

# UC San Diego

## UC San Diego Previously Published Works

### Title

Extracorporeal treatment for ethylene glycol poisoning: systematic review and recommendations from the EXTRIP workgroup.

### Permalink

<https://escholarship.org/uc/item/58g1q5k7>

### Journal

Critical Care (UK), 27(1)

### Authors

Ghannoum, Marc

Gosselin, Sophie

Hoffman, Robert

et al.

### Publication Date

2023-02-10

### DOI

10.1186/s13054-022-04227-2

### Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

RESEARCH

Open Access



# Extracorporeal treatment for ethylene glycol poisoning: systematic review and recommendations from the EXTRIP workgroup

Marc Ghannoum<sup>1,2,3</sup>, Sophie Gosselin<sup>4,5,6</sup>, Robert S. Hoffman<sup>7</sup>, Valery Lavergne<sup>1</sup>, Bruno Mégarbane<sup>8</sup>, Hossein Hassanian-Moghaddam<sup>9,10</sup>, Maria Rif<sup>11</sup>, Siba Kallab<sup>12</sup>, Steven Bird<sup>13</sup>, David M. Wood<sup>14</sup>, Darren M. Roberts<sup>15,16\*</sup> and for the EXTRIP Workgroup

## Abstract

Ethylene glycol (EG) is metabolized into glycolate and oxalate and may cause metabolic acidemia, neurotoxicity, acute kidney injury (AKI), and death. Historically, treatment of EG toxicity included supportive care, correction of acid–base disturbances and antidotes (ethanol or fomepizole), and extracorporeal treatments (ECTRs), such as hemodialysis. With the wider availability of fomepizole, the indications for ECTRs in EG poisoning are debated. We conducted systematic reviews of the literature following published EXTRIP methods to determine the utility of ECTRs in the management of EG toxicity. The quality of the evidence and the strength of recommendations, either strong (“we recommend”) or weak/conditional (“we suggest”), were graded according to the GRADE approach. A total of 226 articles met inclusion criteria. EG was assessed as dialyzable by intermittent hemodialysis (level of evidence = B) as was glycolate (Level of evidence = C). Clinical data were available for analysis on 446 patients, in whom overall mortality was 18.7%. In the subgroup of patients with a glycolate concentration  $\leq 12$  mmol/L (or anion gap  $\leq 28$  mmol/L), mortality was 3.6%; in this subgroup, outcomes in patients receiving ECTR were not better than in those who did not receive ECTR. The EXTRIP workgroup made the following recommendations for the use of ECTR in addition to supportive care over supportive care alone in the management of EG poisoning (very low quality of evidence for all recommendations): i) Suggest ECTR if fomepizole is used and EG concentration  $> 50$  mmol/L OR osmol gap  $> 50$ ; or ii) Recommend ECTR if ethanol is used and EG concentration  $> 50$  mmol/L OR osmol gap  $> 50$ ; or iii) Recommend ECTR if glycolate concentration is  $> 12$  mmol/L or anion gap  $> 27$  mmol/L; or iv) Suggest ECTR if glycolate concentration 8–12 mmol/L or anion gap 23–27 mmol/L; or v) Recommend ECTR if there are severe clinical features (coma, seizures, or AKI). In most settings, the workgroup recommends using intermittent hemodialysis over other ECTRs. If intermittent hemodialysis is not available, CKRT is recommended over other types of ECTR. Cessation of ECTR is recommended once the anion gap is  $< 18$  mmol/L or suggested if EG concentration is  $< 4$  mmol/L. The dosage of antidotes (fomepizole or ethanol) needs to be adjusted during ECTR.

**Keywords** EXTRIP, Hemodialysis, CKRT, Poisoning, Ethylene glycol

\*Correspondence:

Darren M. Roberts

1darren1@gmail.com

Full list of author information is available at the end of the article

## Introduction

Ethylene glycol (EG) poisoning is associated with a high likelihood of acute kidney injury (AKI) [1–3] and mortality [4, 5]. In 2020, the US poison control centers reported



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

6036 calls relating to EG, 586 of which had at least moderate clinical effects and 30 of which resulted in death [6]. Hemodialysis was first reported in the management of an EG-poisoned patient in 1959 [7] and became a critical component of the management of EG poisoning [8]. However, with the advent and wider availability of fomepizole, the indications for extracorporeal treatments (ECTRs), such as intermittent hemodialysis and continuous kidney replacement therapy (CKRT), have evolved and the role of ECTRs is currently being challenged [9–11].

The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup is composed of international experts representing diverse specialties and professional societies (Additional file 1: Table S1). Its mission is to provide recommendations on the use of ECTRs in poisoning (<http://www.extrip-workgroup.org>). The rationale, background, objectives, methodology, and its initial recommendations are previously published [12–14]. The objective of this article is to present EXTRIP’s systematic review of the literature and recommendations for the use of ECTR in patients poisoned with EG. Although diethylene glycol and other alcohols share common characteristics with EG, this review is restricted to EG poisoning.

**Physicochemical characteristics and toxicokinetics**

The toxicokinetics of EG are summarized in Table 1. EG, like other alcohols, is a small water-soluble molecule that is quickly and completely absorbed in the gastrointestinal tract. It has negligible protein binding and distributes in total body water. One third of absorbed EG is eliminated unchanged in urine while two-thirds are oxidized in the liver by the enzyme alcohol dehydrogenase (ADH)

to glycolaldehyde, which is then rapidly converted to glycolate by aldehyde dehydrogenase [15]. Glycolate is converted to glyoxylate by glycolate oxidase which is the rate-limiting step. Glyoxylate is later metabolized by various pathways to oxalate and non-toxic products such as glycine and α-hydroxy-β-ketoacid. EG elimination follows first-order pharmacokinetics but a biphasic elimination profile is described [16]. Total body clearance of EG is approximately 100 mL/min, a fourth of which is attributable to kidney clearance and is directly proportional to kidney function [15]. Consequently, the half-life ( $T_{1/2}$ ) of EG is prolonged in patients with a decreased glomerular filtration rate (GFR). Ethanol and fomepizole both compete with EG for ADH, so their administration prevents the metabolism of EG, prolonging the apparent elimination  $T_{1/2}$  of EG. Because fomepizole has a stronger affinity and inhibition of ADH compared to ethanol [17, 18], EG elimination  $T_{1/2}$  is longer during fomepizole than during ethanol therapy (Table 1).

**Review of ethylene glycol toxicity**

EG is the main component of commercial antifreeze and is present in many industrial products including coolants and de-icers. EG itself has minimal toxicity, but its metabolites are responsible for most of the clinical effects; glycolate contributes to the acidemia, while deposition of calcium oxalate crystals in tissues causes AKI and neurological complications [19–21].

The initial clinical manifestations of EG poisoning mimic those of ethanol ingestion, namely inebriation and ataxia. As EG is metabolized, metabolic acidemia appears after a latent period of approximately 3–6 h after ingestion. Thereafter, progressive neurotoxicity (coma,

**Table 1** Chemical characteristics and toxicokinetics of ethylene glycol

Characteristics	Ethylene glycol	Glycolate	References	
Molecular weight (Da)	62	76		
Bioavailability (%)	100 (rodent data)	N/A	[402]	
Protein binding (%)	Unknown, likely very low	0	[403]	
Volume of distribution (L/kg)	0.5–0.8	0.5–0.6	[15, 19, 148, 178, 202, 209, 210, 342, 404–406]	
$T_{1/2}$ (Hours)	No antidote, no KI	2–5	[15, 16, 28, 41, 50, 119, 143, 144, 148, 160, 163, 165, 168, 172, 177, 178, 185, 186, 188, 202, 210, 211, 218, 221, 222, 224, 227, 242, 278, 385, 404–422]	
	No antidote, KI	4–8	?	
	Ethanol, no KI	8.5–14	1–3	
	Ethanol, KI	20–40	15–40	
	Fomepizole, no KI	12–18	3–5	
Clearance (mL/min)	Fomepizole, KI	40–80	10–15	
	Non-renal (no antidote)*	60–100	80–85	[15, 143, 172, 178, 210, 404, 406, 413, 414, 423–425]
	Non-renal (with antidote)	5–10		
	Renal (no KI)	20–30	5–60	

N/A Not applicable, KI Kidney impairment including both AKI (acute kidney injury) and CKD (chronic kidney disease)

\* No antidote = neither ethanol nor fomepizole

cerebral edema, cranial nerve palsies, and seizures), cardiotoxicity (tachycardia with hypertension or hypotension), respiratory distress, and AKI occur. The incidence of AKI varies between 30 and 70% [22–34]. Multiorgan failure and death can occur at this stage. Cranial nerve palsies, radiculopathy, and other neuropathies may appear several days after ingestion, despite treatment [35–37]. Rarely, brainstem and basal ganglia injuries are reported [38, 39].

A threshold dose for toxicity is poorly defined in humans. Aircraft de-icing workers systemically exposed to an estimated 27 mg/kg from aerosolized EG ( $\approx 2$  mL of pure EG) did not demonstrate any adverse effects [40]. Self-experiments with EG revealed no harm with pure EG ingestions of 10–30 mL [41–43]. In one cohort of 86 unintentional ingestions of < 100 mL EG, all patients survived [44] and only one patient developed mild AKI, although most were treated with ethanol and/or hemodialysis within 3 h of ingestion. The often-quoted lethal dose in an untreated 70 kg adult is 100 mL [45–48], although there are several cases of toxicity and even death below this dose (Additional file 1: Table S7) [37, 49–56]. EG dose is prognostic of outcomes only if there is a delay to treatment [46, 57, 58]. Similarly, a concentration threshold for toxicity is unknown; some sources quote a peak EG concentration > 3.2 mmol/L (20 mg/dL) as a risk for toxicity [59], over which treatment should be initiated [11]. Some authors propose a treatment threshold of 10 mmol/L (62 mg/dL) in asymptomatic patients if base deficit is below 10 mmol/L, based on molar-molar conversion of EG to glycolate in the absence of supporting clinical data [60]; this is not a routine recommendation by most poison centers. Toxicity did not occur in 7 untreated patients who had EG concentrations < 4.8 mmol/L (30 mg/dL) [44, 61, 62]. Reports of toxicity when the EG concentration is < 3.2 mmol/L (20 mg/dL) are exclusively in patients who have already metabolized EG when testing is performed and does not represent peak EG concentrations. Because EG itself causes little toxicity, the EG concentration is poorly predictive of mortality [23, 24, 27, 28, 32, 63–69].

Other than dose and concentration, EG toxicity is modulated by co-ingestion with ethanol because this decreases EG metabolism [25, 29, 69, 70]. Patients in whom medical care is delayed, for example late presentations, develop more toxicity due to a higher concentration of toxic metabolites [23, 63]. Data suggest that a delay of 6–12 h between EG ingestion and treatment initiation is associated with an increased risk of immediate and long-term complications [32, 55, 58], although this was not confirmed in other studies [52, 63, 65].

Complications from EG poisoning are predicted by the concentration of plasma glycolate and associated

acid–base disorders [23, 24, 29, 63, 66, 68, 71–73]. The development of AKI is closely correlated with other outcomes including death [29, 31, 32, 52], as AKI is a marker of metabolite-mediated organ injury, and it delays kidney excretion of EG. Death very seldom occurs if AKI is not present [23, 27, 29]. Other clinical markers of mortality are coma [23, 27, 31, 32, 63, 65, 67, 74], respiratory failure [23, 27, 31, 32], hypotension [23, 31], and seizures [31, 63, 65].

With better supportive care, increasing awareness of treatment priorities, widespread use of antidotes, and greater availability of ECTR, mortality from intentional EG poisoning has steadily decreased: The mortality exceeded 80% prior to 1960 [7, 75, 76] and decreased to 30–40% in the 1970s and 1980s [22, 23, 53, 56, 77–79]. This trend has continued to improve during the 1990s [24, 27, 31, 52, 80] with mortality declining to < 10% today [32, 33, 67, 81]. High mortality rates are still reported when antidotes and/or ECTR are not readily available [4, 5, 51, 63, 82, 83].

Persisting sequelae are unusual in survivors. AKI lasts approximately 7–10 days [27, 65, 84, 85] and kidney function returns to baseline in most patients [27, 86]. However, there are cases of residual chronic kidney disease (CKD) [80, 87–89] including patients who remain dialysis-dependent [26, 36, 84, 90–92] one year later. Similarly, neuropathy regresses over time although there are cases of chronicity [93–99]. The incidence of these sequelae is unclear but appears to be less than 1% [68].

Standard care for patients with an EG exposure includes assessment for and treatment of abnormalities of the airway, breathing and circulation, correction of acid–base disorders, and ADH-inhibitor therapy (Additional file 1: Table S2). Ethanol and fomepizole decrease EG metabolism through competitive inhibition of ADH, and both prevent toxicity and death in EG-poisoned animals [18, 100–103]. Ethanol has been used as an antidote in humans since the 1960s [104]. Fomepizole was approved in the USA in the late 1990s [28] and has largely replaced ethanol as the antidote of choice for EG poisoning in many countries [81]. Thiamine and pyridoxine are used to facilitate the conversion of glyoxylate to non-toxic metabolites rather than oxalate, but their clinical utility has never been determined.

## Methods

The workgroup developed recommendations on the use of ECTR in EG exposures, following the EXTRIP methodology previously published [13], with modifications, updates, and clarifications. The methods and glossary are presented in full in the Supplementary Material, including the PRISMA checklist (Additional file 1: Table S3), dialyzability criteria (Additional file 1: Table S4), quality

assessment of individual toxicokinetic studies (Additional file 1: Table S5), and evidence (Additional file 1: Table S6). These data were assessed according to GRADE methodology (Additional file 1: Figure S1) which also informed the voting process for recommendations (Additional file 1: Figure S2). Cases in which ECTR was performed solely for anuria or related complications were excluded.

Complementary searches were also performed to answer specific questions regarding 1) dialyzability of EG metabolites, 2) dialyzability of ethanol/fomepizole, 3) dialyzability of pyridoxine and thiamine.

### Results

Results of the primary literature search (first performed on March 1, 2019, and last updated February 1, 2022) are presented in Fig. 1.

A total of 1296 articles were identified after removal of duplicates. In the final analysis, 226 articles were included for qualitative analysis, including two animal experiments [105, 106], five cost-evaluation studies [107–111], 31 cohort studies with pooled data [5, 22–24, 27, 28, 31–34, 56, 58, 67, 69, 73, 84–87, 112–123], one toxicokinetic modeling study [124], 181 case reports and case series with individual patient-level data [7, 25, 26, 29, 30, 37–39, 44, 51, 53, 64, 66, 70, 80, 89, 104, 125–288], three comparative studies [52, 55, 63], and three systematic reviews [289–291]. No randomized controlled trials were identified. One fourth of all selected articles were in languages other than English.

Other articles were obtained, although they were not part of the initial systematic literature search, namely relating to dialyzability of EG metabolites [292–306],

dialyzability of ethanol [307–317], dialyzability of fomepizole [318–323], and dialyzability of pyridoxine and thiamine [324–341]. Data from publications reporting the same subjects were merged but the citations were only counted once in the systematic review, e.g., [15, 28, 211] and [19, 147, 151, 342].

### Summary of the evidence: dialyzability

#### Dialyzability of EG

EG and its metabolites have characteristics of dialyzable poisons [343], namely small size, high water solubility, absence of protein binding, and a low volume of distribution (Table 1). EG clearance with high-efficiency intermittent hemodialysis is similar to that of urea [133, 172], approximating plasma flow and can surpass 200 mL/min (Table 2) [15, 148, 209]. EG clearance from hemodialysis increases total clearance by at least 800%, compared to endogenous clearance (assuming adequate ADH blockade). As for other small molecules, increasing blood and effluent flow and using a dialyzer with a higher surface area will increase EG clearance [163]. Mass removal of EG can exceed 100 g during a 6-h hemodialysis [148, 202, 287, 342].

Continuous and hybrid techniques (e.g., CKRT, sustained low-efficiency hemodialysis, extended daily dialysis) provide inferior EG clearances and mass removal compared to standard intermittent hemodialysis, due to their lower blood and/or effluent rates (Table 2) [196, 287]. Nevertheless, these techniques still achieve a substantial increase in total EG clearance. As EG has negligible protein binding, no advantage would be expected from therapeutic plasma exchange, liver support devices,

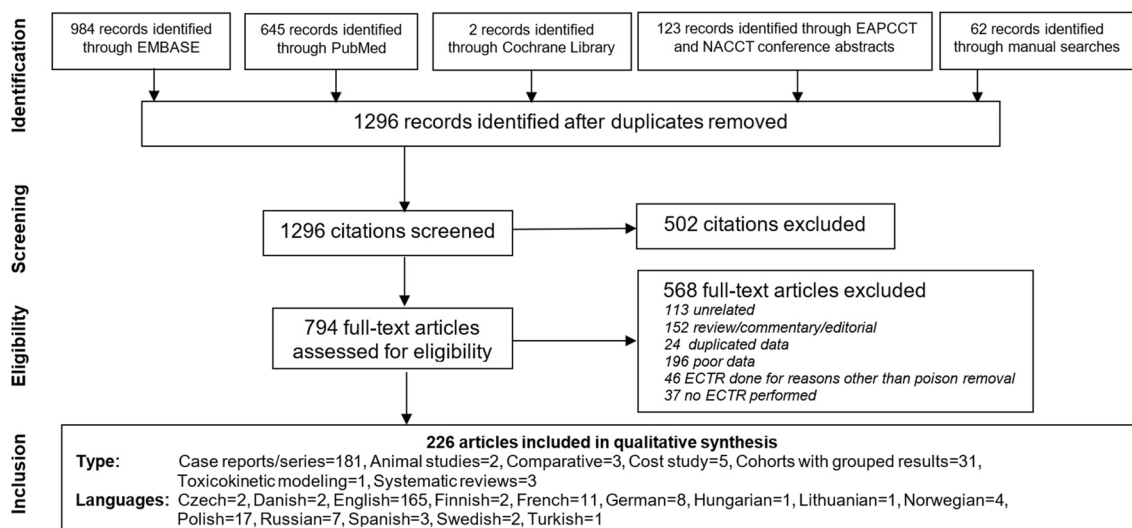


Fig. 1 Article selection

**Table 2** Toxicokinetics of ethylene glycol and metabolites during various extracorporeal treatments

Poison	ECTR	TK (Poisoning)						References
		T <sub>1/2</sub> (hours)*			ECTR clearance (mL/min)**			
		Median	N	Range	Median	N	Range	
Ethylene glycol	PD	13.2	4	6.1–18.6	7.3	3	6.5–17.2	[150, 152]
	CKRT	6.3	3	3.2–10.7	72	1	14.1–130	[196, 197, 252, 287]
	HD	2.9	88	0.6–27.1	163	42	14–260	[15, 23, 38, 67, 115, 123, 133, 140, 145, 148, 149, 156, 159, 160, 163, 166, 168, 171, 172, 178, 183, 185, 188, 189, 192, 198, 202, 209, 210, 214, 216, 219, 224, 227, 244, 270, 273, 278, 288, 342]
	HP				26	1		[143]
Glyoxylate	HD-HP	1.3	1		71	1		[176]
Glycolate	HD	2.4	14	0.4–4.4	146	9	63–205	[164, 178, 185, 211, 224, 426]
Oxalate	HD/HDF***				> 100	26		[300, 301, 303, 304]
	PD				< 8	54		[293, 295–297, 302, 303]

ECTR Extracorporeal treatment, PD Peritoneal dialysis, CKRT Continuous kidney replacement therapy, HD Hemodialysis, HP Hemoperfusion, HDF Hemodiafiltration

\* Regardless of antidote

\*\* The panel noted several cases where clearance was calculated using plasma concentration and blood flow [160, 163, 164, 168, 178, 342] which will overestimate ECTR clearance. When noted, clearances were recalculated with the given or estimated hematocrit

\*\*\* Assuming new technology

and hemoperfusion; in one case, EG clearance during hemoperfusion only reached 50 mL/min and quickly decreased because of extensive cartridge saturation [143]. Low-efficiency techniques like peritoneal dialysis have modest effect on removal of both EG or metabolites [128, 132, 139, 303], but will provide a clearance that exceeds endogenous clearance in the presence of AKI and adequate ADH blockade. No toxicokinetic data exist for exchange transfusion. After completion of ECTR, a rebound increase in EG concentration was observed in 21% of the cohort and the median magnitude of this rebound was 30% of the immediate post-ECTR concentration; in one case [144], the rebound was substantial (200%).

