetaldehyde and then, by aldehyde dehydrogenase (ALDH), in acetic 2-hydroxyethoxy acid (HEAA), whose excretion is mostly renal. HEAA is responsible for metabolic acidosis and organ dysfunction observed in DEG poisoning [12, 13]. In addition, HEAA promotes membrane destabilization and intracellular accumulation of osmotically active particles, with a consequent fluid diversion through the plasma membrane [12, 13].

Another product of DEG metabolism that has been related to renal injury is diglycolic acid (DGA), also known as oxydiacetic acid, formed from HEAA. DGA undergoes glomerular filtration and is transported to proximal tubular cells by atypical sodium dicarboxylate transporters-1 or carriers of organic anions [9, 11]. In the proximal tubule, the compound inhibits the citric acid cycle enzyme, succinate dehydrogenase, causing cell death by blocking the production of adenosine triphosphate [14]. Robinson et al. [15] demonstrated that direct administration of DGA to rats produced renal injury at a dose of 300 mg/kg. However, no toxicity was observed at a dose of 100 mg/kg. Renal histopathology of rats receiving the high dose of DGA showed marked degeneration and necrosis of the proximal tubules. These pathologic findings are also reported in cases of human toxicity [2, 9, 11, 15]. Furthermore, Landry et al. [16] showed that the DGA, at the concentration of 50 mmol/L, promoted a reduction in ATP levels of the proximal tubule cells, besides reducing oxygen consumption by these cells. Therefore, the substance acts by interfering both in energy production and in the use of mitochondrial oxygen [16, 17]. The increased urinary levels of kidney injury molecule 1 indicated proximal tubule lesions [15].

Another mechanism of injury that has been frequently identified in the cells of the proximal tubule due to the use of toxic compounds is the increased production of reactive oxygen species (ROS) in mitochondria [18, 19]. In addition to NADPH in the cytoplasm, and ketoglutarate dehydrogenase in the mitochondrial matrix, other important sources of ROS include electron carrier chain complexes I and II. In the presence of hypoxia, succinate dehydrogenase (complex II) has been shown to generate superoxide by undergoing the conversion of dehydrogenase to fumarate reductase. Thus, fumarate receives its electrons from complex I in a reverse electron transport mechanism, functioning as a final electron

acceptor and generating ROS [20]. DGA, by inhibiting the cell's ability to consume oxygen, places the cell in a condition of "pseudohypoxia". This condition, then, may trigger the process described above, culminating in the generation of ROS [17].

In many cases, antioxidant compounds such as N-Acetyl-L-Cysteine and L-ascorbic acid were able to inhibit the production of ROS induced by toxic agents, in addition to stimulating the growth and regeneration of mitochondrial functions [21–23]. However, Landry et al. [16] showed the use of antioxidants in cells exposed to DGA was not able to reduce cell death at the highest concentration of 50 mmol/L. This result indicated that DGA-induced cytotoxicity occurred independently of ROS production, probably by an alternative mechanism. One possible alternative mechanism would be the inhibition of succinate dehydrogenase by DGA, considering that antioxidants are not able to antagonize this process. Inhibition of succinate dehydrogenase results in decreased ATP and cell death. In this case, the production of ROS would be a by-product of cell death. In the case of lower concentrations of DGA (25 mmol/L), the antioxidant can reduce DGA-induced cell death, suggesting that, at smaller concentrations, the production of ROS has a role in cell death. Inhibition of succinate dehydrogenase seems to represent the main mechanism by which DGA produces its toxic effects. This inhibition promotes ROS production, decreased oxygen consumption, and ATP levels, which result in cell death. [17]

Thus, kidney injury in DEG poisoning is secondary to proximal tubular necrosis caused by DGA. In addition, marked vacuolization and edema of epithelial cells obstruct the lumen, reducing urine flow and, consequently, resulting in anuria and uremia [17].

Figure 1 shows metabolic pathways of DEG metabolism.