As mentioned, once ADH is blocked by ethanol or fomepizole, endogenous EG clearance is at best 30 mL/min, which is modest relative to extracorporeal EG clearances with modern-day efficient ECTRs (Table 2) [148, 192, 209, 211]. For this reason, dialyzability was not graded based on kidney function. Although most of the toxicokinetic data are dated with technology considered substandard today, EG was considered “dialyzable” with intermittent hemodialysis (level of evidence = B, Table 3), “moderately dialyzable” with CKRT (level of evidence = D), “slightly dialyzable” with peritoneal dialysis (level of evidence = C), and “slightly dialyzable” with hemoperfusion (level of evidence = D). No data exist on

**Table 3** Final toxicokinetic grading of ethylene glycol and glycolate during extracorporeal treatments

Poison	Toxicokinetic grading	Number of patients fulfilling toxicokinetic grading			
		Hemodialysis	Peritoneal dialysis	Continuous kidney replacement therapy	Hemoperfusion
Ethylene glycol	Dialyzable	19		1	
	Moderately dialyzable	6			
	Slightly dialyzable	1	2	1	1
	Not dialyzable		1		
	<i>Final grading and level of evidence</i>	<i>Dialyzable (B)</i>	<i>Slightly dialyzable, (C)</i>	<i>Moderately dialyzable, (D)</i>	<i>Slightly dialyzable, (D)</i>
Glycolate	Dialyzable	3			
	Moderately dialyzable	1			
	Slightly dialyzable				
	Not dialyzable				
	<i>Final grading and level of evidence</i>	<i>Dialyzable (C)</i>			



intermittent hemodiafiltration, but it is expected to perform as well as hemodialysis, based on achievable urea clearance. In the rare scenario in which no antidote is available, high-efficiency hemodialysis would increase endogenous clearance at least 100% [278], i.e., “moderate” dialyzability.

#### **Dialyzability of ethylene glycol metabolites**

EG metabolites have physicochemical characteristics indicative of being dialyzable, as is confirmed by data; however, caution is required when grading dialyzability according to half-life comparison, during and off ECTR, as these may be influenced by ongoing variable production of metabolites, especially when ADH inhibition is inadequate.

**Glycolate:** High glycolate clearance (> 150 mL/min) and high mass removal of glycolate (up to 50 g) are reported during hemodialysis [19, 164, 211]. There are reports of glycolate concentrations increasing modestly during ECTR suggesting that production surpassed elimination and that ADH blockade was inadequate [165]. Glycolate can also reaccumulate after ECTR, especially if ADH blockade is not continued [181, 185, 344]. Based on 4 patients in whom dialyzability could be assessed, glycolate was rated as “dialyzable” with hemodialysis (level of evidence = C) (Table 3).

**Oxalate:** Oxalate was detected in blood in only 4 of the 10 patients in whom it was measured, in concentrations at least 20 times lower than those observed for glycolate [150, 241, 250, 252]. In one report, three sessions of hemodialysis removed on average of 380 mg of oxalate, although dialyzability could not be estimated [131]. From studies in dialysis-dependent CKD patients with primary or secondary oxalosis, oxalate clearance surpasses 150 mL/min with hemodialysis and hemodiafiltration [301, 303–305], which is at least 300% more than the kidney elimination capacity [292, 297]. Oxalate clearance in peritoneal dialysis is consistently less than 8 mL/min [139, 293, 295, 296, 303].

**Glyoxylate:** Glyoxylate extracorporeal clearance by hemoperfusion–hemodialysis was 71 mL/min in one patient [176].

#### **Dialyzability of ethanol/fomepizole**

Both ethanol [316] and fomepizole [318, 322, 345] are extensively removed by ECTR. If the dose of either of these antidotes is not increased during the ECTR session, a risk of inadequate inhibition of EG metabolism during ECTR exists. The elimination  $T_{1/2}$  of ethanol and fomepizole during hemodialysis and hemodiafiltration ranges between 1.5 and 3.0 h [308, 310, 312, 313, 315, 319, 321, 345, 346], and ECTR clearance surpasses 100 mL/min [198, 202, 272, 308, 310, 319, 345]. Considerably lower

amounts of these antidotes are removed during CKRT [272, 320, 347, 348], and particularly during peritoneal dialysis [307, 311].

#### **Dialyzability of pyridoxine and thiamine**

**Pyridoxine:** In vivo clearance of pyridoxal-5'-phosphate with cellulose filter membranes averaged 170 mL/min in 6 subjects [328], while it was < 1 mL/min with peritoneal dialysis [329].

**Thiamine:** Thiamine concentration decreased between 5 and 40% during hemodialysis, but extracorporeal clearance was not calculated [325, 332, 336, 340].

#### **Summary of the evidence: pre-clinical data**

Three animal studies with group comparisons were identified [105, 106, 349]. In one experiment, an LD<sub>400</sub> dose of EG was given to 23 dogs; 13 were treated with intravenous NaHCO<sub>3</sub> and 10 were treated with a single session of hemodialysis for 20–24 h. All died in the NaHCO<sub>3</sub> group while two died in the hemodialysis group ( $p < 0.0001$ ), suggesting a beneficial effect of hemodialysis [105]. In one experiment of six EG-poisoned dogs, five received 3 h hemoperfusion within 5 h of poisoning and one was a control. All died and no improvement was seen from hemoperfusion [106].

#### **Summary of the evidence: clinical data**

##### **Comparative data**

We identified one retrospective study in which supportive care with ECTR ( $n = 28$ ) was directly compared to supportive care alone ( $n = 28$ , Table 4) [63]. The mortality was the same in both groups ( $8/28 = 28.6\%$ ), although the ECTR group was sicker at baseline (higher EG dose, lower pH or HCO<sub>3</sub><sup>-</sup> concentration, higher anion gap, greater percent with coma and respiratory failure, longer delay to admission, longer delay to antidotal therapy). An important limitation is that only about half of the entire cohort received antidotal therapy (ethanol).

Cohorts in which the effect of ECTR could be analyzed were extracted and analyzed (Table 4) [5, 24, 25, 29, 32, 44, 107, 118]. Unfortunately, none of these studies were designed to appropriately determine the effect of ECTR, and all contained critical methodological flaws that preclude meaningful conclusions. These limitations include small sample size, retrospective design (except for poison control data which have other limitations), unclear patient selection, variable definitions of EG poisoning (reported amount ingested vs laboratory testing), unreported baseline characteristics and exposure details (especially co-ingestion with ethanol, volume EG ingested, time from EG ingestion to admission, antidote used), imprecise indications for ECTR, and confounding-by-indication, i.e., ECTR is preferentially used in

**Table 4** Included studies comparing the effect of extracorporeal treatments vs no extracorporeal treatments

References	Location, Year of recruitment	Study design (analysis)	Number and type of patients	Intervention	Comparator	Reported outcomes and conclusion	Baseline comparison	Noticeable limitations, and overall interpretation
Grigorasi [63] (published as a conference abstract in 2018)	Romania; January 2012–October 2017	Retrospective multicenter chart review in the context of a large EG poisoning epidemic; (cooperative study between regional hospitals, a university hospital, and a poison information center)	(n = 56) confirmed by blood EG measurement. All had plasma creatinine > 88 µmol/L (1 mg/dL) on admission Global severity of included population: death occurred in 16/56 (29%) of patients	HD (n = 28) 18/28 patients (64%) also received the antidote ethanol	No HD (n = 28) 14/28 patients (50%) also received the antidote ethanol	Comparable mortality (8/28 died in each group) and CKD between groups Neither delay to admission, dialysis use, HCO <sub>3</sub> <sup>-</sup> concentration or ingested alcohol volume were related to death Death was more likely in patients with seizures, coma, severe acidosis (pH 7.05) or AKI on admission;	Patients who received HD were more symptomatic on admission, had higher blood EG concentration, lower initial pH and HCO <sub>3</sub> <sup>-</sup> , higher peak creatinine at 24 h, and had a longer ingestion-to-admission time as well as door-to-antidote time, compared to group who did not receive HD group Co-ingestion with ethanol was comparable between the 2 groups	Comparable mortality between the groups despite a clear confounding-by-indication bias (HD group sicker on admission than the no-HD group) supports a potential beneficial effect of HD, but the low usage of ethanol in the cohort and a small sample size lessen the generalizability of these findings
Lung [32]	California Poison Control System; CA, USA; January 1999–December 2008	Retrospective chart review (non-secutive)	(n = 121) confirmed by blood EG measurement Global severity of included population: Death (n = 9, 7.4%) or AKI requiring dialysis for more than 3 days (n = 50, 41.3%)	HD (n = 102) 97.5% of the cohort (118/121) received an antidote: 65 received fomepizole, 29 received ethanol and 24 received both. Antidotes were administered within 3 h in half of the patients	No HD (n = 19)	Mortality and prolonged AKI were associated with the use of HD, 58/59 (98.3%) vs 43/62 (69.4%) in those who survived without AKI	Patients who received HD had worse indices of illness: lower initial pH, higher initial and peak plasma creatinine	Confounding-by-indication limits conclusions from the data Outcomes were not adjusted for pH despite it being a strong predictor of worse outcome
Swiderska [5]	Poland Health Services; Poland; year 2010	Retrospective chart review	(n = 174) identified through ICD-10 coding reported by medical facilities to the National Health Fund Global severity of included population: deaths = 47/174 (23.6%)	ECTR (n = 98) Antidote was recommended but not known if it was given	no ECTR (n = 78)	Comparable mortality between groups: mortality in patients not treated with ECTR = 21/78 (26.9%) vs 26/98 (26.5%) in those treated with ECTR	No comparison at baseline	The groups were not compared at baseline, limiting conclusions from the data



**Table 4** (continued)

References	Location, Year of recruitment	Study design (analysis)	Number and type of patients	Intervention	Comparator	Reported outcomes and conclusion	Baseline comparison	Noticeable limitations, and overall interpretation
White [118]	US poison centers USA; 1995–2005	Retrospective chart review of prospectively collected information	(n = 3623) with intentional, suspected suicidal ingestion of EG Global severity of included population: Deaths (n = 147/2773, 5.3%) and “major effect” (1089/2773, 39.3%)	HD (n = 1611) Antidote (fomepizole, ethanol or both) was administered in a total of 2205 patients (60.9%)	no HD (n = 2012)	Receiving HD increased the odds of severe outcomes (death or major effect) and being admitted to a critical care unit, while receiving an antidote was associated with a decrease in the odds of severe outcomes	Logistic regression model to identify variables associated with severe outcomes (life-threatening major effects or fatal cases); adjusted for age, time (beginning vs end of study), gender, antidote administered, HD, critical care and bit-tering agent. Logistic model included n = 1790 (numbers HD vs no HD not reported). HD: adjusted OR 16.93 (13.16 to 21.77). Also, statistically significant: male gender, antidote administered, critical care	Confounding-by-indication (all variables associated with severe outcomes are also associated with severity of illness) limits conclusions from the data
Krenova [44]	Czech Toxicological Information Center, Czech Republic; 2000–2004	Retrospective chart review	(n = 86) hospitalized for an accidental EG ingestion (1–3 swallows), for whom the amount of EG ingested was known and/or the blood EG concentration were measured Global severity of included population: no deaths, AKI (10%), CNS depression (9%)	HD (n = 17) 15/17 patients (88%) received ethanol: 8 as first aid and 15 as antidote in hospital	No HD (n = 69) 63/69 patients (91%) received ethanol: 15 as first aid and 59 as antidote in hospital	Comparable mortality and CKD between groups (no mortality; one case of temporary deterioration of baseline CKD in the HD group)	No comparison at baseline (only descriptive reporting)	Confounding-by-indication and very few events (CKD or mortality) limits conclusions from the data

**Table 4** (continued)

References	Location, Year of recruitment	Study design (analysis)	Number and type of patients	Intervention	Comparator	Reported outcomes and conclusion	Baseline comparison	Noticeable limitations, and overall interpretation
Porter [29]	Kentucky, USA; 1997–2000	Retrospective chart review	(n = 41) admissions (in 39 patients), confirmed by initial plasma EG and glycolate concentrations Global severity of included population: Deaths (n = 8/41, 19.5%)	Ethanol + HD (n = 33)	Ethanol + no HD (n = 8)	Overall, receiving HD was associated with a reduction in the risk of death at the univariate analysis (mortality of group vs 3/8 (37.5%) in the no-HD group) (RR: 0.30 95%CI (0.10–0.87) The authors concluded that HD might not be required in patients with glycolate less than 8 mmol/L (correlated surrogates = anion gap less than 20 mmol/L or pH more than 7.30) with adequate antidote therapy since they are not likely to develop AKI	A stratified analysis according to severity in the survivor group is presented (based on presence of AKI and plasma glycolate), but no matched or adjusted analysis on baseline data	Few patients treated without HD and there was marked variability in clinical severity (too sick or barely sick) in the HD group The authors' conclusions regarding the predictive value of glycolate is confounded since 10/17 patients with glycolate less than 8 mmol/L received HD Critical lack of detail
Donovan [107] (Conference abstract)	Philadelphia, USA. Reported in 1998, timing of recruitment unclear	Retrospective single-center chart review	(n = 4) Global severity of included population: no deaths (0%)	HD + fomepizole (n = 2)	no ECTR, fomepizole alone (n = 2)	All patients had good outcomes without progression of acidosis or development of AKI The LOS was longer in patients who only received fomepizole. There was no direct correlation between costings and use of HD vs fomepizole alone	No comparison at baseline (only descriptive reporting)	Too underpowered to make any meaningful comparison (either of baseline characteristics or clinical outcomes). Cost analysis is dated and not likely valid outside this institution

**Table 4** (continued)

References	Location, Year of recruitment	Study design (analysis)	Number and type of patients	Intervention	Comparator	Reported outcomes and conclusion	Baseline comparison	Noticeable limitations, and overall interpretation
Stompor [25]	Krakow, Poland; 1990–1994	Retrospective single-center (department of toxicology) chart review	(n = 36) Global severity of included population: Death (n = 18/36; 50%)	ECTR (n = 24) (one HD session, 3 to 9 h after admission, for 6–16 h) Unknown use of antidotes.	no ECTR (n = 12). Unknown use of antidotes.	Overall, receiving ECTR was associated with a non-statistically significant increase in mortality (14/24 (58.3%) in the ECTR group vs 4/11 (36.4%) in the no ECTR group), but was associated with the presence of AKI (16/24 (66.7%) vs 1/11 (9.1%))	When comparing the no ECTR group to the ECTR group, no statistical difference was observed in ethanol co-ingestion, pH, HCO <sub>3</sub> <sup>-</sup> , base excess, or 24 h urine output. However, plasma EG concentration was higher in the ECTR group compared to the no ECTR group (153.5 mg/dL vs 15.2 mg/dL, respectively)	Difficult to interpret: no difference in clinical outcomes between the two groups despite the ECTR group having higher plasma EG concentrations and AKI, but likely underpowered. No mention of antidotal therapy
Karlson-Stiber and Hylander [24, 65]	Sweden; 1987 Two publications with overlapping data	Retrospective chart review (telephone consultation to a poison center and chart review of county and university hospitals)	(n = 36) (charts were reviewed in only 17 patients) Diagnosed by plasma EG concentration in 24 patients, and by urinary calcium oxalate crystals in 6 patients Global severity of included population: Death (n = 6/36, 16.7%)	ECTR (n = 29, 28 HD, 1 PD alone) 88% of patients received IV ethanol	no ECTR (n = 7)	Comparable mortality between groups: mortality of 4/29 (13.8%) in the ECTR group vs 2/7 (28.7%) in the no ECTR group	No comparison at baseline reported	Both groups were not compared at baseline and the study is underpowered which limits conclusions from the data Furthermore, confounding-by-indication might have biased the study since the decision to not perform ECTR was due to mild symptoms or to a poor clinical status

ECTR Extracorporeal treatment, PD Peritoneal dialysis, HD Hemodialysis, HDF Hemodiafiltration, LOS Length of stay, AKI Acute kidney injury, IV Intravenous, EG Ethylene glycol, HCO<sub>3</sub><sup>-</sup> Bicarbonate

those with more severe clinical features. Some cohorts included patients that could have been plausibly managed without ECTR [44]. One study suggested that hemodialysis increased the odds of severe outcomes 17-fold [118], after adjusting for age, gender, year, addition of bittering agent, administration of antidote and admission to critical care. This likely quantifies the extent of confounding-by-indication and selection bias in real-life presentations. There were studies that compared types of ECTR [5, 24, 52, 55] (Additional file 1: Tables S8 and S9), number of treatments [65], or the impact of time to ECTR initiation on clinical outcomes [32, 56] (Additional file 1: Tables S8 and S9). No meaningful conclusions can be inferred from these studies, as the same major limitations apply. Therefore, clinical data were not considered suitable for inclusion in a meta-analysis comparing ECTR to no ECTR.

### Clinical cases

A total of 446 cases had sufficient patient-level data, the summary of which are shown in Table 5. Most patients received ethanol rather than fomepizole for ADH blockade, reflecting older literature or country of origin. Intermittent hemodialysis was by far the most used ECTR. Fifty-four percent of patients received more than one ECTR session (usually for management of uremia), comparable to other cohorts [32]. Acidemia was corrected quickly in most cases receiving high-efficiency hemodialysis, usually within four hours. Peritoneal dialysis was switched to hemodialysis because of clinical failure in one patient [160]. Mortality from the entire cohort was 18.7% and the median time to death was 96 h after ingestion. Some patients with massive ingestions (>1 L) or very high EG concentrations (>200 mmol/L or >1240 mg/dL) survived [123, 214, 238, 274, 281, 282], as did some with extreme acid–base abnormalities (e.g., pH < 6.60 or  $\text{HCO}_3^- < 2$  mmol/L) [25, 26, 29, 104, 180, 190, 191, 215, 223, 226, 236, 244, 248, 254, 257, 264, 276]. As suggested in one review [71], poor outcomes were infrequent when the glycolate concentration is <12 mmol/L or the anion gap (with potassium, calculated as  $\text{Na}^+ + \text{K}^+ - \text{Cl}^- - \text{HCO}_3^-$ ) is <28 mmol/L (Additional file 1: Table S10); three such patients who received ECTR died, in two cases there were limited details reported [51], and one died without receiving an ADH inhibitor [126]. Mortality in patients who had an anion gap over 28 mmol/L was much higher (20.4%).

Several complications occurred during ECTR although in most cases, these can be attributed to EG poisoning rather than the procedure itself. Complications assessed as likely related to ECTR included hypotension [7, 127, 130, 153, 166, 181, 258, 265, 275, 276], bleeding related to heparin [141], catheter-related thrombosis [291], catheter-related bacteremia [166, 183], cardiac arrest [167], and death [153,

155]. ECTR can potentially increase intracranial pressure [350–352] and may have aggravated EG-related cerebral edema leading to seizures [141, 177, 178]. Some authors mentioned concerns related to rapid fluid and solute shifts during ECTR, although it is unclear if these resulted in injury [178, 219]. In one cohort of 72 patients receiving hemodialysis for toxic alcohol poisoning (34 for EG), 20 patients experienced a hemodialysis-related adverse reaction including three cases of hypotension and one case of arterial tear during catheter insertion leading to internal bleeding, shock, and cardiac arrest (the patient eventually recovered) [353].

Persistent sequelae were seldomly reported in case reports and observational cohorts. The median duration of kidney replacement therapy for patients who developed AKI was 9 days [IQR 3,14], while the median duration of serum creatinine concentration elevation was 21 days [IQR 7,40], similar to results in published cohorts [23, 25, 27, 65, 84, 85]. Some degree of CKD was present in 16.8% of patients and 2.9% remained dialysis-dependent; however, in most cases, these were noted on hospital discharge and the duration of follow-up, when reported, was often short, so it is expected that these numbers are overestimated. On extended follow-up, <1% of patients remained dialysis-dependent at 6 weeks and <5% had CKD at 6 months [30, 52, 65, 68, 86], although there are rare reports of patients who remained dialysis-dependent after 1 year [26, 36, 84, 90–92]. Among other sequelae, there were rare cases of anoxic brain injury, basal ganglia injury, and irreversible cranial nerve palsies [37–39, 80, 94, 128, 151, 201, 215, 221, 254, 354].

### Cost analysis of ECTR

In patients presenting prior to the development of acidemia or AKI, ECTR may shorten length of stay and associated morbidity due to nosocomial complications and reduce overall healthcare costs. Studies (mostly performed in the USA) report a cost advantage when hemodialysis is added to fomepizole, especially at higher EG concentrations (Table 6) [107–111, 227, 267, 355]. However, these data are dependent on many factors, including health care delivery model, patient location (medical ward vs high-dependency unit), type of ECTR, initial concentration of EG, need for transfer to another institution, and cost of fomepizole, all of which vary between countries and institutions, and are therefore not generalizable.

### Clinical data informing the evidence table

The evidence table is shown in Table 7. It was not possible to reliably populate the evidence table for patients with advanced or late EG poisoning (e.g., glycolate concentration >12 mmol/L or anion gap with

**Table 5** Clinical summary of included cases with ethylene glycol poisoning

		All cases (n = 446)	Early EG poisoning (glycolate concentration ≤ 12 mmol/L or an anion gap ≤ 28 mmol/L; n = 84) <sup>&amp;</sup>	Late EG poisoning (glycolate concentration > 12 mmol/L or an anion gap > 28 mmol/L; n = 147) <sup>&amp;</sup>	
Patient characteristics	Age (Years)	42 [28, 52]	42 [28, 54]	45 [28, 55]	
	Male gender	80%	67%	84%	
Poisoning information	Ingested dose (mL)	250 [150, 500]	300 [120, 600]	300 [200, 946]	
	Ethanol co-ingestion	55%	61%	36%	
	Time from ingestion to admission (hours)	10 [4, 18]	6 [2, 11]	12 [7, 22]	
	Peak ethylene glycol concentration (mmol/L)	17.6 [6.9, 41.9]	26.8 [10.5, 57.0]	29.4 [9.0, 56.4]	
Signs/Symptoms	Altered mental status*	n = 237	n = 42	n = 115	
	Coma*	n = 127	n = 14	n = 62	
	Cerebral edema*	n = 10	n = 0	n = 8	
	Seizure*	n = 44	n = 4	n = 26	
	Hypotension*	n = 26	n = 0	n = 11	
	Acute kidney injury (KDIGO stage 2 or 3 AKI)	n = 295	n = 32	n = 132	
	Lowest pH	7.08 [6.89, 7.23]	7.30 [7.16, 7.38]	7.00 [6.89, 7.11]	
	Lowest HCO <sub>3</sub> <sup>-</sup> , (mmol/L)	6.9 [3.2, 13.3]	16 [11, 21]	5 [3, 7]	
	Calcium oxalate crystals in the urine*	n = 85	n = 14	n = 14	
	Lowest total calcium concentration (mmol/L)	2.1 [1.9, 2.5]	2.1 [1.9, 2.3]	2.0 [1.9, 2.5]	
	Anion gap (mmol/L; with potassium)**	32 [25, 39]	22 [16, 26]	37 [32, 43]	
	Osmol gap	40 [27, 82]	48 [27, 97]	38 [26, 78]	
	Nadir base excess (mmol/L)	- 25 [- 19, - 32]	- 17 [- 11, - 18]	- 24 [- 21, - 31]	
	Peak glycolate concentration (mmol/L)	15.9 [5.1, 22.6]	1.6 [0, 7.4]	21.2 [16.4, 25.0]	
	Other treatments	Gastric lavage*	n = 47	n = 13	n = 11
		Ethanol (any type)*	n = 246	n = 49	n = 81
Fomepizole*		n = 69	n = 18	n = 35	
Thiamine*		n = 56	n = 8	n = 26	
Pyridoxine*		n = 54	n = 8	n = 25	
Sodium bicarbonate*		n = 196	n = 17	n = 70	
Vasopressors*		n = 25	n = 1	n = 12	
Mechanical ventilation*		n = 155	n = 24	n = 77	
ECTR	Hemodialysis	86.5%	91.7%	91.6%	
	Hemoperfusion	0.2%	0%	0%	
	Exchange transfusion	0.2%	0%	0%	
	Continuous kidney replacement therapy	4.3%	4.8%	6.1%	
	Slow low-efficiency daily dialysis	0.2%	0%	0.7%	
	Peritoneal dialysis	2.7%	0%	0.7%	
	More than 1 ECTR	5.9%	3.6%	1.4%	
	Time from admission to ECTR (hours)	6 [3, 12]	6 [3, 10]	6 [3, 10]	
	Time from ingestion to ECTR (hours)	20 [12, 30]	13 [6, 24]	18 [13, 24]	

**Table 5** (continued)

		All cases (n = 446)	Early EG poisoning (glycolate concentration $\leq$ 12 mmol/L or an anion gap $\leq$ 28 mmol/L; n = 84) <sup>&amp;</sup>	Late EG poisoning (glycolate concentration > 12 mmol/L or an anion gap > 28 mmol/L; n = 147) <sup>&amp;</sup>
Outcome	Hospital stay (days)	16 [7, 23.0]	8 [2, 15]	18 [9, 26]
	Intensive care unit stay (days)	5 [3, 11]	5 [2, 8]	3 [3, 8]
	Chronic kidney disease sequelae	16.8%	7.4%	18.8%
	Dialysis-dependent chronic kidney disease sequelae	2.9%	1.2%	5.1%
	Central nervous system sequelae	3.3%	0%	4.3%
	Time requiring kidney replacement therapy for acute kidney injury (days)	9 [3, 14]	7 [2, 16]	12 [8, 22]
	Time of serum creatinine concentration normalization after AKI (days)	21 [7, 40]	5 [1, 24]	21 [11, 40]
	Death	18.7%	3.6%	20.4%
	Time to death (hours)	96 [24, 264]	No data	72 [31, 276]

Data were expressed as medians and interquartile range when applicable,

AKI acute kidney injury, ECTR Extracorporeal treatments,  $\text{HCO}_3^-$  bicarbonate concentration, and KDIGO Kidney Disease Improving Global Outcomes

\* when stated to be present

\*\* The anion gap was calculated  $\text{Na}^+ + \text{K}^+ - \text{HCO}_3^- - \text{Cl}^-$ . If calculated without  $\text{K}^+$ , 4 mmol/L was added. If no mention, 2 mmol/L was added

<sup>&</sup> There were 215 other patients in whom neither the anion gap nor glycolate concentrations were reported, so they are not included here

potassium > 28 mmol/L) because very few controls (i.e., not treated with ECTR) exist. The exceptions are patients i) too sick to undergo hemodialysis; ii) who died before hemodialysis was initiated; iii) in whom EG poisoning was not diagnosed; or iv) when ECTR was unavailable [85, 356, 357]. For obvious reasons, these patients are not adequate controls. Patient cohorts published before hemodialysis became widely available report extremely high mortality, although this could also be explained by inadequate standard care and absent antidotal therapy. A prospective randomized trial of ECTR in late EG poisoning would not be considered ethical because of a lack of clinical equipoise. (It is assumed that ECTR would produce a large survival effect.)

The evidence table was therefore populated with the subset of patients known to have a good prognosis without ECTR, i.e., those with a glycolate concentration  $\leq$  12 mmol/L or an anion gap with potassium  $\leq$  28 mmol/L ("Early EG poisoning," Table 7) [29, 66, 71, 358]. As expected, the addition of ECTR to fomepizole did not seem to improve the prognosis of these patients, namely mortality, length of stay, or requirement of ECTR for AKI. ECTR appears to reduce costs, although this must be weighed against possible risks of complications of ECTR. When ethanol is used in low-risk patients, ECTR reduces the duration of time during

which a patient is exposed to risks related to ethanol (decreased consciousness, dysphoria) and may limit the risk of ethanol failure. In rare cases in which neither fomepizole nor ethanol can be used (a situation described by some panel members), ECTR would theoretically markedly reduce the risk of mortality and AKI.

#### Clinical recommendations

The EXTRIP recommendations for ECTR in EG poisoning are presented in Table 8. Current indirect evidence suggests that ECTR is lifesaving when significant acidemia and/or Stage 2 or 3 AKI are present as it corrects metabolic disequilibria and removes EG, oxalate, and glycolate. EG-related mortality increases substantially once the plasma glycolate concentration exceeds 12 mmol/L [71]. Uncertainty remains on the expected magnitude of effect of ECTR compared to no ECTR on mortality and other patient-important outcomes at different plasma glycolate concentrations. When neither AKI nor acidemia is present, the advantages of ECTR when added to an ADH inhibitor are mainly to limit costs, reduce length of hospitalization, and limit risks of ethanol therapy when used, rather than reducing the occurrence of major adverse outcomes from EG. These recommendations may be used to prioritize and triage ECTR in cases of group poisoning [24, 359]. Because of the lack



**Table 6** Summary of studies evaluating costs of ECTR vs no ECTR in ethylene glycol poisoned patients

References	Population	Conclusion
Ellsworth, 2011 [109]	Average expected patient charges in 1 institution, USA	For [EG] > 8.1 mmol/L HD (1 session) + Fomepizole (2 doses): <b>\$4,823 and 24 h ICU LOS</b> Fomepizole (3 doses): <b>\$5,631 and 8 h LOS</b>
Donovan, 1998 [107]	Actual hospital charges of 4 adult patients in 1 institution, within 1 month, USA	2 patients receiving HD + Fomepizole: <b>\$15,616 and \$24,315 for LOS of 2.5 days</b> 2 patients receiving Fomepizole alone: <b>\$30,072 and \$16,790 for LOS of 4.5 and 3.5 days</b>
Cannarozzi, 2010 [108]	Expected hospital charges, USA	Weight < 75 kg: <b>Costs of Fomepizole + HD &gt; Fomepizole at all [EG], except [EG] = 81–97 mmol/L</b> Weight 75–100 kg and [EG] = 0–48 mmol/L: <b>Costs of Fomepizole + HD = Fomepizole</b> Weight 75–100 kg and [EG] > 48 mmol/L: <b>Costs of Fomepizole + HD &lt; Fomepizole</b> Weight > 100 kg and [EG] > 12.1 mmol/L: <b>Costs of Fomepizole + HD &lt; Fomepizole</b>
Darracq, 2013 [267]	Expected hospital costs in same adult patient, USA	Fomepizole + HD = <b>\$2,576 for 24 h LOS</b> Fomepizole = <b>\$4,246 for estimation 48 h LOS</b>
Wiles, 2014 [110]	Direct costs based on US national statistics, USA	For [EG] < 29 mmol/L: Fomepizole + HD = <b>\$15,054</b> Fomepizole = <b>\$15,657</b>
Vasavada, 2003 [227]	Cost estimates based on 1 patient, USA	Ethanol + HD + ICU: <b>\$3,368</b> Fomepizole + HD + intermediate ward: <b>\$3,804</b> Fomepizole alone + intermediate ward: <b>\$5,897</b>
Boyer, 2001 [355]	Expected hospital costs in 1 patient, USA	Fomepizole + ward admission: <b>\$9,524</b> Ethanol + ICU + Mechanical ventilation + HD: <b>\$15,723</b>
Roberts, 2019 [111]	Expected costs, based on local estimates, Australia	[EG] ≤ 8 mmol/L: <b>Costs of Fomepizole + ward &lt; ICU + CKRT</b> [EG] > 8 mmol/L: <b>Costs of Fomepizole + HD + ward &lt; Fomepizole + ward &lt; Fomepizole + CKRT + ICU</b>

Bold text was inserted to highlight the result

HD Hemodialysis, ICU Intensive care unit, EG Ethylene glycol, [EG] Blood ethylene glycol concentration, CKRT Continuous kidney replacement therapy, LOS length of stay

All presented currencies are in US\$, as reported in the studies

of reliable comparative studies and the aforementioned uncertainties, the quality of evidence was very low for all recommendations.

### Indications

The following indications should be considered independent of each other. For example, if a criterion recommending ECTR is met, then evaluation of the other criteria is not necessary.

#### EG Dose

- a. In patients presenting with EG poisoning, **we recommend against** ECTR based solely on the reported EG dose ingested (strong recommendation, very low-quality evidence)

Rationale: A reported EG dose ingested is never by itself an indication for ECTR as it may be imprecise and requires complementary confirmation from other diagnostic cues such as the presence of EG in blood, an elevated osmol gap and/or an elevated anion gap, or other

non-specific tests (calcium oxalate crystals in urine). However, a history of ingestion may prompt early contact and consideration of transfer to a center where ECTR can be performed should this be required. Similarly, neither oxalate crystals in urine, urine immunofluorescence nor hypocalcemia nor a history of EG exposure alone are indications for ECTR (but may help to diagnose EG poisoning).

#### Plasma EG concentration

- a. Fomepizole is used:
  - i. In patients presenting with EG poisoning, **we suggest** ECTR if EG concentration is > 50 mmol/L (> 310 mg/dL) (weak recommendation, very low-quality evidence)
- b. Ethanol is used
  - i. In patients presenting with EG poisoning, **we recommend** ECTR if EG concentration

**Table 7** Evidence profile table: ECTR + standard care compared to standard care in patients with “early” ethylene glycol poisoning<sup>#</sup>

Certainty assessment		Summary of findings						Importance		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECTR + standard care* ECTR + standard (controls)	Impact	Certainty	
<b>Inpatient mortality</b>										
Early EG poisoning n = 2 <sup>a</sup>	Observational studies	Very serious <sup>b</sup>	Not serious	Serious <sup>c</sup>	Serious <sup>d</sup>	Publication bias strongly suspected <sup>e</sup>	This systematic review: 3.6% Fomepizole: 0.0% [358] Ethanol: 0.0% [358] No antidote: Expected high	No reduction with ECTR No reduction with ECTR Very probable reduction with ECTR	⊕○○○ VERY LOW	CRITICAL
<b>Dialysis dependence at 3 months</b>										
Early EG poisoning n = 2 <sup>a</sup>	Observational studies	Very serious <sup>b</sup>	Not serious	Serious <sup>c</sup>	Serious <sup>d</sup>	Publication bias strongly suspected <sup>e</sup>	This systematic review: 1.2% Fomepizole: 0% [358] Ethanol: 0% [358] No antidote: Expected high	No reduction with ECTR No reduction with ECTR Probable reduction with ECTR	⊕○○○ VERY LOW	CRITICAL
<b>Irreversible neurological damage</b>										
Early EG poisoning n = 2 <sup>a</sup>	Observational studies	Very serious <sup>b</sup>	Not serious	Serious <sup>c</sup>	Serious <sup>d</sup>	Publication bias strongly suspected <sup>e</sup>	This systematic review: 0% Fomepizole: 0% [358] Ethanol: 0% [358] No antidote: Expected high	No reduction with ECTR No reduction with ECTR Probable reduction with ECTR	⊕○○○ VERY LOW	CRITICAL
<b>AKI requiring short-term dialysis</b>										
Early EG poisoning n = 2 <sup>a</sup>	Observational studies	Very serious <sup>b</sup>	Not serious	Serious <sup>c</sup>	Serious <sup>d</sup>	Publication bias strongly suspected <sup>e</sup>	This systematic review: 15.5% Fomepizole: 0.0% [358] Ethanol alone: 3.8% [358] No antidote: Expected high	No reduction with ECTR No reduction with ECTR Probable reduction with ECTR	⊕○○○ VERY LOW	CRITICAL

**Table 7** (continued)

Certainty assessment		Summary of findings						Importance			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECTR + standard care* care*	Standard care (controls)	Impact	Certainty	
<b>Length of ICU stay</b>											
Early EG poisoning n = 1 <sup>f</sup>	Observational studies	Very serious <sup>b</sup>	Not serious	Serious <sup>c</sup>	Serious <sup>d</sup>	Publication bias strongly suspected <sup>e</sup>	This systematic review: Median 5 days [2, 8]	Fomepizole: Theoretically, ICU admission not needed  Ethanol: requires ICU admission and this would be prolonged	No reduction with ECTR  Data incomplete	⊕○○○  VERY LOW	IMPORTANT
<b>Length of hospital stay</b>											
Early EG poisoning n = 2 <sup>a</sup>	Observational studies	Very serious <sup>b</sup>	Not serious	Serious <sup>c</sup>	Serious <sup>d</sup>	Publication bias strongly suspected <sup>e</sup>	This systematic review: Median 8 days [2, 15]	Fomepizole: Median 4 days [3, 5] [358]  Ethanol: Median 3 days [2,4] [358]	No reduction with ECTR  No reduction with ECTR	⊕○○○  VERY LOW	IMPORTANT
<b>Cost</b>											
Early EG poisoning n = 8 <sup>g</sup>	Observational studies	Very serious <sup>b</sup>	Not serious	Serious <sup>c</sup>	Serious <sup>d</sup>	Publication bias strongly suspected <sup>e</sup>	Fomepizole: varies (See Table 6) [107–111, 227, 355, 427]	Fomepizole: Analyses and/or reporting incomplete. Cost of ECTR and fomepizole vary across countries and across institutions. HD appears cost-effective in smaller patients and high EG concentration	Analyses and/or reporting incomplete. Cost of ECTR and fomepizole vary across countries and across institutions. HD appears cost-effective in smaller patients and high EG concentration	⊕○○○  VERY LOW	IMPORTANT
						Ethanol: data incomplete (see Table 6) [227, 355]	Ethanol: No data	Ethanol: No data	Data incomplete		
						No antidote: No data	No antidote: No data	No antidote: No data	No data		

**Table 7** (continued)

Certainty assessment		Summary of findings					Importance			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECTR + standard care* (controls)	Impact	Certainty	
<b>Serious complications of catheter insertion<sup>h</sup></b>										
n = 5 <sup>i</sup>	Observational studies	Not serious	Not serious <sup>j</sup>	Not serious <sup>k</sup>	Not serious <sup>l</sup>	Strong association <sup>m</sup>	Rate of serious complications of catheter insertion varies from 0.1% to 2.1%	Rate of serious complications of catheter insertion varies from 0.1% to 2.1%	⊕⊕⊕⊕	CRITICAL
<b>Serious complications of ECTR<sup>n</sup></b>										
n = 6 <sup>o</sup>	Observational studies	Not serious	Not serious	Not serious	Not serious	Strong association <sup>p</sup>	Rate of serious complications of ECTR varies according to the type of ECTR performed from 0.005% (HD and CKRT), to 1.9% (HP)	Absolute effect is estimated to be varying from > 0 to 19 more serious complications per 1000 patients in the ECTR group	⊕⊕⊕⊕	CRITICAL
<b>Complications related to antidote</b>										
n = 7 <sup>q</sup>	Observational studies	Very serious <sup>b</sup>	Not serious	Serious <sup>c</sup>	Serious <sup>d</sup>	Publication bias strongly suspected <sup>e</sup>	Formepizole: Rare cases of anaphylaxis, bradycardia, hypotension [68, 428–432]  Ethanol: Altered consciousness in 5–15%, occasionally requiring mechanical ventilation [68, 431, 432], hypoglycemia in 16% of children [433], bradycardia in 10–12% [431, 432]	Smaller incidence with ECTR but minimal impact  Smaller incidence with ECTR because of shorter duration of ethanol and lower risk of hypoglycemia because of dextrose in dialysate bath	⊕⊕⊕⊕	IMPORTANT
									⊕⊕⊕⊕	VERY LOW