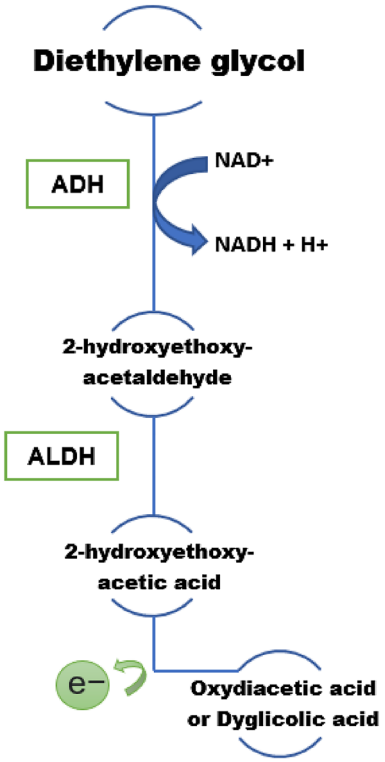


Fig. 1 Metabolic pathways of diethylene glycol. DEG is oxidized by alcohol dehydrogenase (ADH) to 2-hydroxyethoxy acetaldehyde. After that, 2-hydroxyethoxy acetaldehyde is converted by aldehyde dehydrogenase (ALDH) to 2-hydroxyethoxy acetic acid (HEAA), responsible for metabolic acidosis and organ dysfunction. As shown in Fig. 1, calcium oxalate crystals are not involved in DEG poisoning. Adapted from: Kraut JA, Kurtz I (2008) Toxic alcohol ingestions: clinical features, diagnosis, and management. Clin J Am Soc Nephrol 3(1): 208–225. https://doi.org/10.2215/cjn.03220807

Morphological aspects of diethylene glycol kidney toxicity

Diethylene glycol (DEG) is a similar molecule to ethylene glycol. Both molecules can be produced in analogous processes and can cause acute renal failure. Initially, DEG was thought to be metabolized by endogenous cleavage of any bond to form ethylene glycol, which would be responsible for the adverse effects. Some experimental models with rats showed oxalate crystals in the urine of animals receiving DEG suggesting that toxic effects could be caused by the formation and subsequent metabolism of the ethylene glycol [23]. However, other studies in dogs and rabbits did not show any increase in urinary oxalate concentrations after oral administration of DEG [22, 26]. Successive studies using radiolabeled DEG in rats and dogs confirmed this last observation [12]. In addition, DEG-poisoned patients did not show urinary oxalate formation. This finding supports the argument that endogenous conversion of DEG to ethylene glycol does not occur [27–29]. Based on these results, it appears that DEG is not metabolized to two ethylene glycol molecules, likely due to its metabolically stable structure. It was hypothesized that the experiments suggesting oxalate formation may have involved products contaminated with ethylene glycol. The overwhelming evidence is that DEG metabolism does not lead to the formation of oxalate crystals within the kidney [27].

Renal acute injuries appear to arise mainly from tubular cytoplasm degeneration, markedly presenting as diffuse/severe vacuolation. Cytoplasmic vacuolization (also called cytoplasmic vacuolation) is a well-known morphological phenomenon observed in mammalian cells after exposure to bacterial or viral pathogens as well as to various toxic natural and artificial low-molecular-weight compounds. The vacuolization can be transient, but it is more likely to cause irreversible damage. The vacuolation due to DEG poisoning is not fully understood. This process may be related to the hydropic degeneration (swelling) secondary to increased

osmotic pressure, steatosis associated with basic amine-containing lipophilic compounds, complex lipids, and ion pump dysfunction as a consequence of alterations on Na, K-ATPase or Calcium-Activated Potassium Channels [30]. Vacuolization often accompanies cell death; however, its role in cell death processes remains unclear. There is an accentuated clear (negative image) dilatation of the cytoplasm like ballooned or fatty degeneration in tubular cells [27, 31]. Tubular lesions mainly occur in the proximal convoluted tubules and are restricted to the cortical regions of the kidney [24]. Toxic lesions of proximal tubules also manifest as cortical infarctions and/or necrosis, with vascular congestion, diffuse interstitial hemorrhage, and edema [25]. In addition, a profound swelling of the tubular epithelium can cause complete obliteration of the lumen [2, 32]. Depending on the amount or intensity of the exposure to the poison, vascular lesions, such as vascular necrosis and thrombotic microangiopathy, could be found (see images of renal biopsies from our personal archive in Figs. 2 and 3). Vacuolization may occur in podocytes and the parietal epithelium of Bowman's capsule cells. Swelling of the organelles, including the mitochondria, may also be seen (see images of renal biopsies from our personal archive in Figs. 2 and 3).

Chronic changes are nonspecific, sharing the same findings as other end-stage renal diseases, including globally sclerosed glomeruli, atrophic tubules, diffuse interstitial fibrosis and discrete infiltrate of inflammatory cells [33].

Clinical findings

Three case series and five case reports were included in this review, accounting for 69 cases [2, 7–9, 11, 34–36]. Twenty-eight patients (40.58%) were female and the unintentional ingestion of contaminated drug solutions was the major form of intoxication, corresponding to 58 (84.05%)

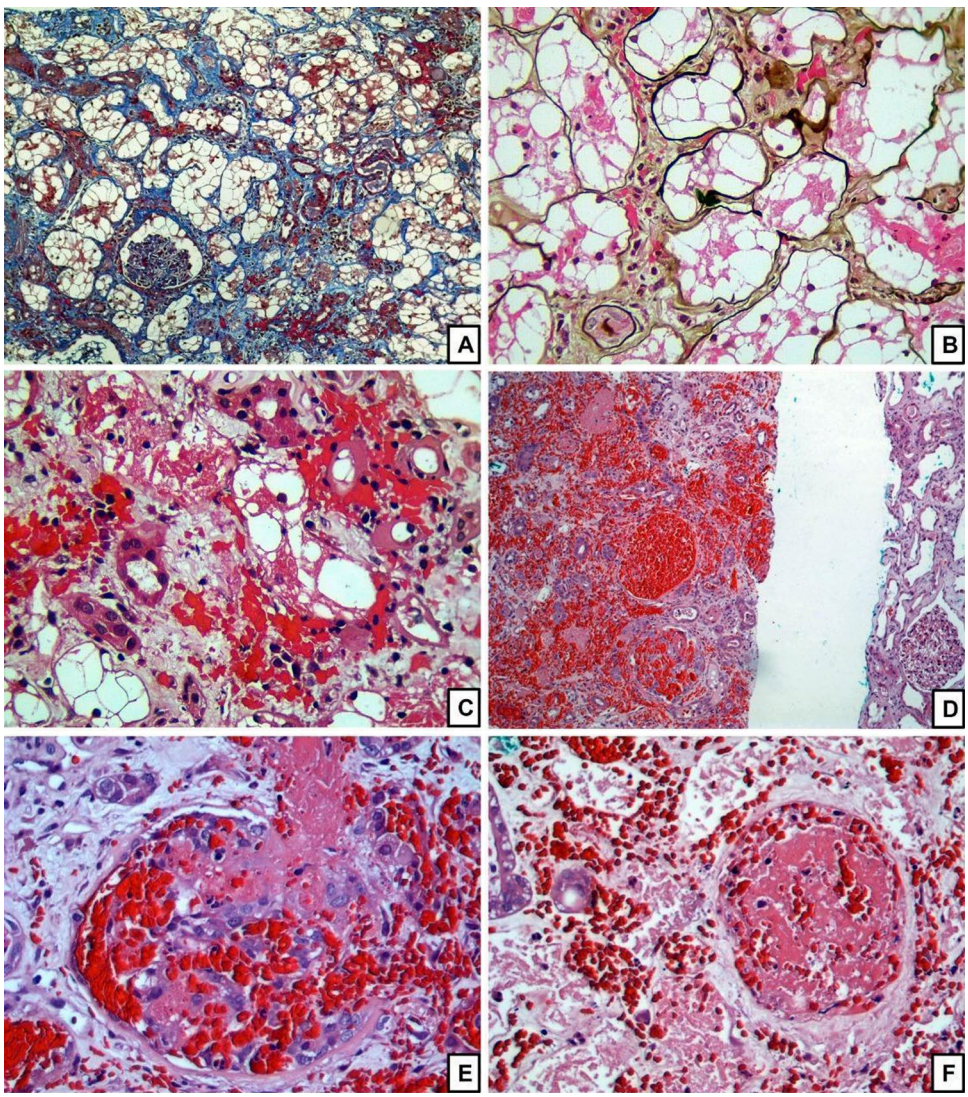


Fig. 2 Renal Biopsies from patients intoxicated with Diethylene Glycol (personal archive). **A** Masson Trichrome (10X) shows diffuse tubular proximal tubular dilatation, with extreme cellular edema, and vacuolization, causing obliteration of the lumen. Capsular Bowman's cells and podocytes vacuolization can also be seen. **B** Silver Jone´s Stain (40X) shows details of cellular vacuolization. **C** H&E (40X) shows diffuse