**Table 7** (continued)

Bold text was inserted to highlight the result

*ECTR* Extracorporeal treatments, *HD* Hemodialysis, *CKRT* Continuous kidney replacement therapy, *HP* Hemoperfusion, *US* Ultrasound, *ICU* Intensive care unit

<sup>#</sup> Refers to patients with a glycolate concentration  $\leq 12$  mmol/L or an anion gap with potassium  $\leq 28$  mmol/L. As mentioned, an evidence profile table could not be constructed for patients with "late" ethylene glycol poisoning, i.e., those with a serum glycolate over 12 mmol/L, or an anion gap over 28 mmol/L, although *ECTR* would be considered lifesaving in this context

\* Cases of *ECTR* were regrouped regardless of antidote used

- a. Includes our systematic review of the literature on *ECTR* (181 case reports and 446 patients; 84 of which had "Early EG poisoning") and 1 systematic review on standard care alone
- b. Case reports published on effect of *ECTR*. Uncontrolled and unadjusted for confounders such as severity of poisoning, co-ingestions, supportive and standard care, and co-interventions. Confounding-by-indication is inevitable since *ECTR* was usually attempted when other therapies have failed
- c. *ECTR* and standard care performed may not be generalizable to current practice (literature pre-dating 2000)
- d. Few events in small sample size, optimal information size criteria not met
- e. Publication bias is strongly suspected due to the study design (case reports published in toxicology)
- f. Includes our systematic review of the literature on *ECTR* 181 case reports (446 patients; 84 of which had "Early EG poisoning")
- g. Includes 8 articles
- h. For venous catheter insertion: serious complications include hemothorax, pneumothorax, hemothorax, hemothorax, hydrothorax, subcutaneous emphysema retroperitoneal hemorrhage, embolism, nerve injury, arteriovenous fistula, tamponade, and death. Hematoma and arterial puncture were judged not serious and thus excluded from this composite outcome. DVT and infection complications were not included considering the short duration of catheter use
- i. Based on 5 single-arm observational studies: 2 meta-analyses comparing serious mechanical complications associated with catheterization using or not an ultrasound, which included 6 RCTs in subclavian veins [434] and 11 in internal jugular veins [435]; 2 RCTs comparing major mechanical complications of different sites of catheterization [436, 437]; and one large multicenter cohort study reporting all mechanical complications associated with catheterization [438]. Rare events were reported from case series and case reports
- j. Not rated down for inconsistency since heterogeneity was mainly explained by variation in site of insertion, use of ultrasound, experience of the operator, populations (adults and pediatric), urgency of catheter insertion, practice patterns and methodological quality of studies
- k. Not rated down for indirectness since cannulation and catheter insertion was judged similar to the procedure for other indications
- l. Not rated down for imprecision since wide range reported explained by inconsistency
- m. The events in the control group are assumed to be zero (since no catheter is installed for *ECTR*), therefore, the magnitude of effect is at least expected to be large, which increases the confidence in the estimate of effect. Furthermore, none of the studies reported 95%CI which included the null value and all observed complications occurred in a very short time frame (i.e., few hours)
- n. For HD and CKRT: serious complications (air emboli, shock and death) are exceedingly rare especially if no net ultrafiltration. Minor bleeding from heparin, transient hypotension, and electrolytes imbalance were judged not serious. For HP: serious complications include severe thrombocytopenia, major bleeding, and hemolysis. Transient hypotension, hypoglycemia, hypocalcemia, and thrombocytopenia were judged not serious
- o. HD/CKRT: Based on 2 single-arm studies describing severe adverse events per 1000 treatments in large cohorts of patients [439, 440]. HP: Based on 2 small single-arm studies in poisoned patients [441, 442]. Rare events were reported in case series and case reports
- p. Assuming that patients in the control group would not receive any form of *ECTR*, the events in the control group would be zero; therefore, the magnitude of effect is at least expected to be large, which increases the confidence in the estimate of effect. Furthermore, none of the studies reported 95%CI which included the null value and all observed complications occurred in a very short time frame (i.e., few hours)
- q. Includes seven observational cohorts of patients receiving ethanol or fomepizole

**Table 8** Final EXTRIP recommendations on the use of ECTR in ethylene glycol poisoning

INDICATIONS*	1
EG Dose	
a. In patients presenting with EG poisoning, <b>we recommend against</b> ECTR based solely on the reported EG dose	
Plasma EG concentration	
a. Fomepizole is used	
i. In patients presenting with EG poisoning, <b>we suggest</b> ECTR if EG concentration is > 50 mmol/L (> 310 mg/dL)	
b. Ethanol is used	
i. In patients presenting with EG poisoning, <b>we recommend</b> ECTR if EG concentration is > 50 mmol/L (> 310 mg/dL)	
ii. In patients presenting with EG poisoning, <b>we suggest</b> ECTR if EG concentration is 20–50 mmol/L (124–310 mg/dL)	
c. No antidote is available	
i. In patients presenting with EG poisoning, <b>we recommend</b> ECTR if EG concentration is > 10 mmol/L (> 62 mg/dL)	
Osmol gap (calculated as measured osmolality – calculated osmolality, in SI units and adjusted for ethanol) when there is evidence of EG exposure	
a. Fomepizole is used	
i. In patients presenting with EG poisoning, <b>we suggest</b> ECTR if the osmol gap is > 50	
b. Ethanol is used	
i. In patients presenting with EG poisoning, <b>we recommend</b> ECTR if the osmol gap is > 50	
ii. In patients presenting with EG poisoning, <b>we suggest</b> ECTR if the osmol gap is 20–50	
c. No antidote is available	
i. In patients presenting with EG poisoning, <b>we recommend</b> ECTR if the osmol gap is > 10	
Plasma glycolate concentration	
a. In patients presenting with EG poisoning, <b>we recommend</b> ECTR if the glycolate concentration is > 12 mmol/L	
b. In patients presenting with EG poisoning, <b>we suggest</b> ECTR if the glycolate concentration is 8–12 mmol/L	
Anion gap (calculated as $\text{Na}^+ + \text{K}^+ - \text{Cl}^- - \text{HCO}_3^-$ ) when there is evidence of EG exposure	
a. In patients presenting with EG poisoning, <b>we recommend</b> ECTR if the anion gap is > 27 mmol/L	
b. In patients presenting with EG poisoning, <b>we suggest</b> ECTR if the anion gap is 23–27 mmol/L	
Clinical indications	
a. Coma	
i. In patients presenting with coma due to EG poisoning, <b>we recommend</b> ECTR	
b. Seizures	
i. In patients presenting with EG poisoning and seizures, <b>we recommend</b> ECTR	
c. Kidney Impairment	
i. In patients presenting with EG poisoning and CKD (eGFR < 45 mL/min/1.73m <sup>2</sup> ), <b>we suggest</b> ECTR	
ii. In patients presenting with EG poisoning and AKI (KDIGO stage 2 or 3), <b>we recommend</b> ECTR	
<b>MODALITY</b>	
a. In patients presenting with EG poisoning requiring ECTR, when all ECTR modalities are available, <b>we recommend</b> using intermittent hemodialysis rather than any other type of ECTR	
b. In patients presenting with EG poisoning requiring ECTR, <b>we recommend</b> using continuous kidney replacement therapy over other types of ECTR if intermittent hemodialysis is not available	
<b>CESSATION</b>	
a. <b>We recommend</b> stopping ECTR when the anion gap (calculated as $\text{Na}^+ + \text{K}^+ - \text{Cl}^- - \text{HCO}_3^-$ ) is < 18 mmol/L	
b. <b>We suggest</b> stopping ECTR when the EG concentration is < 4 mmol/L (25 mg/dL)	
c. <b>We suggest</b> stopping ECTR when acid–base abnormalities are corrected	

Bold text was inserted to highlight the result

ECTR extracorporeal treatment, EG Ethylene glycol, CKD Chronic kidney disease, AKI Acute kidney injury, KDIGO Kidney Disease Improving Global Outcomes

\* If any of indication criteria fulfills a recommendation for ECTR, then ECTR should be performed regardless of the presence of other conditions

- |   |   |
|---|---|
| <p>is &gt; 50 mmol/L (&gt; 310 mg/dL) (strong recommendation, very low-quality evidence)</p> <p>ii. In patients presenting with EG poisoning, <b>we suggest</b> ECTR if EG concentration is 20 to 50 mmol/L (124 to 310 mg/dL) (weak recommendation, very low-quality evidence)</p> <p>c. No antidote is available</p> <p>    i. In patients presenting with EG poisoning, <b>we recommend</b> ECTR if EG concentration</p> | <p>is &gt; 10 mmol/L (&gt; 62 mg/dL) (strong recommendation, very low-quality evidence)</p> <p>Rationale: The EG concentration is poorly prognostic of clinical outcomes because EG itself causes little toxicity. In fact, patients receiving fomepizole alone have excellent outcomes regardless of the EG concentration, assuming there is no kidney impairment and minimal academia [358]. The benefit of ECTR in this context is to presumably reduce length of stay and total hospital costs, especially at high EG concentration, rather than reducing</p> |
|---|---|



the incidence of outcomes such as mortality or AKI and explains why this is "suggested" rather than "recommended" [107–111, 227, 267]. However, the workgroup acknowledges that these decisions need to be individualized (which GRADE emphasizes for weak/conditional recommendations) as cost considerations are dependent on the setting and institution; for example, costs for ECTR and fomepizole may exceed fomepizole alone if a patient needs to be transferred to another center for ECTR.

The same EG concentration cutoff was chosen when ethanol was used as an antidote, although this was a recommendation. The rationale being that ADH blockade with ethanol is more unpredictable and there are cases of treatment failure even with little to no acidosis or kidney impairment present on admission [358]. Prolonged ethanol therapy also carries risks and requires admission to a high-dependency unit which may be shortened by using ECTR. With EG concentration > 50 mmol/L, assuming an endogenous EG  $T_{1/2} = 14$  h during ethanol therapy, a patient would need treatment for > 48 h before reaching a safe EG concentration, during which the risks of side effects from ethanol (central nervous system depression, dysphoria) and/or therapeutic failure become considerable. If no ADH inhibitor can be used, an EG concentration > 10 mmol/L (> 62 mg/dL) should prompt ECTR, as adverse outcomes are generally reported in untreated patients over this concentration; however, until there is a better understanding of threshold ethylene glycol concentrations, the workgroup recognizes that a more cautious cutoff may be preferable (see research gap below). From a known EG concentration and using local cost of fomepizole, ethanol, hospitalization, and ECTR, and using the EG  $T_{1/2}$  during specific circumstances (ECTR, AKI, antidote used, Table 1 and Table 2), clinicians can estimate the time to reach a safe concentration and decide if ECTR would be cost-effective in the specific scenario (Additional file 1: Figure S3). The decision to transfer a patient to another institution to receive ECTR should be individualized.

At extremely high EG concentrations with an associated high plasma osmolality, there is a potential risk of inducing osmotic disequilibrium with ECTR. However, these complications are considered unlikely because of the acute onset of the hyperosmolality and were only reported in one out of the 27 cases with an EG concentration > 100 mmol/L (> 620 mg/dL) [268]. The workgroup's recommendations remain applicable for these patients.

*The osmol gap (calculated as measured osmolality – calculated osmolality, in SI units and adjusted for ethanol) when there is evidence of EG exposure*

- a. Fomepizole is used
  - i. In patients presenting with EG poisoning, **we suggest** ECTR if the osmol gap is > 50 (weak recommendation, very low-quality evidence)
- b. Ethanol is used
  - i. In patients presenting with EG poisoning, **we recommend** ECTR if the osmol gap is > 50 (strong recommendation, very low-quality evidence)
  - ii. In patients presenting with EG poisoning, **we suggest** ECTR if the osmol gap is 20 to 50 (weak recommendation, very low-quality evidence)
- c. No antidote is available
  - i. In patients presenting with EG poisoning, **we recommend** ECTR if the osmol gap is > 10 (strong recommendation, very low-quality evidence)

Rationale: EG assays are seldom available locally in an appropriate time frame to influence clinical decisions [360, 361], and so the osmol gap is often used as a surrogate to predict the EG concentration [113, 119, 172, 342, 362–364]. Unfortunately, many clinical conditions and ingestion of other alcohols increase the osmol gap [365]. Conversely, the osmol gap may be "normal" or even below 0 if EG is already metabolized or if too little EG is ingested [24, 366–369]. For these reasons, the osmol gap is a poor screening test for EG ingestion, especially at low osmol gap values [370–373]. However, at high EG concentration, the osmol gap correlates linearly with the EG concentration (Additional file 1: Table S11), despite considerable inter- and intra-patient variability [371]. The panel proposed that the same cutoffs for osmol gap and EG concentrations be used for initiation of ECTR, especially if there is a confirmed history of EG ingestion. Since the osmol gap may overestimate the EG concentration, the panel acknowledges that using these cutoffs may lead to unnecessary ECTRs. If no antidote is available, an osmol gap > 10, in the context of EG exposure, is a reasonable criterion for hemodialysis, with the above caveats [371]. The workgroup did not provide an osmol gap cutoff when there is no/very low suspicion of EG poisoning. The workgroup also acknowledges that there are many formulas to calculate to osmol gap [368, 369, 374, 375].

#### *Plasma glycolate concentration*

- a. In patients presenting with EG poisoning, **we recommend** ECTR if the glycolate concentration

is >12 mmol/L (strong recommendation, very low-quality evidence)

- b. In patients presenting with EG poisoning, **we suggest** ECTR if the glycolate concentration is >8 mmol/L (weak recommendation, very low-quality evidence)

Rationale: Glycolate is the EG metabolite in highest concentration in blood [19] and correlates with AKI and death [71]. There was only one death reported when the glycolate concentration was <12 mmol/L [376]; however, the mortality rate rises substantially once the glycolate concentration exceeds 12 mmol/L [71].

#### *Anion gap when there is evidence of EG exposure*

- a. In patients presenting with EG poisoning, **we recommend** ECTR if the anion gap (calculated as  $\text{Na}^+ + \text{K}^+ - \text{Cl}^- - \text{HCO}_3^-$ ) is >27 mmol/L (strong recommendation, very low-quality evidence)
- b. In patients presenting with EG poisoning, **we suggest** ECTR if the anion gap is 23–27 mmol/L (weak recommendation, very low-quality evidence)

Rationale: Glycolate assays are not available in most institutions. The anion gap is by far the best surrogate marker for glycolate and correlates linearly with glycolate and is associated with clinical outcomes [29, 67, 71, 72, 74]. Based on previous reviews [71], the workgroup agreed that an anion gap of 24–28 mmol/L and >28 mmol/L, respectively, would best correlate with the suggested and recommended indications for ECTR based on plasma glycolate concentrations. To support this, there were only 3 patients out of 84 with an anion gap  $\leq$  28 mmol/L or glycolate concentration  $\leq$  12 mmol/L on admission who died; in all these cases, the clinical and metabolic data were incomplete (Additional file 1: Table S10). Because the relationship between glycolate concentration and prognosis require confirmation, the workgroup chose slightly more conservative cutoffs, accepting that this may lead to unnecessary ECTRs.

The anion gap may overestimate (e.g., concomitant AKI or ketoacidosis) or underestimate (e.g., hypoalbuminemia or co-ingestions of lithium or barium) [377–379] the glycolate concentration. In such circumstances, other acid–base parameters such as pH,  $\text{HCO}_3^-$ , and base excess can also be consulted with due consideration of the extent to which they are also influenced by other factors such as inadequate respiratory compensation or exogenous bicarbonate. It is important to note that the anion gap is only useful to predict glycolate concentrations if there is a high pre-test probability of EG exposure. Its value to predict the need for ECTR is poor if it is used

indiscriminately; when there is little or no evidence of EG exposure, an elevated anion gap is not by itself an indication for ECTR as this may be caused by various factors.

An elevated glycolate concentration can falsely elevate the plasma lactate concentration on some analyzers [239, 380–384], which has prompted some to suggest using the “lactate gap” as a surrogate of glycolate. However, this requires knowledge of the specific analyzer’s cross-reactivity so it cannot be simply formalized into a recommendation.

Some authors suggest that hemodialysis may be obviated even in cases of severe acidemia [385] or that fomepizole may lower glycolate concentrations faster than hemodialysis [124], although the EXTRIP panel strongly cautions against these viewpoints.

#### *Clinical indications*

- a. Coma
- i. In patients presenting with coma due to EG poisoning, **we recommend** ECTR (strong recommendation, very low-quality evidence)
- b. Seizures
- i. In patients presenting with EG poisoning and seizures, **we recommend** ECTR (strong recommendation, very low-quality evidence)
- c. Kidney Impairment
- i. In patients presenting with EG poisoning and CKD (eGFR < 45 mL/min/1.73 m.<sup>2</sup>), **we suggest** ECTR (weak recommendation, very low-quality evidence)
- ii. In patients presenting with EG poisoning and AKI (KDIGO stage 2 or 3), **we recommend** ECTR (strong recommendation, very low-quality evidence)

Rationale: AKI is correlated with mortality [27, 29] and kidney impairment reduces endogenous elimination of EG, which is pertinent once antidotal therapy is started, as elimination of EG and metabolites are dependent on functional kidneys. The presence of kidney impairment lowers the EG concentration thresholds for initiating ECTR. Coma and seizures are associated with a poor prognosis and become a clinical justification for ECTR [23, 27, 31, 32, 63, 65, 67, 74]. Mild inebriation may be due to EG early after ingestion and is not an indication for ECTR.

Other clinical manifestations are not recommendations for ECTR; respiratory failure and pulmonary edema would occur after already stated indications for ECTR.

Cranial nerve defects may occur long after exposure despite repeated ECTR.

**Special populations** The workgroup proposed that these recommendations remain applicable for other populations. A lower EG threshold concentration for ECTR may be applicable in children being treated with ethanol, to minimize adverse effects of ethanol. In pregnancy, ethanol is potentially teratogenic and fomepizole is classed Category C [386]. Although fomepizole was used without complication in the second [387] and third trimesters [388], there may be a preference for lower ECTR threshold to reduce the exposure to these antidotes in the pregnant patient, although ECTR also carries risks in this population. These considerations were discussed with a patient representative who endorsed the recommendations.

### Modality

- In patients presenting with EG poisoning requiring ECTR, when all ECTR modalities are available, **we recommend** using intermittent hemodialysis rather than any other type of ECTR (strong recommendation, very low-quality evidence)
- In patients presenting with EG poisoning requiring ECTR, **we recommend** using continuous kidney replacement therapy (CKRT) over other types of ECTR if intermittent hemodialysis is not available (strong recommendation, very low-quality evidence)

**Rationale:** Hemodialysis remains the ECTR that is most widely available so can be initiated quicker than other ECTRs and is also less costly [389]. High-efficiency hemodialysis is also the most efficient ECTR to remove both EG and metabolites, although intermittent hemodiafiltration would be expected to be equally effective. Intermittent hemodialysis was also shown, in methanol poisoning, to correct acidemia quicker than CKRT [390], although clinical outcomes were comparable with both techniques [391]. CKRT is preferred if it can be initiated faster than hemodialysis (e.g., unavailability of hemodialysis, nursing limitations), leading to attainment of a safe EG concentration, as illustrated in Additional file 1: Figure S3. CKRT is preferable if a patient has marked brain edema, as it increases intracranial pressure to a lesser degree than intermittent hemodialysis [392]. Clinicians performing ECTR should optimize operator settings to maximize EG clearance (e.g., higher blood flow, higher effluent production, filters with higher surface area).