interstitial edema and hemorrhage among tubular degeneration and vacuolization. **D** H&E (10X) shows congestion, hemorrhage, and diffuse necrosis. **E** H&E (10X) shows thrombotic microangiopathy of the glomerular tufts. **F** H&E (40X) shows arterial thrombosis and diffuse acute tubular necrosis. Source: Personal archive of the first author

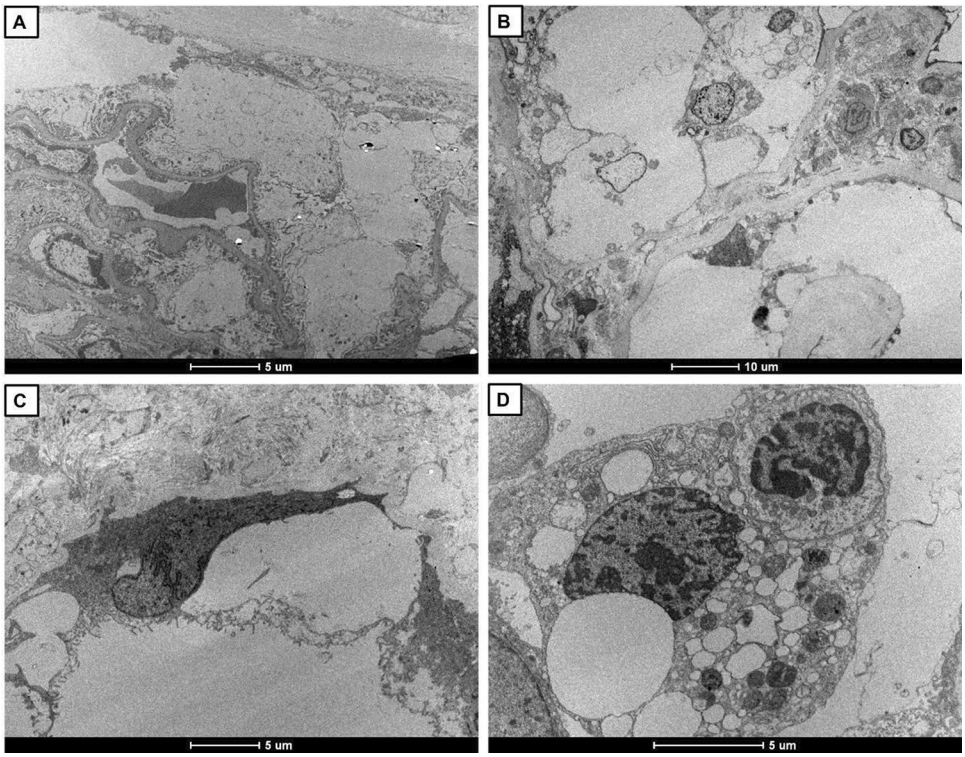


Fig. 3 Transmission Electron Microscopy of renal tissue from patients intoxicated with Diethylene Glycol (personal archive). Renal biopsy was fixed, buffered 10% formalin, and stained with osmium tetroxide, and ruthenium red. **A** Edema and disorganization of the podocyte cytoplasm and parietal Bowman's capsule cells. **B** Diffuse tubular cells edema and vacuolization of the cytoplasm. **C** Proximal tubules with extensive vacuolization and eccentric nuclei seclusion. **D** Detail of the cytoplasmic change and multifocal vacuolization, including swollen mitochondria. Source: Personal archive of the first author