In resource-restricted regions where hemodialysis or CKRT cannot be performed, rapid-exchange peritoneal dialysis using non-lactate-based solutions will at least double EG clearance if kidney impairment is present.

However, peritoneal dialysis should not replace hemodialysis if the latter is available, as there are many cases of clinical worsening during peritoneal dialysis [150, 158, 393]. Although there are authors suggesting adding peritoneal dialysis to hemodialysis, the EXTRIP panel could not imagine a clinical or kinetic rationale for this, as peritoneal dialysis would only add 5% to the clearance obtained with hemodialysis [52] but at much higher cost and complication rate.

### Cessation

- We recommend** stopping ECTR when the AG (calculated as  $\text{Na}^+ + \text{K}^+ - \text{Cl}^- - \text{HCO}_3^-$ ) is  $< 18$  mmol/L (strong recommendation, very low-quality evidence)
- We suggest** stopping ECTR when the EG is  $< 4$  mmol/L (25 mg/dL) (weak recommendation, very low-quality evidence)
- We suggest** stopping ECTR when acid–base abnormalities are corrected (weak recommendation, very low-quality evidence)

**Rationale:** Once ECTR is initiated, it is recommended that all acid–base parameters have normalized, in particular a confirmed and sustained normalization of the glycolate concentration and/or anion gap before stopping ECTR. Some clinical markers such as seizures may reverse quickly once ECTR is initiated and others, such as cranial nerve palsies and AKI in particular, may take weeks to resolve and should therefore not guide cessation. Once acid–base homeostasis is restored, then an acceptable and conservative endpoint for cessation is an EG concentration  $< 4$  mmol/L. If ECTR must be terminated when the EG concentration is higher (e.g., multiple poisoned patients), continuation of ADH blockade is reasonable to prevent further EG metabolism. As noted above, some authors have suggested that an EG concentration  $< 10$  mmol/L is an acceptable endpoint in asymptomatic patients [60], but supporting clinical data are not currently available and there are few downsides to continuing ECTR until lower cutoffs are reached. The clinical significance of rebound in EG concentration after ECTR is uncertain but can be addressed with a repeat ECTR session if clinically indicated. Although the EG concentration is linearly correlated with the osmol gap when elevated, the workgroup did not propose a specific osmol gap cutoff for cessation as there are too many imprecisions at low osmol gap values. The use of validated equations based on expected decay of EG in plasma can be used to predict dialysis time [67, 115, 233]. These formulas assume high-efficiency hemodialysis, with good and constant blood flows, and no sampling errors [394]. These formulas may be useful for planning purposes, especially in cases of

multiple poisoned patients where ECTR triage is required [67], although the workgroup reiterates that all acid–base abnormalities should be reversed before stopping ECTR.

### Miscellaneous

There are various reported approaches to ADH blockade once ECTR is started. Some centers switch from fomepizole to ethanol and others use ethanol in the dialysate bath. Both fomepizole and ethanol are readily dialyzable (see above) and require increased dosage during ECTR (Additional file 1: Table S12). Some centers withhold ADH blockade during ECTR, claiming that ECTR will remove metabolites quickly enough to avoid harm [395]. This appeared to be safe in 5 patients in a retrospective study [123], but more data are required and this approach cannot be currently recommended.

Several EG-poisoned patients have concomitant alcohol use disorder, and are at risk for alcohol withdrawal, especially if ECTR is performed [282]; usual measures should be in place to mitigate this risk. Cerebral hemorrhage is not a common manifestation of EG poisoning (as opposed to methanol) but occasionally occurs [396, 397], and so the decision to anticoagulate the ECTR circuit should be individualized.

EXTRIP strongly advocates for widespread and rapid (2–4 h) hospital availability of glycolate and EG measurements, as recommended by the National Academy of Clinical Biochemistry [398]. These would permit precise diagnosis and targeted treatment, avoiding costly unnecessary treatments [399, 400].

### Research gap

Cost and clinical outcome studies should be performed to evaluate the use of fomepizole versus ethanol versus no ADH blockade during ECTR. Further, in patients with no acidosis, it would be useful to determine if the addition of ECTR to ADH blockade significantly reduces cost and/or length of stay. These questions can be ideally answered by prospective randomized trials, but adequately powered studies require multicenter collaborations which can be complicated. Well-conducted single-center studies with complete reporting of relevant clinical outcomes including biomarkers of EG toxicity (for example, changes in acidosis and kidney function), preferably with statistical matching of baseline variables, will also be informative. Of course, cost-effectiveness studies will vary between institutions and health systems, so the development of algorithms that allow for the incorporation of all relevant components and their cost to facilitate local decision-making is anticipated to be informative. Studies should identify what represents “safe” EG and glycolate concentrations to better define initiation and cessation criteria for ECTR and/or ADH blockade. Cases of osmotic

demyelination syndrome in those that have a very high concentration of EG (e.g., >100 mmol/L or >620 mg/dL) and of “dialysis disequilibrium” during ECTR should be reported to assess the incidence of these phenomena [268, 401]. Cases of EG poisoning treated with exchange transfusion (when no other modality is available) should be reported with proper toxicokinetic data.

### Conclusion

The EXTRIP workgroup reviewed the available literature pertaining to the role of ECTR in ethylene glycol poisoning to propose treatment recommendations based on blood tests with and without the use of ADH blockers. The presence of kidney impairment decreased the thresholds for ECTR use. The workgroup recommends using intermittent hemodialysis over other ECTRs, and to evaluate the cost-benefit between fomepizole use vs ECTR for less severe poisoning. The dosage of antidotes needs to be adjusted during ECTR. The workgroup strongly advocates for the widespread availability of resources for the rapid measurement of glycolate and EG concentrations.

### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13054-022-04227-2>.

**Additional file 1.** Supplemental file.

### Acknowledgements

The EXTRIP workgroup includes: Badria Alhatali, Kurt Anseeuw, Ingrid Berling, Joséé Bouchard, Timothy E Bunchman Diane P Calello, Paul K Chin, Kent Doi, Tais Galvao, David S Goldfarb, Lotte CG Hoegberg, Sofia Kebede, Jan T Kielstein, Andrew Lewington, Yi Li, Etienne M Macedo, Rob MacLaren, James B Mowry, Thomas D Nolin, Marlies Ostermann, Ai Peng, Jean-Philippe Roy, Greene Shepherd, Anitha Vijayan, Steven J Walsh, Anselm Wong, and Christopher Yates. We would like to acknowledge the valuable help of our dedicated translators, librarian, data extractors, and meeting secretary. Official translators were Mrs. Alexandra Angulo, Mrs. Alla Abbott, Mr. Anant Vipat, Mr. Andreas Betz, Mrs. Angelina Kovaleva, Mrs. Denise Gemmellaro, Mrs. Ewa Brodziuk, Mrs. Helen Johnson, Mr. Junzheng Peng, Dr. Marcela Covic, Mrs. Nathalie Eeckhout, Mrs. Rosie Finnegan, Mr. Salih Topal, and Mrs. Vilma Etchard. The librarian was Mrs. Elena Guadagno. Data extractors for EXTRIP-2 included Dr. Maria Rif, Dr. François Filion, Mrs. Karine Mardini, Dr. Tudor Botnaru, Dr. Elizabeth Koo, and Mrs. Gabrielle Wilson. The meeting secretary was Ms. Brenda Gallant.

### Author contributions

We confirm that all authors satisfy the conditions stated for authorship. Specific author contributions are the following: Study design: MG, SG, RSH, VL, BM, HHM, MR, SK, SB, DMW, and DMR; literature searches: EG, MG, VL, and DMR; screening of study titles and abstracts: DMR, DMW, SG, and MG; screening of full text articles: DMR, DMW, SG, and MG; data extraction: MG, SG, RSH, VL, BM, HHM, MR, SK, SB, DMW, and DMR; quality of reporting and risk for bias of each included study: DMR, MG, and VL; draft of the manuscript: MG, SG, RSH, VL, BM, HHM, MR, SK, SB, DMW, and DMR; and reviewing the manuscript: MG, SG, RSH, VL, BM, HHM, MR, SK, SB, DMW, and DMR. All authors read and approved the final manuscript.

### Funding

EXTRIP received support consisting of an unrestricted grant of \$60,633 Canadian from the Verdun Research Fund (the institution of M. Ghannoum) solely for the reimbursement of travel expenses for the in-person guideline meeting



and payment to dedicated translators for retrieval and translation of foreign language articles.

#### Availability of data and materials

The data underlying this article will be shared on reasonable request to the corresponding author.

#### Declarations

##### Ethics approval and consent to participate

Not applicable.

##### Consent for publication

Not applicable.

##### Competing interests

All prospective members were required to disclose any actual, potential, or perceived conflict of interest before inclusion in the workgroup. The disclosures were used to categorize the members as cleared for full participation, allowed to participate with recusal from certain aspects of guideline development, or disqualified from participation. The coauthors remained free of any financial conflict of interest during the entire guideline development process, meaning avoidance of interests and relationships with pharmaceutical or device companies pertaining to the topic of poisoning. Members were required to disclose to the coauthors any new activities that had the potential to be viewed as a conflict of interest before engaging in the activity, at the beginning of face-to-face meeting, and before submission of the manuscript. Coauthors determined if specific activities were allowed under the conflict-of-interest rules. All conflicts of interest deemed as potential appearance of a conflict of interest were required to be included in the manuscript. M. Ghannoum is a scholar of the Fonds de Recherche du Québec-Santé, reports employment with the Government of Quebec, and serves as EXTRIP chair. R.S. Hoffman reports honoraria from UpToDate. V. Lavergne reports employment with the Infectious Diseases Society of America. D.M. Wood reports employment with Guy's and St Thomas' NHS Foundation Trust; research funding from the European Monitoring Centre for Drugs and Drug Addiction; honoraria from the European Monitoring Centre for Drugs and Drug Addiction and the United Nations Office on Drugs and Crime; and serving as a scientific advisor member of the European Association of Poisons Centres and Clinical Toxicologists, the European Monitoring Centre for Drugs and Drug Addiction, the Journal of Medical Toxicology, the UK Advisory Council on the Misuse of Drugs, and the United Nations Office on Drugs and Crime. All remaining authors have nothing to disclose.

##### Author details

<sup>1</sup>Research Center, CIUSSS du Nord-de-l'île-de-Montréal, University of Montreal, Montreal, QC, Canada. <sup>2</sup>Nephrology Division, NYU Langone Health, NYU Grossman School of Medicine, New York, NY, USA. <sup>3</sup>Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands. <sup>4</sup>Centre Intégré de Santé et de Services Sociaux (CISSS) de la Montérégie-Centre Emergency Department, Hôpital Charles-Lemoyne, Greenfield Park, QC, Canada. <sup>5</sup>Faculté de Médecine et Sciences de la Santé, Université de Sherbrooke, Sherbrooke, Canada. <sup>6</sup>Centre Antipoison du Québec, Quebec, QC, Canada. <sup>7</sup>Division of Medical Toxicology, Ronald O. Perleman Department of Emergency Medicine, NYU Grossman School of Medicine, New York, NY, USA. <sup>8</sup>Department of Medical and Toxicological Critical Care, Lariboisière Hospital, INSERM UMRS-1144, Paris Cité University, Paris, France. <sup>9</sup>Social Determinants of Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. <sup>10</sup>Department of Clinical Toxicology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. <sup>11</sup>Ottawa, Ontario, Canada. <sup>12</sup>Department of Internal Medicine-Division of Nephrology, Lebanese American University - School of Medicine, Byblos, Lebanon. <sup>13</sup>Department of Emergency Medicine, U Mass Memorial Health, U Mass Chan Medical School, Worcester, MA, USA. <sup>14</sup>Clinical Toxicology, Guy's and St Thomas' NHS Foundation Trust and King's Health Partners, and Clinical Toxicology, Faculty of Life Sciences and Medicine, King's College London, London, UK. <sup>15</sup>New South Wales Poisons Information Centre, Sydney Children's Hospitals Network, Westmead, NSW, Australia. <sup>16</sup>Drug Health Services, Royal Prince Alfred Hospital, Sydney, NSW, Australia.

Received: 11 August 2022 Accepted: 18 October 2022

Published online: 10 February 2023

#### References

- Mydlik M, Derzsiova K, Frank K. Renal replacement therapy in acute poisonings—one center experience. *Przegl Lek*. 2013;70(6):381–5.
- Ulmeanu CE, Nitescu V, Ulmeanu A. Prevalence of acute renal failure in children's poisoning—10 years study. *Clin Toxicol*. 2009;47:445–6.
- Sentsov V, Brusin KM, Novikova OV, Djakonov V. Epidemiology of acute renal failure in toxicology centre. *Clin Toxicol*. 2007;45:380.
- Brusin KM, Nekhoroshkov RO. A 13-year retrospective study on toxic alcohol poisoning in Middle Urals, Russia. *Asia Pac J Med Toxicol*. 2015;4(1):43–6.
- Swiderska A, Sein Anand J. Selected data of acute poisonings with ethylene glycol and methanol in Poland in the year 2010. *Przegl Lek*. 2013;70(8):479–84.
- Gummin DD, Mowry JB, Spyker DA, Brooks DE, Beuhler MC, Rivers LJ, Hashem HA, Ryan ML. 2018 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 36th Annual Report. *Clin Toxicol (Phila)*. 2019;57(12):1220–413.
- Schreiner GE, Maher JF, Marc-Aurele J, Knowlan D, Alvo M. Ethylene glycol: two indications for hemodialysis. *ASAIO J*. 1959;5(1):81–9.
- Ghannoum M, Lavergne V, Gosselin S, Mowry JB, Hoegberg LC, Yarema M, Thompson M, Murphy N, Thompson J, Purcell R, et al. Practice trends in the use of extracorporeal treatments for poisoning in four countries. *Semin Dial*. 2016;29(1):71–80.
- Buller GK, Moskowitz CB. When is it appropriate to treat ethylene glycol intoxication with fomepizole alone without hemodialysis? *Semin Dial*. 2011;24(4):441–2.
- Megarbane B, Baud F. Is there a remaining place for hemodialysis in toxic alcohol poisonings treated with fomepizole? *Clin Toxicol*. 2003;41(4):396–7.
- Miller H, Barceloux DG, Krenzelok EP, Olson K, Watson W. American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning. Ad Hoc Committee. *J Toxicol Clin Toxicol* 1999;37(5):537–560.
- Ghannoum M, Nolin TD, Lavergne V, Hoffman RS. Blood purification in toxicology: nephrology's ugly duckling. *Adv Chronic Kidney Dis*. 2011;18(3):160–6.
- Lavergne V, Nolin TD, Hoffman RS, Roberts D, Gosselin S, Goldfarb DS, Kielstein JT, Mactier R, MacLaren R, Mowry JB, et al. The EXTRIP (Extracorporeal Treatments In Poisoning) workgroup: Guideline methodology. *Clin Toxicol*. 2012;50:403–13.
- Lavergne V, Ouellet G, Bouchard J, Galvao T, Kielstein JT, Roberts DM, Kanji S, Mowry JB, Calello DP, Hoffman RS, et al. Guidelines for reporting case studies on extracorporeal treatments in poisonings: methodology. *Semin Dial*. 2014;27(4):407–14.
- Sivilotti ML, Burns MJ, McMartin KE, Brent J. Toxicokinetics of ethylene glycol during fomepizole therapy: implications for management. For the Methylpyrazole for Toxic Alcohols Study Group. *Ann Emerg Med* 2000;36(2):114–125.
- Beuhler MC, Kerns W. Ethylene glycol poisoning with biphasic, rapid elimination. *Clin Toxicol*. 2008;46(7):608.
- Lee SL, Shih HT, Chi YC, Li YP, Yin SJ. Oxidation of methanol, ethylene glycol, and isopropanol with human alcohol dehydrogenases and the inhibition by ethanol and 4-methylpyrazole. *Chem Biol Interact*. 2011;191(1–3):26–31.
- Grauer GF, Thrall MA, Henre BA, Hjelle JJ. Comparison of the effects of ethanol and 4-methylpyrazole on the pharmacokinetics and toxicity of ethylene glycol in the dog. *Toxicol Lett*. 1987;35(2–3):307–14.
- Jacobsen D, Ovrebo S, Ostborg J, Sejersted OM. Glycolate causes the acidosis in ethylene glycol poisoning and is effectively removed by hemodialysis. *Acta Med Scand*. 1984;216(4):409–16.
- McMartin K. Are calcium oxalate crystals involved in the mechanism of acute renal failure in ethylene glycol poisoning? *Clin Toxicol (Phila)*. 2009;47(9):859–69.
- McMartin KE, Cenac TA. Toxicity of ethylene glycol metabolites in normal human kidney cells. *Ann NY Acad Sci*. 2000;919:315–7.