cases. After the ingestion of DEG, the main initial symptoms were: oliguria or anuria (52–75.36%), respiratory symptoms (27–39.13%), fever (26–37.68%), diarrhea (24–34.78%), fatigue (11–15.94%), altered level of consciousness (11–15.94%) and abdominal pain (8–11.59%). Furthermore, 64 (92.75%) patients were hospitalized, of which 48 (75%) evolved with the absence of brainstem reflex. Of the analyzed group, 59 (85.5%) presented with high anion gap metabolic acidosis, 64 (92.75%) had acute kidney injury (AKI) and 63 (91.30%) required renal replacement therapy. Finally, 36 (52.17%) patients died.

High anion gap acidosis and acute kidney injury were commonly reported in the cases included in this review. The studies reported that most intoxicated individuals do not know, precisely, the amount of liquid ingested and/or the concentration of DEG in the contaminated liquid [2, 7–9, 34, 35]. The minimum dose reported in selected studies was 0.14 mg/kg and the reported lethal dose (based on one among eight studies) ranged from 1 to 1.63 g/ kg [34]. According to data of animal studies, O'Brien et al. suggested that the clinical repercussions of DEG metabolites are dose-dependent [37].

Based on our review of the selected cases series and reports, it appears there is a 3-phase pattern in presenting features of DEG poisoning (Fig. 4). Initially, the first phase consists of gastrointestinal symptoms including nausea, vomiting, abdominal pain, and diarrhea. At this stage, the patient can also have metabolic acidosis. The second phase

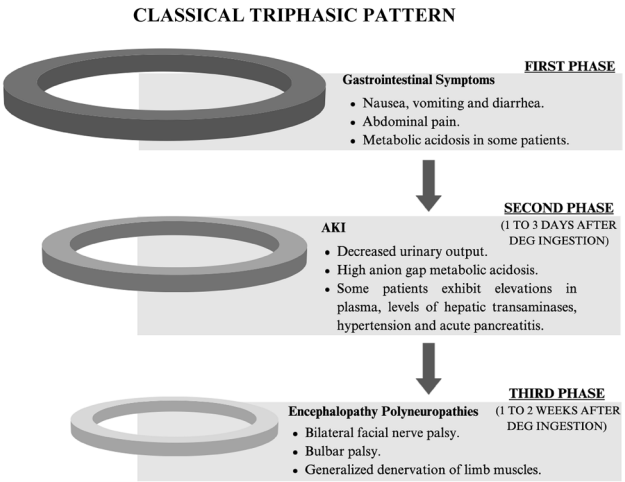


Fig. 4 Classical triphasic pattern of Diethylene glycol (DEG) poisoning. Source: Own authorship

occurs 1 to 3 days after DEG ingestion and is marked by AKI, with decreased urinary output and high anion gap metabolic acidosis. Liver injury has been described in some cases that show the elevation of serum transaminases [9]. In addition, patients may have hypertension [8, 9] and acute pancreatitis [27].

The third phase occurs 1 to 2 weeks after DEG ingestion if the patient survives the initial phases. This phase

is marked by progressive and late neurological syndrome, which is characterized by encephalopathy and polyneuropathies, including bilateral facial nerve palsy, bulbar palsy, and generalized denervation of limb muscles [38].

Although this three-phase pattern has been described, signs and symptoms may be overlapping and can be modified by the ingested dose. The ingestion of DEG combined with other compounds, such as ethanol, can also modify the clinical presentation of intoxication. In this case, ethanol inhibits DEG metabolism and may delay symptoms onset for up to 48 h [5].