22. Deriabin II, Lizanets MN, Danielian FA, Kharkevich IP. Clinical picture and therapy of acute poisoning by ethylene glycol. [Russian]. *Sovetskaiia meditsina* 1973;36(4):100–104.
23. Puka J, Szajewski J. Acute ethylene glycol poisoning—205 cases treated at the Acute Poison Control Center. *Pol Arch Med Wewn.* 1988;80(2–3):88–98.
24. Karlson-Stiber C, Persson H. Ethylene glycol poisoning: experiences from an epidemic in Sweden. *J Toxicol Clin Toxicol.* 1992;30(4):565–74.
25. Stompor T, Szymczakiewicz-Multanowska A, Sulowicz W, Pach J, Groszek B, Winnik L, Kuzniewski M. Ethylene glycol acute poisoning treatment results in Krakow in the years 1990–1994. *Przegl Lek.* 1996;53(4):360–4.
26. Sydor A, Holys S, Witek R. Acute ethylene glycol poisoning in the Tarnow region in the years 1982–1993. *Przegl Lek.* 1996;53(3):138–42.
27. Rzepecki J, Stasiak M, Kolacinski Z. Clinical symptomatology and laboratory diagnosis of 75 cases of ethylene glycol poisonings. *Pol Merkur Lekarski.* 1998;5(26):74–9.
28. Brent J, McMartin K, Phillips S, Burkhart KK, Donovan JW, Wells M, Kulig K. Fomepizole for the treatment of ethylene glycol poisoning. Methylpyrazole for toxic alcohols study group. *N Engl J Med* 1999;340(11):832–838.
29. Porter WH, Rutter PW, Bush BA, Pappas AA, Dunnington JE. Ethylene glycol toxicity: the role of serum glycolic acid in hemodialysis. *J Toxicol Clin Toxicol.* 2001;39(6):607–15.
30. Krenova M, Pelclova D, Navratil T, Merta M, Tesar V. Ethylene glycol poisoning in the Czech Republic (2000–2002). *Blood Purif.* 2006;24(2):180–4.
31. Czyewska S, Winnicka R, Rzepecki J, Kolacinski Z, Politanski P, Sawicka J, Krakowiak A. Acute ethylene glycol poisoning among patients of Nofer Institute of Occupational Medicine in Lodz, Toxicology Unit, hospitalized in the years 2000–2009. *Przegl Lek.* 2013;70(8):500–5.
32. Lung DD, Kearney TE, Brasiel JA, Olson K. Predictors of death and prolonged renal insufficiency in ethylene glycol poisoning. *J Intensive Care Med.* 2015;30(5):270–7.
33. Plackova S, Caganova B, Faltanova P, Liptak T, Otrubova O, Kresanek J. Ethylene glycol poisonings associated with acute kidney injury in the Slovak Republic. *Clin Toxicol.* 2015;53(4):325.
34. Stonys A, Kuzminskis V, Seputyte A, Astasauskaite S, Jeseviciute A. Acute renal failure in patients with alcoholic surrogate intoxication. *Medicina (Kaunas).* 2007;43(Suppl 1):36–9.
35. Reddy NJ, Sudini M, Lewis LD. Delayed neurological sequelae from ethylene glycol, diethylene glycol and methanol poisonings. *Clin Toxicol (Phila).* 2010;48(10):967–73.
36. Palmer BF, Eigenbrodt EH, Henrich WL. Cranial nerve deficit: a clue to the diagnosis of ethylene glycol poisoning. *Am J Med.* 1989;87(1):91–2.
37. Spillane L, Roberts JR, Meyer AE. Multiple cranial nerve deficits after ethylene glycol poisoning. *Ann Emerg Med.* 1991;20(2):208–10.
38. Reddy NJ, Lewis LD, Gardner TB, Osterling W, Eskey CJ, Nierenberg DW. Two cases of rapid onset Parkinson's syndrome following toxic ingestion of ethylene glycol and methanol. *Clin Pharmacol Ther.* 2007;81(1):114–21.
39. Morgan BW, Ford MD, Follmer R. Ethylene glycol ingestion resulting in brainstem and midbrain dysfunction. *J Toxicol Clin Toxicol.* 2000;38(4):445–51.
40. Gerin M, Patrice S, Begin D, Goldberg MS, Vyskocil A, Adib G, Drolet D, Viau C. A study of ethylene glycol exposure and kidney function of aircraft de-icing workers. *Int Arch Occup Environ Health.* 1997;69(4):255–65.
41. Reif G. Self-experiments with ethylene glycol. *Pharmazie.* 1950;5(6):276–8.
42. Bachem C. Pharmacological studies on glycol and its use in pharmacy and medicine. *Med Klin.* 1917;13(1):7.
43. Page IH. Ethylene glycol—a pharmacological study. *J Pharmacol Exp Therap.* 1927;30(4):313–20.
44. Krenova M, Pelclova D. Does unintentional ingestion of ethylene glycol represent a serious risk? *Hum Exp Toxicol.* 2007;26(1):59–67.
45. Hess R, Bartels MJ, Pottenger LH. Ethylene glycol: an estimate of tolerable levels of exposure based on a review of animal and human data. *Arch Toxicol.* 2004;78(12):671–80.
46. Krenova M, Pelclova D, Navratil T, Merta M. Experiences of the Czech toxicological information centre with ethylene glycol poisoning. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2005;149(2):473–5.
47. Hunt S. Antidotes to antifreeze. *Journal of Hospital Medicine* 2011;2:S191–S192.
48. Hunt R. Toxicity of ethylene and propylene glycol. *Ind Eng Chem.* 1932;24(361):836.
49. Nadeau G, Cote R, Delaney FJ. Two cases of ethylene glycol poisoning. *Can Med Assoc J.* 1954;70(1):69–70.
50. Mégarbane B, Baud F. Acute ethylene glycol intoxication: a case report. *Medecine Therapeutique.* 2001;7(2):163–7.
51. Tanasescu A, Macovei RA, Tudosie MS. Outcome of patients in acute poisoning with ethylene glycol—factors which may have influence on evolution. *J Med Life.* 2014;7(3):81–6.
52. Sabeel AI, Kurkus J, Lindholm T. Intensified dialysis treatment of ethylene glycol intoxication. *Scand J Urol Nephrol.* 1995;29(2):125–9.
53. Kidawa Z, Trznadel K. Haemodialysis in the treatment of acute ethylene glycol poisoning. *Biul WAM.* 1987;30:1–13.
54. Widman C. A few cases of ethylene glycol intoxication. *Acta Med Scand.* 1946;126(4):295–306.
55. Rydel JJ, Carlson A, Sharma J, Leikin J. An approach to dialysis for ethylene glycol intoxication. *Vet Hum Toxicol.* 2002;44(1):36–9.
56. Krivoshapkin VG, Shutov AM, Shcherbak EN, Lopatin AI, Krugliakov VV. Hemodialysis in antifreeze poisoning. *Sov Med.* 1983;11:89–91.
57. Krenova M, Pelclova D, Navratil T. Ethylene glycol poisoning: different course in suicidal and non-intentional ingestions. *Clin Toxicol.* 2005;43:467–9.
58. Krenova M, Pelclova D. Analysis of the renal damage following ethylene glycol poisoning. *Clin Toxicol.* 2006;44:565–6.
59. Caravati EM, Erdman AR, Christianson G, Manoguerra AS, Booze LL, Woolf AD, Olson KR, Chyka PA, Scharman EJ, Wax PM, et al. Ethylene glycol exposure: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila).* 2005;43(5):327–45.
60. McMartin K, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohols that form toxic metabolites. *Br J Clin Pharmacol.* 2016;81(3):505–15.
61. Akhtar J, Petersen BA, Krenzelo E. When to stop fomepizole administration? Is 20 mg/dl too low? *Clin Toxicol.* 2007;45:362.
62. Bigaillon C, Thefenne H, Samy S, Batjom E, Salle S, Cirodde A, Ramirez JM. Ethylene glycol intoxication: a case report. *Ann Biol Clin (Paris).* 2007;65(4):437–42.
63. Grigorasi GR, Nistor I, Corlade-Andrei M, Voroneanu L, Siroopol D, Apetrei M, Cimpoesu DC, Covic A. Outcomes of death and prolonged renal insufficiency in ethylene glycol poisoned patients. *Int Urol Nephrol.* 2022;54(1):149–55.
64. Stankova E, Gesheva M, Mechkarska B. Early haemodialysis in acute ethylene glycol poisonings? *Clin Toxicol.* 2008;46:418.
65. Hylander B, Kjellstrand CM. Prognostic factors and treatment of severe ethylene glycol intoxication. *Intensive Care Med.* 1996;22(6):546–52.
66. Tuero G, Gonzalez J, Sahuquillo L, Freixa A, Gomila I, Elorza MA, Barcelo B. Value of glycolic acid analysis in ethylene glycol poisoning: a clinical case report and systematic review of the literature. *Forensic Sci Int.* 2018;290:e9–14.
67. Iliuta IA, Lachance P, Ghannoum M, Begin Y, Mac-Way F, Desmeules S, De Serres SA, Julien AS, Douville P, Agharazii M. Prediction and validation of the duration of hemodialysis sessions for the treatment of acute ethylene glycol poisoning. *Kidney Int.* 2017;92(2):453–60.
68. Thanacoody RH, Gilfillan C, Bradberry SM, Davies J, Jackson G, Vale AJ, Thompson JP, Eddleston M, Thomas SH. Management of poisoning with ethylene glycol and methanol in the UK: a prospective study conducted by the National Poisons Information Service (NPIS). *Clin Toxicol.* 2016;54(2):134–40.
69. Jokiniemi T, Ikaheimo R. Ethylene glycol poisonings in Northern Savo 1984–98. *Duodecim.* 2001;117(1):23–7.
70. Krenova M, Pelclova D. Course of intoxications due to concurrent ethylene glycol and ethanol ingestion. *Przegl Lek.* 2005;62(6):508–10.
71. Roberts DM, Hoffman RS, Brent J, Laverne V, Hovda KE, Porter WH, McMartin KE, Ghannoum M. The serum glycolate concentration: its prognostic value and its correlation to surrogate markers in ethylene glycol exposures. *Clin Toxicol (Phila)* 2022:1–10.



72. Coulter CV, Farquhar SE, McSherry CM, Isbister GK, Duffull SB. Methanol and ethylene glycol acute poisonings—predictors of mortality. *Clin Toxicol (Phila)*. 2011;49(10):900–6.
73. Asauliuk IK, Stanislavskii OK. The prognosis of the degree of severity of acute ethylene glycol poisoning. *Vrach Delo*. 1989;3:103–5.
74. Roth B, Forrester M, Labat L. Correlation of the dsurrogate markers of anion gap, osmolar gap, and drowsiness to outcome in a large case series of ethylene glycol exposures. *Clin Toxicol*. 2008;46:599.
75. Kahn HS, Brotchner RJ. A recovery from ethylene glycol (anti-freeze) intoxication; a case of survival and two fatalities from ethylene glycol including autopsy findings. *Ann Intern Med*. 1950;32(2):284–94.
76. Julsrud AC, Marcussen JM, Hovig T. [Ethylene glycol poisoning. 5 Cases of which 3 had fatal outcome]. *Tidsskr Nor Laegeforen* 1960;80:9–12.
77. Gaultier M, Conso F, Rudler M, Leclerc JP, Mellerio F. Acute ethylene glycol poisoning. *Eur J Toxicol Environ Hyg*. 1976;9(6):373–9.
78. Walton EW. An epidemic of antifreeze poisoning. *Med Sci Law*. 1978;18(4):231–7.
79. Petit J, Viel D, Lapert D. Acute ethylene-glycol poisoning. A nine case report and review of literature. *Convergences Medicales* 1983, 2(6):487–491.
80. Mackowski J, Niemczyk S, Grochowski J, Brzozowska M. Glycol ethylene poisoning as a cause of chronic renal failure. *Przegl Lek*. 1996;53(12):879–82.
81. Ghannoum M, Hoffman RS, Mowry JB, Lavergne V. Trends in toxic alcohol exposures in the United States from 2000 to 2013: a focus on the use of antidotes and extracorporeal treatments. *Semin Dial*. 2014;27(4):395–401.
82. Rogaczewska A, Kobza-Sindlowska K, Krakowiak A, Piekarska-Wijatkowska A. Acute alcohol poisonings among patients in Toxicology Unit, Nofer Institute of Occupational Medicine in the period of time 2007–2012. *Przegl Lek*. 2014;71(9):479–83.
83. Sommerfeld K, Lukasik-Glebocka M, Zielinska-Psuja B. Ethylene glycol poisoning—the significance of analytical diagnosis based on reports from Wielkopolska. *Przegl Lek*. 2012;69(8):435–8.
84. Mydlik M, Derzsiova K, Mizla P, Boor A, Macingova E, Slosarcikova L. Diagnosis and therapy of ethylene glycol poisoning—analysis of 20 patients. *Vnitr Lek*. 2002;48(11):1054–9.
85. Haapanen E, Pellinen T, Partanen J. Ethylene glycol poisoning. *Duodecim*. 1984;100(4):214–9.
86. Marraffa J, Stork CM, Cantor R. Risk for long-term nephrotoxicity after ethylene glycol poisoning. *Clin Toxicol*. 2004;42(5):737.
87. Krenova M, Pelclova D. Analysis of the ethylene glycol poisoning: a 5-year study in the Czech Republic. *Clin Toxicol*. 2006;44:702–3.
88. Martinez Miguel P, Rengel MA, Ortega M, Rodriguez Ferrero M, Goicoechea M, Verde E, Munoz-Blanco JL, Luno J. Prolonged acute renal failure and severe polyradiculopathy in ethylene glycol intoxication. *Nefrologia*. 2006;26(6):738–40.
89. Seeff LB, Hendler ED, Hosten AO, Shalhoub RJ. Ethylene glycol poisoning. Survival after ingestion of 400 ml. with 42 days of oliguria and 17 days of coma. *Med Ann Dist Columbia* 1970;39(1):31–36.
90. Lewis LD, Smith BW, Mamourian AC. Delayed sequelae after acute overdoses or poisonings: cranial neuropathy related to ethylene glycol ingestion. *Clin Pharmacol Ther*. 1997;61(6):692–9.
91. Mackowski J, Niemczyk S, Grochowski J. Ethylene glycol poisoning as a cause of chronic renal failure. *Polski merkuriusz lekarski : organ Polskiego Towarzystwa Lekarskiego*. 1997;2(9):221–3.
92. Tobe TJM, Braam GB, Meulenbelt J, Van Dijk GW. Ethylene glycol poisoning mimicking Snow White. *Lancet*. 2002;359(9304):444–5.
93. Eroglu E, Kocyigit I, Bahcebasi S, Unal A, Sipahioglu MH, Kocyigit M, Tokgoz B, Oymak O. Unusual clinical presentation of ethylene glycol poisoning: Unilateral facial nerve paralysis. *Case Rep Med* 2013;2013 (no pagination)(460250).
94. Sydor A, Kolasa M, Czapkowicz-Gryszkiewicz L, Dubiel-Bigaj M, Banach M. Late complications after ethylene glycol poisoning—case history. *Przegl Lek*. 1996;53(3):190–3.
95. Auzepy P, Masnou P, Metral S, Foucher R, Charpentier B. Diaphragm paralysis and facial diplegia with albumin-cell count dissociation in acute ethylene glycol poisoning. *Presse Med*. 1997;26(18):856.
96. Alzouebi M, Sarrigiannis PG, Hadjiyassiliou M. Acute polyradiculoneuropathy with renal failure: mind the anion gap. *J Neurol Neurosurg Psychiatry*. 2008;79(7):842–4.
97. Bouattar T, Madani N, Hamzaoui H, Alhamamy Z, El Quessar A, Benamar L, Rhou H, Abouquail R, Zeggwagh A, Bayahia R et al. Severe ethylene glycol intoxication by skin absorption. *Nephrol Ther* 2009.
98. Mallya KB, Mendis T, Guberman A. Bilateral facial paralysis following ethylene glycol ingestion. *Can J Neurol Sci*. 1986;13(4):340–1.
99. Freilich BM, Altun Z, Ramesar C, Medalia A. Neuropsychological sequelae of ethylene glycol intoxication: a case study. *Appl Neuropsychol*. 2007;14(1):56–61.
100. Tarr BD, Winters LJ, Moore MP, Cowell RL, Hayton WL. Low-dose ethanol in the treatment of ethylene glycol poisoning. *J Vet Pharmacol Ther*. 1985;8(3):254–62.
101. Chou JY, Richardson KE. The effect of pyrazole on ethylene glycol toxicity and metabolism in the rat. *Toxicol Appl Pharmacol*. 1978;43(1):33–44.
102. Peterson DI, Peterson JE, Hardinge MG, Linda L, Wacker WE. Experimental treatment of ethylene glycol poisoning. *JAMA*. 1963;186:955–7.
103. Clay KL, Murphy RC. On the metabolic acidosis of ethylene glycol intoxication. *Toxicol Appl Pharmacol*. 1977;39(1):39–49.
104. Wacker WE, Haynes H, Druyan R, Fisher W, Coleman JE. Treatment of ethylene glycol poisoning with ethyl alcohol. *JAMA*. 1965;194(11):1231–3.
105. Pendras J. Ethylene glycol poisoning as an indication for hemodialysis. *Clin Res*. 1963;1:118.
106. Auda AO, Oehme FW. An activated charcoal hemoperfusion system for the treatment of barbitol or ethylene glycol poisoning in dogs. *Clin Toxicol*. 1981;18(9):1105–15.
107. Donovan JW, Burkhart KK, McMartin KE. A comparison of fomepizole with hemodialysis vs fomepizole alone in therapy of severe ethylene glycol toxicity. *Clin Toxicol*. 1998;36(5):451–2.
108. Cannarozzi AA, Mullins ME. A cost analysis of treating patients with ethylene glycol poisoning with fomepizole alone versus hemodialysis and fomepizole. *Clin Toxicol*. 2010;48(3):299–300.
109. Ellsworth H, Engebretsen KM, Hlavenka LM, Kim AK, Cole J, Harris CR, Stellpflug SJ. A cost comparison of fomepizole and hemodialysis in the treatment of methanol and ethylene glycol toxicity. *Clin Toxicol*. 2011;49:590–1.
110. Wiles D, Tzeng J, Russell J, Casavant MJ. Comment on treatment methods for ethylene glycol intoxication. *Neth J Med*. 2014;72(7):383–4.
111. Roberts D. Cost-assessment of the use of fomepizole for the treatment of toxic alcohol poisonings in Australian practice. *Clin Toxicol*. 2019;57(12):1202–3.
112. Kutlunin VP, Sakharov G, Kotliarova EL, Grankin VI. Toxicokinetics of ethylene glycol during treatment of acute ethylene glycol poisoning. *Ter Arkh*. 1984;56(7):117–9.
113. Leikin JB, Toerne T, Burda A, McAllister K, Erickson T. Summertime cluster of intentional ethylene glycol ingestions. *J Am Med Assoc*. 1997;278(17):1406.
114. Borron SW, Megarbane B, Baud FJ. Fomepizole in treatment of uncomplicated ethylene glycol poisoning. *Lancet*. 1999;354(9181):831.
115. Hirsch DJ, Jindal KK, Wong P, Fraser AD. A simple method to estimate the required dialysis time for cases of alcohol poisoning. *Kidney Int*. 2001;60(5):2021–4.
116. Lister D, Tierney M, Dickinson G. Effectiveness of IV ethanol therapy combined with hemodialysis in the treatment of methanol and ethylene glycol poisoning. *Can J Hosp Pharm*. 2005;58(3):142–7.
117. Ybarra J, Donate T, Pou JM, Madhun ZT. Ethylene glycol intoxication with and without simultaneous diabetic ketoacidosis: a report of nine cases and review of the literature. *Int J Diabetes Metab*. 2005;13(2):83–7.
118. White NC, Litovitz T, White MK, Watson WA, Benson BE, Horowitz BZ, Marr-Lyon L. The impact of bittering agents on suicidal ingestions of antifreeze. *Clin Toxicol*. 2008;46(6):507–14.
119. Hovda KE, Julsrud J, Ovrebø S, Brors O, Jacobsen D. Studies on ethylene glycol poisoning: one patient—154 admissions. *Clin Toxicol*. 2011;49(6):478–84.
120. Lasala GS, Veairier D, Cresswell A, Greenberg MI. Initial ethylene glycol levels as a predictor of intensive care unit admission or hemodialysis. *Clin Toxicol*. 2014;52(7):747.
121. Colibao L, Kim T, DesLauriers C, Bryant S. Unintentional ethylene glycol exposures: Pediatric pearls in management. *J Med Toxicol*. 2018;14(1):61–2.