Table 1 summarizes the clinical findings of the studies with DEG poising.

Diagnosis

Treatment is often initiated based on history, clinical presentation, and clinical suspicion. Gas chromatographic methods can confirm exposure although these exams are not readily available [11]. During the first hours of intoxication, there is an increase in the osmolal gap, which can be greater than 20 mOsm/L, suggesting the presence of an unknown substance of low-molecular-weight in the body. After DEG is converted to 2-hydroxyethoxy acetic acid, the osmolal gap narrows, but the anion gap increases with consequent metabolic acidosis [11].

Elevations in the plasma levels of hepatic transaminases and amylases can also be detected [9, 27]. These laboratory markers, in addition to helping the diagnosis of DEG poisoning, also allow the assessment of the patient's evolution and the poisoning severity.

Treatment

Although data are scarce, reported management of DEG poisoning includes supportive care, gastric decontamination, correction of acid–base disorders, and hemodialysis [5]. In addition, patients who survived DEG poisoning should be followed-up to assess possible medium and long-term consequences.

The use of fomepizole or ethanol has also been suggested [39, 40] as a means of inhibiting alcohol dehydrogenase in an attempt to block the metabolism of DEG (Fig. 5). Fomepizole has an approximately 500 times greater affinity for ADH than ethanol and can completely inhibit its activity at lower serum concentrations [39, 40]. The compound is approved for the treatment of poisoning by methanol and ethylene glycol. However, fomepizole has a high cost and low availability, while ethanol is easy to access at a low cost. In cases of DEG poisoning, fomepizole is used off-label and administered by intravenous infusion [41, 42].

Besenhofer et al. [13] demonstrated that rats receiving high doses of DEG and fomepizole had no increase in urea and creatinine, with only one of the six rats developing mild renal tubular necrosis. In contrast, rats that received only high doses of DEG had significant elevation of markers of kidney injury, and renal tubular necrosis was found in 5 of 6 rats. Thus, fomepizole may be an useful antidote for acute DEG poisoning [13, 43], especially at centers in which acute hemodialysis may not be readily available [43].

In addition, hemodialysis may also be required to correct serious metabolic abnormalities and increase the elimination of DEG and its metabolites [5, 39, 43]. Hemodialysis should be continued until metabolic acidosis [5, 43], the anion gap, and the osmolal gap improve, and the systemic signs of toxicity disappear. Thus, it seems that the early use of fomepizole together with prompt hemodialysis can minimize the effects of DEG ingestion, representing an effective management plan for these patients.

Figure 5 shows the summary of treatment of DEG poisoning.

Concluding remarks

The pathophysiology of DEG poisoning is not well understood and needs further studies. Renal biopsies of patients poisoned with DEG show diffuse interstitial edema and hemorrhage associated with tubular degeneration and vacuolization. The diagnosis of DEG poisoning is not easy, resulting in delays to start the treatment. Thus, DEG poisoning should be suspected in case of high anion gap metabolic acidosis with multisystem involvement. The treatment is mainly based on supportive care measures and the use of fomepizole seems to be beneficial, but further studies are necessary to establish its indication.

Our review has limitations. First, we have searched a single database, pubmed, which may have resulted in missed literature. Moreover, the designs of the studies, up to now, are not so robust, thus precluding definitive conclusions. Nevertheless, our study summarizes important and available data on kidney injury secondary to DEG poisoning.

In conclusion, the understanding of the metabolic processes related to DEG poisoning may contribute to its management, preventing death, serious sequels, or irreversible lesions.