122. Tung RC, Thornton SL. Characteristics of laboratory confirmed ethylene glycol and methanol exposures reported to a regional poison control center. *Kans J Med*. 2018;11(3):67–9.
123. Sidlak AM, Marino RT, Van Meerbeke JP, Pizon AF. Single versus continued dosing of fomepizole during hemodialysis in ethylene glycol toxicity. *Clin Toxicol (Phila)*. 2021;59(2):106–10.
124. Corley RA, McMartin KE. Incorporation of therapeutic interventions in physiologically based pharmacokinetic modeling of human clinical case reports of accidental or intentional overdosing with ethylene glycol. *Toxicol Sci*. 2005;85(1):491–501.
125. Flanagan P, Libcke JH. Renal biopsy observations following recovery from ethylene glycol nephrosis. *Am J Clin Pathol*. 1964;41:171–5.
126. Munro KM, Adams JH. Acute ethylene glycol poisoning: report of a fatal case. *Med Sci Law*. 1967;7(4):181–4.
127. Pinter J, Cszaszar J, Mihalecz K, Wolfer E. Combined treatment of ethylene glycol poisoning. *Orv Hetil*. 1967;108(17):790–2.
128. Joly JB, Huault G, Frossard C, Fabiani P, Thieffry S. Acute poisoning by ethylene glycol (apropos of 4 cases in young children). *Bulletins et memoires de la Societe medicale des hopitaux de Paris*. 1968;119(1):27–45.
129. Castaing R, Wone C, Dupoux J, Cardinaud JP, Favarel-Garrigues JC, Michon D. Extra-renal purification in poisoning. A case of acute poisoning with ethylene-glycol. *Bordeaux medical* 1970;3(3):691–702.
130. Collins JM, Hennes DM, Holzgang CR, Gourley RT, Porter GA. Recovery after prolonged oliguria due to ethylene glycol intoxication. The prognostic value of serial, percutaneous renal biopsy. *Archives of internal medicine* 1970;125(6):1059–1062.
131. Gaultier M, Pebay-Peyroula F, Rudler M, Leclerc JP, Duvaldestin P. Acute ethylene glycol poisoning. *Eur J Toxicol*. 1970;3(3):227–34.
132. Leclerc JP, Morel-Maroger L, Galian A, Pebay-Peyroula F, Bismuth C. Acute ethylene glycol poisoning. Apropos of a case. *La semaine des hopitaux : organe fonde par l'Association d'enseignement medical des hopitaux de Paris* 1971;47(9):566–571.
133. Underwood F, Bennett WM. Ethylene glycol intoxication. Prevention of renal failure by aggressive management. *JAMA* 1973;226(12):1453–1454.
134. Parry MF, Wallach R. Ethylene glycol poisoning. *Am J Med*. 1974;57(1):143–50.
135. Poplawski A, Olenska T. A case of acute poisoning with ethylene glycol (Polish). [Polish]. *Wiadomosci Lekarskie* 1974;27(9):819–822.
136. Shimanko II, Yaroslavsky AA. Early hemodialysis in severe poisoning with ethylene glycol, quinine and pachycarpine (Russian). [Russian]. *Sovetskaya Meditsina* 1974;37(1):92–96.
137. Haacke E, Fuhrmeister U, Berndt SF. Pseudoencephalitis in ethylene glycol poisoning. [German]. *Intensivmedizin* 1976;13(1):84–89.
138. Michelis MF, Mitchell B, Davis BB. "Bicarbonate resistant" metabolic acidosis in association with ethylene glycol intoxication. *Clin Toxicol*. 1976;9(1):53–60.
139. Vale JA, Bluett NH, Widdop B. Ethylene glycol poisoning. *Postgrad Med J*. 1976;52(611):598–602.
140. Lavelle KJ. Ethylene glycol poisoning. *J Indiana State Med Assoc*. 1977;70(5):249–52.
141. Slucznanowski W, Dziewanowski K, Remigolski L. Acute renal failure in ethylene glycol poisoning treated with hemodialysis. *Wiad Lek*. 1978;31(14):983–5.
142. Scully R, Galdabini J, McNeely B. Case Records of the Massachusetts General Hospital. *N Engl J Med*. 1979;301(12):650–7.
143. Sangster B, Prenen JA, de Groot G. Case 38–1979: ethylene glycol poisoning. *N Engl J Med*. 1980;302(8):465.
144. Stokes JB 3rd, Aueron F. Prevention of organ damage in massive ethylene glycol ingestion. *JAMA*. 1980;243(20):2065–6.
145. Tomilin VV, Berezhnoi RV, Sergeev SN. Significance of the therapeutic measures for the forensic medical expertise of acute ethylene glycol poisonings. *Sud Med Ekspert*. 1980;23(3):51.
146. Berger JR, Ayyar DR. Neurological complications of ethylene glycol intoxication. Report of a case. *Archives of Neurology* 1981, 38(11):724–726.
147. Jacobsen D, Ostby N, Kornstad S. Poisoning with ethylene glycol and oxalic acid. [Norwegian]. *Tidsskrift for den Norske Laegeforening* 1981, 101(12):689–692+728.
148. Peterson CD, Collins AJ, Himes JM, Bullock ML, Keane WF. Ethylene glycol poisoning: pharmacokinetics during therapy with ethanol and hemodialysis. *N Engl J Med*. 1981;304(1):21–3.
149. Frommer JP, Olivero JJ, Ayus JC. Hemodialysis with a high bicarbonate-containing dialysate in the treatment of acute ethylene glycol intoxication. *Dial Transplant*. 1982;11(12):1108–11.
150. Gordon HL, Hunter JM. Ethylene glycol poisoning. A case report. *Anaesthesia*. 1982;37(3):332–8.
151. Jacobsen D, Ostby N, Bredesen JE. Studies on ethylene glycol poisoning. *Acta Med Scand*. 1982;212(1–2):11–5.
152. Vale JA, Prior JG, O'Hare JP, Flanagan RJ, Feehally J. Treatment of ethylene glycol poisoning with peritoneal dialysis. *Br Med J (Clin Res Ed)*. 1982;284(6315):557.
153. Chmielewska J, Mysliwiec M. Acute ethylene glycol poisoning treated with hemodialysis. *Wiad Lek*. 1983;36(2):165–8.
154. Dolinska-Laskos C, Hadzlik-Makarewicz H, Starzyk J. Acute renal failure after poisoning with Enwogol, a coolant. *Wiad Lek*. 1983;36(11):913–5.
155. Kuska J. Ethylene glycol poisoning. *Polski tygodnik lekarski (Warsaw, Poland : 1960)* 1983;38(50):1583–1585.
156. Kutlunin VP, Sakharov G, Kotliarova EL, Grankin VI, Nemov VV. Quantitative evaluation of the efficacy of early hemodialysis in poisoning with technical liquids containing ethylene glycol. *Ter Arkh*. 1983;55(6):101–3.
157. Nielsen CT, Olesen JL, Olsen PG, Bartels PD. Poisoning with ethylene glycol. *Ugeskr Laeger*. 1983;145(26):2026–8.
158. Okell RW, Derbyshire DR. Ethylene glycol poisoning. *Anaesthesia*. 1983;38(2):168–70.
159. Ostborg J, Jacobsen D. Ethylene glycol poisoning. Diagnosis and treatment. *Tidsskr Nor Laegeforen*. 1983;103(11):912–4.
160. Szpirt W, Vedegaard E, Angelo H. [Ethylene glycol poisoning. Symptoms and treatment]. *Ugeskr Laeger* 1983, 145(26):2003–2006.
161. DaRoza R, Henning RJ, Sunshine I, Sutheimer C. Acute ethylene glycol poisoning. *Crit Care Med*. 1984;12(11):1003–5.
162. Catchings TT, Beamer WC, Lundy L, Prough DS. Adult respiratory distress syndrome secondary to ethylene glycol ingestion. *Ann Emerg Med*. 1985;14(6):594–6.
163. Bobbitt WH, Williams RM, Freed CR. Severe ethylene glycol intoxication with multisystem failure. *West J Med*. 1986;144(2):225–8.
164. Gabow PA, Clay K, Sullivan JB, Lepoff R. Organic acids in ethylene glycol intoxication. *Ann Intern Med*. 1986;105(1):16–20.
165. Hewlett TP, McMartin KE, Lauro AJ, Ragan FA, Jr. Ethylene glycol poisoning. The value of glycolic acid determinations for diagnosis and treatment. *J Toxicol Clin Toxicol* 1986;24(5):389–402.
166. Linnanvuo-Laitinen M, Huttunen K. Ethylene glycol intoxication. *J Toxicol Clin Toxicol*. 1986;24(2):167–74.
167. Nogue S, Mas A, Pares A. Intoxication by ethyleneglycol in a diabetic patient: problems with diagnosis. *Med Clin (Barc)*. 1986;86:65–6.
168. Rothman A, Normann SA, Manoguerra AS, Bastian JF, Griswold WR. Short-term hemodialysis in childhood ethylene glycol poisoning. *J Pediatr*. 1986;108(1):153–5.
169. Turk J, Morrell L. Ethylene glycol intoxication. *Arch Intern Med*. 1986;146(8):1601–3.
170. Wright N, Gupta RN. The role of the laboratory in acute poisoning: case histories. *Clin Biochem*. 1986;19(2):127–31.
171. Younossi-Hartenstein A, Roth B, Iffland R, Sticht G. Short-term hemodialysis for ethylene glycol poisoning. *J Pediatr*. 1986;109(4):731–2.
172. Cheng JT, Beysolow TD, Kaul B, Weisman R, Feinfeld DA. Clearance of ethylene glycol by kidneys and hemodialysis. *J Toxicol Clin Toxicol*. 1987;25(1–2):95–108.
173. Flanagan RJ, Dawling S, Buckley BM. Measurement of ethylene glycol (ethane-1,2-diol) in biological specimens using derivatization and gas-liquid chromatography with flame ionisation detection. *Ann Clin Biochem*. 1987;24(1):80–4.
174. Kawiak W, Hasiel T. Acute poisoning with ethylene glycol. *Wiad Lek*. 1987;40(19):1345–8.
175. Gabow PA. Ethylene glycol intoxication. *Am J Kidney Dis*. 1988;11(3):277–9.
176. Garibotto G, Paoletti E, Acquarone N. Glyoxylic acid in ethylene glycol poisoning. *Nephron*. 1988;48(3):248–9.

177. Haupt MC, Zull DN, Adams SL. Massive ethylene glycol poisoning without evidence of crystalluria: a case for early intervention. *J Emerg Med*. 1988;6(4):295–300.
178. 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(1):145–52.
179. Lomaestro BM. Ethylene glycol toxicity—misinterpretation of laboratory data. *Drug Intell Clin Pharm*. 1988;22(11):915–6.
180. Sabatini S, Morris R, Kurtzman N, Newsom G. Severe metabolic acidosis in an intoxicated patient. *Am J Nephrol*. 1988;8(4):323–33.
181. Introna F, Jr., Smialek JE. Antifreeze (ethylene glycol) intoxications in Baltimore. Report of six cases. *Acta morphologica Hungarica* 1989;37(3–4):245–263.
182. Kjeldgaard M, Kulling P, Molin L, Rajs J, Ovrebø S. A lack of ethylene glycol in the blood doesn't exclude severe poisoning. *Lakartidningen*. 1989;86(13):1181–3.
183. Momont SL, Dahlberg PJ. Ethylene glycol poisoning. *Wis Med J*. 1989;88(9):16–20.
184. Robinson D, McCoy CA. Ethylene glycol toxicity. *Crit Care Nurse*. 1989;9(6):70–4.
185. Ullman B, Malmund HO, Berg A. Treatment of various stages of ethylene glycol poisoning. *Lakartidningen*. 1989;86(13):1183–5.
186. Meatherall R, Krahn J. Excess serum osmolality gap after ingestion of methanol. *Clin Chem*. 1990;36(11):2004–7.
187. Nogue S, Campistol J, Torras A, Munne P, Revert L. Acute kidney insufficiency in ethylene glycol poisoning. *Rev Clin Esp*. 1990;186(3):124–6.
188. Curtin L, Kraner J, Wine H, Savitt D, Abuelo JG. Complete recovery after massive ethylene glycol ingestion. *Arch Intern Med*. 1992;152(6):1311–3.
189. Aarstad K, Dale O, Aakervik O, Ovrebø S, Zahlsen K. A rapid gas chromatographic method for determination of ethylene glycol in serum and urine. *J Anal Toxicol*. 1993;17(4):218–21.
190. Andreelli F, Blin P, Codet MP, Fohrer P, Lambrey G, Massy Z. Diagnostic and therapeutic management of ethylene glycol poisoning. Importance of crystalluria. Apropos of a case. *Nephrologie* 1993;14(5):221–225.
191. Blakeley KR, Rinner SE, Knochel JP. Survival of ethylene glycol poisoning with profound acidemia. *N Engl J Med*. 1993;328(7):515–6.
192. Durakovic Z. Ethylene glycol poisoning treated by haemodialysis. *J Indian Med Assoc*. 1993;91(7):182–3.
193. Gaillard Y, Auboyer C, Guy C, Gay-Montchamp JP, Ollagnier M. Treatment's scheme with in an intoxication by ethylene glycol. *Lyon Pharm*. 1993;44(4):259–63.
194. Kaiser W, Steinmauer HG, Biesenbach G, Janko O, Zazgornik J. Chronic ethylene glycol poisoning. *Dtsch Med Wochenschr*. 1993;118(17):622–6.
195. Paulsen D, Kronborg J, Borg EB, Hagen T. Cigar-like oxalate crystals in ethylene glycol poisoning. *Tidsskr Nor Laegeforen*. 1994;114(4):435–6.
196. Walder AD, Tyler CK. Ethylene glycol antifreeze poisoning. Three case reports and a review of treatment. *Anaesthesia* 1994;49(11):964–967.
197. Christiansson LK, Kaspersson KE, Kulling PE, Ovrebø S. Treatment of severe ethylene glycol intoxication with continuous arteriovenous hemofiltration dialysis. *J Toxicol Clin Toxicol*. 1995;33(3):267–70.
198. Faessel H, Houze P, Baud FJ, Scherrmann JM. 4-methylpyrazole monitoring during haemodialysis of ethylene glycol intoxicated patients. *Eur J Clin Pharmacol*. 1995;49(3):211–3.
199. Seidelmann S, Kubic V, Burton E, Schmitz L. Combined superwarfarin and ethylene glycol ingestion. A unique case report with misleading clinical history. *Am J Clin Pathol* 1995;104(6):663–666.
200. Tadokoro M, Ozono Y, Hara K, Taguchi T, Harada T, Ideguchi M, Senju M. A case of acute renal failure due to ethylene glycol intoxication. *Nippon Jinzo Gakkai Shi*. 1995;37(6):353–6.
201. Courtin P, Brugiere E, Gremaud H, Gassiot P, Magnin D. Ethylene glycol poisoning. A propos of a case. *Cahiers d'anesthesiologie* 1996;44(1):77–80.
202. Jobard E, Harry P, Turcant A, Roy PM, Allain P. 4-Methylpyrazole and hemodialysis in ethylene glycol poisoning. *J Toxicol Clin Toxicol*. 1996;34(4):373–7.
203. Niederstadt C, Lerche L, Steinhoff J. Proteinuria in ethylene glycol-induced acute renal failure. *Nephron*. 1996;73(2):316–7.
204. Baur M, Staedt U, Kirschstein W, Heene DL. 70-year-old patient with rapidly progressing dysphasia, disorientation and somnolence. *Internist (Berl)*. 1997;38(9):854–7.
205. Chow MT, Chen J, Patel JS, Ali S, Noghogh AA, Leehey DJ, Ing TS. Use of a phosphorus-enriched dialysate to hemodialyze patients with ethylene glycol intoxication. *Int J Artif Organs*. 1997;20(2):101–4.
206. 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):653–67.
207. Taylor R, Bower J, Salem MM. Acidosis and coma after hemodialysis. *J Am Soc Nephrol*. 1997;8(5):853–7.
208. Chow MT, Lin HJ, Mitra EA, Singh S, Lee E, Leehey DJ, Ing TS. Hemodialysis-induced hypophosphatemia in a normophosphatemic patient dialyzed for ethylene glycol poisoning: treatment with phosphorus-enriched hemodialysis. *Artif Organs*. 1998;22(10):905–7.
209. Eder AF, McGrath CM, Dowdy YG, Tomaszewski JE, Rosenberg FM, Wilson RB, Wolf BA, Shaw LM. Ethylene glycol poisoning: toxicokinetic and analytical factors affecting laboratory diagnosis. *Clin Chem*. 1998;44(1):168–77.
210. Kowalczyk M, Halvorsen S, Ovrebø S, Bredesen JE, Jacobsen D. Ethanol treatment in ethylene glycol poisoned patients. *Vet Hum Toxicol*. 1998;40(4):225–8.
211. Moreau CL, Kerns W, 2nd, Tomaszewski CA, McMartin KE, Rose SR, Ford MD, Brent J. Glycolate kinetics and hemodialysis clearance in ethylene glycol poisoning. META Study Group. *J Toxicol Clin Toxicol* 1998;36(7):659–666.
212. Aouizerate P, Dume L, Astier A. Simultaneous determination of ethylene glycol and its metabolites in acute poisoning. [French]. *Journal de Pharmacie Clinique* 1999;18(4):321–324.
213. Duvic C, Herody M, Sarret D, Nedelec G. Ethylene glycol poisoning. *Ann Med Interne (Paris)*. 1999;150(5):440–2.
214. Johnson B, Meggs WJ, Bentzel CJ. Emergency department hemodialysis in a case of severe ethylene glycol poisoning. *Ann Emerg Med*. 1999;33(1):108–10.
215. Nau T, Seitz H, Kapral S, Schalupny J, Templ E. Ethylene glycol poisoning and brain injury—a dangerous combination. *Anesthesiol Intensivmed Notfallmed Schmerzther*. 1999;34(5):318–20.
216. Nzerue CM, Harvey P, Volcy J, Berdzenshvili M. Survival after massive ethylene glycol poisoning: role of an ethanol enriched, bicarbonate-based dialysate. *Int J Artif Organs*. 1999;22(11):744–6.
217. Wisse B, Thakur S, Baran D. Recovery from prolonged metabolic acidosis due to accidental ethylene glycol poisoning. *Am J Kidney Dis*. 1999;33(2):E4.
218. Baum CR, Langman CB, Oker EE, Goldstein CA, Aviles SR, Makar JK. Fomepizole treatment of ethylene glycol poisoning in an infant. *Pediatrics*. 2000;106(6):1489–91.
219. Benitez JG, Swanson-Biearman B, Krenzlok EP. Nystagmus secondary to fomepizole administration in a pediatric patient. *J Toxicol Clin Toxicol*. 2000;38(7):795–8.
220. Lopez A, Ceppia F, Graine H, Buisine A, Khoury N, Toumi K, Lefevre G. Intoxication by ethylene glycol. *Ann Biol Clin*. 2001;59(5):655–9.
221. Vecer J, Kubatova H, Charvat J, Soucek M, Kvapil M. Ethylene glycol poisoning. *Cas Lek Cesk*. 2001;140(12):381–2.
222. Aakervik O, Svendsen J, Jacobsen D. Severe ethylene glycol poisoning treated with fomepizole (4-methylpyrazole). *Tidsskr Nor Laegeforen*. 2002;122(25):2444–6.
223. Bey TA, Walter FG, Gibly RL, James ST, Gharahbaghian L. Survival after ethylene glycol poisoning in a patient with an arterial pH of 6.58. *Veter Huma Toxicol* 2002;44(3):167–168.
224. Fraser AD. Clinical toxicologic implications of ethylene glycol and glycolic acid poisoning. *Ther Drug Monit*. 2002;24(2):232–8.
225. Hantson P, Vanbinst R, Mahieu P. Determination of ethylene glycol tissue content after fatal oral poisoning and pathologic findings. *Am J Forensic Med Pathol*. 2002;23(2):159–61.
226. Rottinghaus D, Bryant S, Harchelroad F. Survival after ethylene glycol overdose with blood pH of 6.54. *Clin Toxicol* 2003;41(5):674.
227. Vasavada N, Williams C, Hellman RN. Ethylene glycol intoxication: case report and pharmacokinetic perspectives. *Pharmacotherapy*. 2003;23(12):1652–8.