Table 1 Main findings of the studies about Diethylene glycol (DEG) poisoning

Author	Study design	Main findings
Rentz et al. [1]	Case–control study	Cases ($n=42$) were admitted to the hospital with acute renal failure of unknown etiology or with an acute worsening of pre-existing chronic kidney disease. Controls ($n=140$) were admitted to the same hospital for reasons other than renal failure, age and sex-matched with cases. The primary exposure of interest was the consumption of cough syrup within a specified time period prior to hospital admission. A significant association was found between the intake of cough syrup and the onset of the disease. Laboratory analyses confirmed the presence of diethylene glycol (DEG) in samples of the cases. Cases had more general, gastrointestinal, respiratory, urinary, and neurological signs and symptoms than controls. The mean serum creatinine was significantly higher in cases than in controls
Alfred et al. [2]	Case series	Seven male patients ingested variable amounts of DEG. Three patients that ingested the largest quantities, presented severe metabolic acidosis and acute renal failure requiring hemodialysis. They remained dialysis-dependent and developed neuropathies. One of them died due to cerebral edema. Two other patients had normal renal function and moderate metabolic acidosis requiring hemodialysis. They remained well. The last two patients did not require any therapy
Alkantani et al. [3]	Review	Several epidemics of acute renal failure affecting predominantly young children were caused by DEG poisoning. The children had gastrointestinal bleeding, seizures, liver and renal failure. The poisoning has been the result of either contamination of the medicinal products or the illegal use of DEG as a solvent. More than 300 children worldwide died from DEG poisoning
Wittschieber et al. [7]	Case report	A previously healthy 26-year-old man ingested about 400 ml of a liquid contaminated with DEG. Two days later, the patient developed severe abdominal pain, nausea and vomiting. After admission to the hospital, the patient was diagnosed with acute renal failure and started on dialysis. The patient died eight days after consuming the liquid. A forensic autopsy was performed three days later showing alterations in the kidneys (smooth and with necrosis), liver, lung and brain. Significant changes in kidney histology included acute diffuse coagulation necrosis of the upper two-thirds of the cortical structures, accompanied by severe interstitial hemorrhage and neutrophils infiltration
Hari et al. [8]	Case series	Eleven children (9 were boys) from 7 to 42 months had acute renal failure. They received an oral medication with high concentration of DEG. All children developed anuria, 7 (64%) had diarrhea, and 9 (82%) had altered sensorium. All patients developed encephalopathy and required ventilation. Eight patients (72%) died due to encephalopathy and the 3 (27%) who survived had neurological sequelae and abnormal renal function. Renal biopsies were done in 5 patients and showed acute tubular necrosis predominantly in the proximal convoluted tubules
Gopalakrishnan et al. [9]	Case report	A 14-year-old boy was admitted to the hospital with acute abdominal pain and vomiting after accidental consumption of 100 ml of brake fluid. He developed severe renal failure, hypertension, oliguria and generalized tonic–clonic seizures. The neurologic condition worsened with bilateral sensorineural hearing loss. Laboratory studies showed high anion gap metabolic acidosis and hemodialysis was started. Renal biopsy showed severe acute tubulointerstitial nephritis with tubular necrosis. After 4 months, the patient showed complete improvement
Devoti et al. [11]	Case report	A 29-year-old African man without significant medical history developed anuria, gastrointestinal symptoms, and hypertension after the contact in his skin with the brake fluid containing DEG. Laboratory studies showed high anion gap metabolic acidosis and the neurologic situation progressively worsened. He needed mechanical ventilation and hemodialysis. Renal biopsy showed acute proximal tubular necrosis without oxalate crystals. He progressively improved renal and neurologic function
Morelle et al. [27]	Case report	A previously healthy 40 year-old man had a 4-day history of nausea, general weakness, abdominal pain, diarrhea, and progressive anuria. He ingested a "special drink" 5 days earlier. Laboratory data showed acute renal failure and high anion-gap metabolic acidosis. Serum toxicological screening failed to detect methanol, ethylene glycol or ethanol. Renal biopsy revealed acute and extensive tubular injuries, without tubular oxalate crystals. Intermittent hemodialysis was initiated. By the seventh day, the patient developed a flaccid tetraparesis and an acute loss of visual acuity. Facial electromyography confirmed severe axonal neuropathy and fundoscopic examination showed bilateral papillary edema. The vision recovered early, whereas tetraparesis began to resolve on day 27. Renal replacement therapy was interrupted on day 28 and the patient was able to walk on day 34. Eight months later, complete peripheral facial diplegia and a slight impairment in renal function persisted

Table 1 (continued)

Author	Study design	Main findings
Jain et al. [34]	Case report	A 5-year-old boy received an oral medication with high concentration of DEG. The initial symptoms were: anuria, respiratory symptoms, and fever. He had high anion gap metabolic acidosis, uremia, and increased transaminases. The boy developed hypertension, encephalopathy and respiratory failure. Renal ultrasonography showed bilateral cortical hyperechogenicity. The treatment included antimicrobials, hemodialysis, mechanical ventilation, and supportive measures. He was discharged with normal renal function, but severe neurological sequels and quadriparesis
Sosa et al. [35]	Retrospective cohort	Forty-six patients (24 females) with median age of 67 years were admitted with acute kidney injury or acute worsening of chronic kidney disease. Most common initial signs/symptoms were oliguria/anuria (74%), respiratory alterations (54%), and nausea/vomiting (50%). Forty patients (87%) developed neurologic signs, 42 (93%) needed hemodialysis and 27 (59%) died. Autopsies were performed in 8 patients showing tubular epithelial necrosis and luminal dilatation consistent with acute tubular necrosis without oxalate crystals
Marraffa et al. [36]	Case report	A 27-year-old man intentionally ingested 16 oz of wallpaper containing 26% DEG. Laboratory tests revealed metabolic acidosis and acute renal failure. The patient developed progressive lethargy, dysphonia, facial diparesis, dilated non-reactive pupils, loss of corneal and gag reflexes, and loss of visual and auditory function. An electromyography/neuronal conduction velocity (EMG/NCV) study showed mild generalized sensorimotor peripheral neuropathy without definitive evidence of demyelination. The patient needed mechanical ventilation, hemodialysis, and remained unresponsive until day 47, when he recovered pupillary light reflexes. On day 56, another EMG/NCV study showed severe peripheral sensorimotor demyelinating polyneuropathy. Renal ultrasound revealed markedly atrophic kidneys with severe cortical thinning. The neurological status improved and, after 6 months, he was discharged home, but still dependent on hemodialysis
O`Brien et al. [37]	Case–control study	Cases were defined as Haitian residents less than 18 years of age with idiopathic anuria or severe oliguria for 24 h or more. Febrile hospitalized children without renal failure were enrolled as controls. The study detected 109 cases of acute renal failure. The clinical features included renal failure, hepatitis, pancreatitis, central nervous system impairment, coma, and death. Among 87 patients who remained in Haiti, 85 died (98%). The acetaminophen syrup was highly associated with disease. DEG was found in the bottles of the syrup in a median concentration of 14.4%. Glycerin, a raw material used in the formulation of acetaminophen, was contaminated with 24% DEG

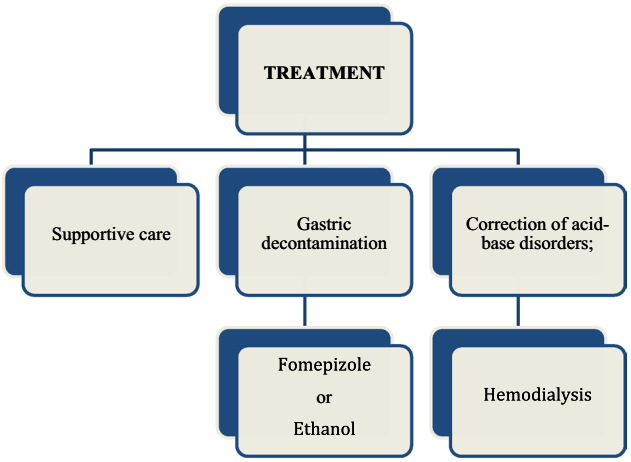


Fig. 5 Main steps of the treatment of Diethylene glycol (DEG) poisoning. Source: Own authorship

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Data availability Not applicable.

Declarations

Conflict of interest The authors declare no conflicts of interest.

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