228. Woo MY, Greenway DC, Nadler SP, Cardinal P. Artifactual elevation of lactate in ethylene glycol poisoning. *J Emerg Med.* 2003;25(3):289–93.
229. Cox RD, Phillips WJ. Ethylene glycol toxicity. *Mil Med.* 2004;169(8):660–3.
230. Hilliard NJ, Robinson CA, Hardy R, Daly TM. Pathologic quiz case: repeated positive ethylene glycol levels by gas chromatography. Central venous line contamination of blood samples by propylene glycol from intravenous lorazepam injections. *Arch Pathol Lab Med* 2004;128(6):e79–80.
231. Johnson-Arbor K, Bayer M, McKay CA. Severe ethylene glycol ingestion complicated by refractory acidosis and death. *Clin Toxicol.* 2005;43(5):467.
232. Meier M, Nitschke M, Perras B, Steinhoff J. Ethylene glycol intoxication and xylitol infusion—metabolic steps of oxalate-induced acute renal failure. *Clin Nephrol.* 2005;63(3):225–8.
233. Youssef GM, Hirsch DJ. Validation of a method to predict required dialysis time for cases of methanol and ethylene glycol poisoning. *Am J Kidney Dis.* 2005;46(3):509–11.
234. Armstrong EJ, Engelhart DA, Jenkins AJ, Balraj EK. Homicidal ethylene glycol intoxication: a report of a case. *Am J Forensic Med Pathol.* 2006;27(2):151–5.
235. Fijen JW, Kemperman H, Ververs FFT, Meulenbelt J. False hyperlactatemia in ethylene glycol poisoning. *Intensive Care Med.* 2006;32(4):626–7.
236. Kralova I, Stepanek Z, Dusek J. Ethylene glycol intoxication misdiagnosed as eclampsia. *Acta Anaesthesiol Scand.* 2006;50(3):385–7.
237. Krenova M, Pelclova D. Complete recovery after repeated suicidal ethylene glycol ingestion. *Prague Med Rep.* 2006;107(1):130–6.
238. Pizon AF, Brooks DE. Hyperosmolality: another indication for hemodialysis following acute ethylene glycol poisoning. *Clin Toxicol.* 2006;44(2):181–3.
239. Brindley PG, Butler MS, Cembrowski G, Brindley DN. Falsely elevated point-of-care lactate measurement after ingestion of ethylene glycol. *CMAJ.* 2007;176(8):1097–9.
240. Green R. The management of severe toxic alcohol ingestions at a tertiary care center after the introduction of fomepizole. *Am J Emerg Med.* 2007;25(7):799–803.
241. Lovric M, Granic P, Cubrilo-Turek M, Lalic Z, Sertic J. Ethylene glycol poisoning. *Forensic Sci Int.* 2007;170(2–3):213–5.
242. Sabeva Y, Marinov P, Zlateva S. Significance of the toxicological analysis for the treatment of the ethylene glycol poisoning. *J IMAB Annu Proc (Sci Pap).* 2007;13(1):99–100.
243. Akhtar J, Campbell MC, Kotagal V, Krenzok EP. Treatment of methanol poisoning without maintenance doses of fomepizole during dialysis. *Clin Toxicol.* 2008;46(7):642.
244. Castanares-Zapatero D, Fillee C, Philippe M, Hantson P. Survival with extreme lactic acidosis following ethylene glycol poisoning? *Can J Anesth.* 2008;55(5):318–9.
245. Cooperman J, Keadey M, Morgan B. Falsely elevated lactate level in ethylene glycol poisoning: a case for better understanding the limitations of our laboratory equipment. *Clin Toxicol.* 2008;46:607.
246. Koopmans A, Hilken M, van der Hoeven JG. An unconscious patient with extreme anion gap metabolic acidosis and an uneventful recovery. *Neth J Crit Care.* 2008;12(5):210–2.
247. Lepik KJ, Brubacher JR, DeWitt CR, Lam GS, Lawson EJ, Erhardt GD, Pursell RA, Kennedy JR, Brignall JL. Bradycardia and hypotension associated with fomepizole infusion during hemodialysis. *Clin Toxicol.* 2008;46(6):570–3.
248. Peces R, Fernandez R, Peces C, Gonzalez E, Olivas E, Renjel F, Jimenez M, Costero O, Montero A, Selgas R. Effectiveness of pre-emptive hemodialysis with high-flux membranes for the treatment of life-threatening alcohol poisoning. *Nefrologia.* 2008;28(4):413–8.
249. Schorn R, Kalicki R, Renschmidt C, Schley G, Hofliger N, Aregger F. Sweet and sour—a patient with life-threatening metabolic acidosis and acute renal failure. *NDT Plus.* 2008;1(6):433–6.
250. Stapenhorst L, Hesse A, Hoppe B. Hyperoxaluria after ethylene glycol poisoning. *Pediatr Nephrol.* 2008;23(12):2277–9.
251. Takahashi S, Kanetake J, Kanawaku Y, Funayama M. Brain death with calcium oxalate deposition in the kidney: clue to the diagnosis of ethylene glycol poisoning. *Leg Med.* 2008;10(1):43–5.
252. Britton ML, Podoll AS, Finkel KW. Severe systemic oxalosis causing premature CVVHD failure after ethylene glycol ingestion. *Blood Purif.* 2009;27(3):277–8.
253. Gupta AK, Majilesi N, Ajagbe O, Chan GM, Lee DC, Carracio T, McGuigan M, Greller HA, Su M. Increased intracranial pressure and cranial nerve palsies associated with ethylene glycol toxicity. *Clin Toxicol.* 2009;47(7):722.
254. Muller R, Planck J, Heveling T. Ethylene glycol intoxication. Important differential diagnosis in comatose patients with metabolic acidosis. *Anaesthesist* 2009;58(1):35–38.
255. Barbas AS, Sweeney TE, Collins BH, Tuttle-Newhall JE, Sudan DL, Marroquin CE. Kidney-pancreas transplantation in the setting of donor ethylene glycol poisoning. *Dial Transplant.* 2010;39(5):216–7.
256. Gilbert C, Baram M, Marik P. Continuous venovenous hemodiafiltration in severe metabolic acidosis secondary to ethylene glycol ingestion. *South Med J.* 2010;103(8):846–7.
257. Montjoy CA, Rahman A, Teba L. Ethylene glycol and methanol poisonings: case series and review. *The West Virginia Med J.* 2010;106(6):17–23.
258. Kostek H, Kujawa A, Szponar J, Danielewicz P, Majewska M, Drelich G. Is it possible to survive metabolic acidosis with pH measure below 6.8? A study of two cases of inedible alcohol intoxication. *Przegl Lek* 2011;68(8):518–520.
259. Kujawa A, Kostek H, Szponar J, Majewska M, Ossowska B. Extremely severe metabolic acidosis and multi-organ complications in ethylene glycol intoxication: a case study. *Przegl Lek.* 2011;68(8):530–2.
260. Araque Arroyo P, Manzano Manzano F, Cuesta Santos P, Pla Hernandez A, Valenzuela Gamez JC, Calleja Hernandez MA. Monitoring of serum and urinary levels of ethylene glycol after large intake concomitant with ethanol consumption. *Atencion Farmaceutica.* 2012;14(5):376–8.
261. Gardias W, Szponar J, Kujawa A, Majewska M, Drelich G, Lewandowska-Stanek H. Three-fold ethylene glycol poisoning over 3 years—a case report. *Przegl Lek.* 2012;69(8):592–4.
262. Latus J, Kimmel M, Alschner MD, Braun N. Ethylene glycol poisoning: A rare but life-threatening cause of metabolic acidosis—a single-centre experience. *Clin Kidney J.* 2012;5(2):120–3.
263. Rahman SS, Kadakia S, Balsam L, Rubinstein S. Autonomic dysfunction as a delayed sequelae of acute ethylene glycol ingestion: a case report and review of the literature. *J Med Toxicol.* 2012;8(2):124–9.
264. Seo JW, Lee JH, Son IS, Kim YJ, Kim DY, Hwang Y, Chung HA, Choi HS, Lim SD. Acute oxalate nephropathy caused by ethylene glycol poisoning. *Kidney Res Clin Pract.* 2012;31(4):249–52.
265. Szponar J, Kwicien-Obara E, Krajewska A, Kostek H, Wysokinski A, Wacinski P, Lewandowska-Stanek H. Myocardial infarction in the course of ethylene glycol poisoning—a case report. *Przegl Lek.* 2012;69(8):603–5.
266. Arora A. The ‘gap’ in the ‘plasma osmolar gap’. *BMJ Case Rep* 2013, (no pagination)(200250).
267. Darracq MA, Rentmeester LL, Clark RF, Tomaszewski CA, Schneur AB, Cantrell FL. Cost of hemodialysis versus fomepizole-only for treatment of ethylene glycol intoxication. *Clin Toxicol.* 2013;51(3):188.
268. Ahmed A, Tschetter PA, Krasowski MD, Engelman A. Massive ethylene glycol poisoning triggers osmotic demyelination syndrome. *J Emerg Med.* 2014;46:e69–74.
269. Kamps MJA, Vermeulen Windsant-van den tweel AMA, de Jager CPC. Intoxication with ethylene glycol treated with fomepizole: A case report. *Netherlands Journal of Critical Care* 2014;18(4):24–26.
270. Riquier T, Geri G, Mongardon N, Bourgogne E, Pene F. False hyperlactatemia in life-threatening ethylene glycol poisoning. *Ann Fr Anesth Reanim.* 2014;33(4):e79–81.
271. Ruimy A, Keyser M, Pottecher J, Kremer S, Diemunsch P. Extensive brain necrosis secondary to acute ethylene glycol poisoning. *Ann Fr Anesth Reanim.* 2014;33(6):444–6.
272. Hovda KE, Vartdal T, Latimer B, Gadeholt G, McMartin KE, Jacobsen D. Fomepizole kinetics during intermittent (IHD) and continuous hemodialysis (CVVHD): a case study. *Clin Toxicol.* 2015;53:248–9.
273. Kim Y. Plotting of ethylene glycol blood concentrations using linear regression before and during hemodialysis in a case of intoxication and pharmacokinetic review. *Case Rep Nephrol.* 2015;2015: 359101.

274. Nguyen V, Lucyk SN, Howland MA, Su MK, Nelson LS. Too bad to be true? Osmol gap > 300 mOsm/L. *Clin Toxicol*. 2015;53:299–300.
275. Szmigielska A, Szymanik-Grzelak H, Kuzma-Mroczkowska E, Roszkowska-Blaim M. Hemodiafiltration efficacy in treatment of methanol and ethylene glycol poisoning in a 2-year-old girl. *Dev Period Med*. 2015;19(2):174–7.
276. Altıparmak B, Uysal AI, Tarakci E, Sahan L, Demirbilek S. Suicide attempt with rodenticides (ratsbane) and ethylene glycol (antifreeze). [Turkish]. *Anestezi Dergisi* 2016;24(3):200–203.
277. Falkowitz D, Jacob J. Profound acidosis and hyperkalemia without renal failure in a pediatric patient after ethylene glycol ingestion. *Clin Toxicol*. 2016;54(8):733.
278. Schoen JC, Cain MR, Robinson JA, Schiltz BM, Mannenbach MS. Adolescent presents with altered mental status and elevated anion gap after suicide attempt by ethylene glycol ingestion. *Pediatr Emerg Care*. 2016;32(10):688–90.
279. Singh R, Arain E, Buth A, Kado J, Soubani A, Imran N. Ethylene glycol poisoning: an unusual cause of altered mental status and the lessons learned from management of the disease in the acute setting. *Case Rep Crit Care*. 2016;2016:9157393.
280. Cacelin-Garza JR, Cacelin-Miranda RS. Intoxication due to ethylene glycol. *Medicina Interna de Mexico*. 2017;33(2):259–84.
281. Sugunaray JP, Thakur LK, Jha KK, Bucaloiu ID. Sequential episodes of ethylene glycol poisoning in the same person. *BMJ case reports* 2017, 2017 (no pagination)(bcr-2017–220108).
282. Bakos A. Estimation of the dialysis time for patient with extremely high ethylene glycol concentration. *Clin Toxicol*. 2018;56(6):527.
283. Hauvik LE, Varghese M, Nielsen EW. Lactate gap: a diagnostic support in severe metabolic acidosis of unknown origin. *Case Rep Med*. 2018;2018:5238240.
284. Sahutoglu T, Sahutoglu E. Hemodialysis during cardiopulmonary resuscitation with severe metabolic acidosis. *Int J Artif Organs*. 2018;41(8):431–6.
285. Noronha B, Kuster M, Forster C, Studhalter M. A sweet drink with consequences. *Praxis*. 2019;108(16):1097–9.
286. Prinz J, Boll B, von Bergwelt M, Burst V, Becker JU, Carvalho-Fiel D, Shimabukuro-Vornhagen A, Kochanek M. Antifreeze poisoning: the case of a patient with repeated ethylene glycol poisoning. *Med Klin Intensivmed Notfmed*. 2019;114(2):159–63.
287. Drick N, Schmidt JJ, Wiesner O, Kielstein JT. Fomepizole, ethanol or dialysis in the case of life-threatening ethylene glycol intoxication? *Medizinische Klinik Intensivmedizin und Notfallmedizin* 2020.
288. Shakoore MT, Tang J. Hemodialysis prescription in ethylene glycol overdose: a mathematical approach. *J Am Soc Nephrol*. 2020;31:815.
289. Battistella M. Fomepizole as an antidote for ethylene glycol poisoning. *Ann Pharmacother*. 2002;36(6):1085–9.
290. Druteika DP, Zed PJ, Ensom MH. Role of fomepizole in the management of ethylene glycol toxicity. *Pharmacotherapy*. 2002;22(3):365–72.
291. Beatty L, Green R, Magee K, Zed P. A systematic review of ethanol and fomepizole use in toxic alcohol ingestions. *Emerg Med Int*. 2013;2013: 638057.
292. Ramsay AG, Reed RG. Oxalate removal by hemodialysis in end-stage renal disease. *Am J Kidney Dis*. 1984;4(2):123–7.
293. Watts RW, Veall N, Purkiss P. Oxalate dynamics and removal rates during haemodialysis and peritoneal dialysis in patients with primary hyperoxaluria and severe renal failure. *Clin Sci (Lond)*. 1984;66(5):591–7.
294. Chimienti S, Mele G, Perrone F, Muscogiuri P, Cristofano C. Oxalate depuration during biofiltration with AN69 and in conventional hemodialysis in chronic renal failure (CRF) patients. *Int J Artif Organs*. 1986;9(Suppl 3):73–4.
295. Yamauchi A, Fujii M, Shirai D, Mikami H, Okada A, Imai E, Ando A, Orita Y, Kamada T. Plasma concentration and peritoneal clearance of oxalate in patients on continuous ambulatory peritoneal dialysis (CAPD). *Clin Nephrol*. 1986;25(4):181–5.
296. Morgan SH, Maher ER, Purkiss P, Watts RW, Curtis JR. Oxalate metabolism in end-stage renal disease: the effect of ascorbic acid and pyridoxine. *Nephrol Dial Transplant*. 1988;3(1):28–32.
297. Costello JF, Sadovnic MJ, Cottingham EM. Plasma oxalate levels rise in hemodialysis patients despite increased oxalate removal. *J Am Soc Nephrol*. 1991;1(12):1289–98.
298. Marangella M, Petrarulo M, Vitale C, Cosseddu D, Linari F. Kinetics of oxalate in hemodialysis. *Minerva Urol Nefrol*. 1991;43(3):165–9.
299. Costello JF, Sadovnic MC, Smith M, Stolarski C. Effect of vitamin B6 supplementation on plasma oxalate and oxalate removal rate in hemodialysis patients. *J Am Soc Nephrol*. 1992;3(4):1018–24.
300. Yamauchi T, Quillard M, Takahashi S, Nguyen-Khoa M. Oxalate removal by daily dialysis in a patient with primary hyperoxaluria type 1. *Nephrol Dial Transplant*. 2001;16(12):2407–11.
301. Franssen CF. Oxalate clearance by haemodialysis—a comparison of seven dialysers. *Nephrol Dial Transplant*. 2005;20(9):1916–21.
302. Illies F, Bonzel KE, Wingen AM, Latta K, Hoyer PF. Clearance and removal of oxalate in children on intensified dialysis for primary hyperoxaluria type 1. *Kidney Int*. 2006;70(9):1642–8.
303. Mydlik M, Derzsiova K. Oxalic acid as a uremic toxin. *J Ren Nutr*. 2008;18(1):33–9.
304. Tang X, Voskoboev NV, Wannarka SL, Olson JB, Milliner DS, Lieske JC. Oxalate quantification in hemodialysate to assess dialysis adequacy for primary hyperoxaluria. *Am J Nephrol*. 2014;39(5):376–82.
305. Ermer T, Kopp C, Asplin JR, Granja I, Perazella MA, Reichel M, Nolin TD, Eckardt KU, Aronson PS, Finkelstein FO, et al. Impact of regular or extended hemodialysis and hemodiafiltration on plasma oxalate concentrations in patients with end-stage renal disease. *Kidney Int Rep*. 2017;2(6):1050–8.
306. D'Costa MR, Winkler NS, Milliner DS, Norby SM, Hickson LJ, Lieske JC. Oxalosis associated with high-dose vitamin C ingestion in a peritoneal dialysis patient. *Am J Kidney Dis*. 2019;74(3):417–20.
307. Dickerman JD, Bishop W, Marks JF. Acute ethanol intoxication in a child. *Pediatrics*. 1968;42(5):837–40.
308. Elliott RW, Hunter PR. Acute ethanol poisoning treated by haemodialysis. *Postgrad Med J*. 1974;50(586):515–7.
309. Hartleib H, Stolpe HJ. Ethanol poisoning in childhood. *Z Arztl Fortbild (Jena)*. 1986;80(12):499–501.
310. Durakovic Z, Gasparovic V, Bosnic D, Plavsic F. Ethanol poisoning treated with hemodialysis. *Arh Hig Rada Toksikol*. 1988;39(1):47–50.
311. Woelfel D, Zellinger G, Wendt-Goeknur MA. The value of peritoneal dialysis in the treatment of severe ethanol intoxication in childhood revised. *Acta Paediatr*. 1992;81(3):280–2.
312. Marcovigi P, Gudenzi P, Granata A, Leoni S, Urbini S, Scaioni S. Severe ethanol poisoning. Management by hemodiafiltration. Clinical case. *Gazzetta Medica Italiana Archivio per le Scienze Mediche* 1994;153(1):39–40.
313. Morgan DL, Durso MH, Rich BK, Kurt TL. Severe ethanol intoxication in an adolescent. *Am J Emerg Med*. 1995;13(4):416–8.
314. Jones AW, Hahn RG. Pharmacokinetics of ethanol in patients with renal failure before and after hemodialysis. *Forensic Sci Int*. 1997;90(3):175–83.
315. Atassi WA, Noghnogh AA, Hariman R, Jayanthi S, Cheung SF, Kjellstrand CM, Ing TS. Hemodialysis as a treatment of severe ethanol poisoning. *Int J Artif Organs*. 1999;22(1):18–20.
316. Quispe Gonzales JO, Gomez Giralda B, Ruiz-Zorrilla Lopez C, Acosta Ochoa MI, Ampuero Anachuri K, Molina Miguel A. Severe ethanol poisoning treated by haemodialysis. *Nefrologia*. 2011;31(2):226–7.
317. Driscoll D, Bleecker G, Francis J, Jaber A. Acute hemodialysis for treatment of severe ethanol intoxication. *Kidney Med* 2020.
318. Jacobsen D, Ostensen J, Bredesen L, Ullstein E, McMartin K. 4-Methylpyrazole (4-MP) is effectively removed by haemodialysis in the pig model. *Hum Exp Toxicol*. 1996;15(6):494–6.
319. McMartin KE, Brent J. Pharmacokinetics of fomepizole (4MP) in patients. *Clin Toxicol*. 1998;36(5):450–1.
320. Schier JG, Shapiro WB, Howland MA, Nelson LS, Hoffman RS. Fomepizole is not substantially eliminated by continuous arteriovenous hemodialysis (CAVHD). *Clin Toxicol*. 2003;41(5):664–5.
321. Mowry JB, McMartin KE, Wedin GP, Hornfeldt CS, Hardy AE. The effect of high flux hemodialysis on serum fomepizole concentrations. *Clin Toxicol*. 2005;43(6):774–5.
322. Hayoun MA, Filigenzi MS, Nguyen S, Chenoweth JA, Ford JB. Fomepizole levels in ethylene glycol poisoned pediatric twins treated with CRRT. *J Med Toxicol*. 2020;16(2):120.

323. Lao Y, Jacobsen D, McMartin K, Latimer B, Froyshov S, Hovda KE. New dosing regimen for fomepizole during CRRT: a case report. *Clin Toxicol.* 2020;58(4):323.
324. Kleiner MJ, Tate SS, Sullivan JF, Chami J. Vitamin B6 deficiency in maintenance dialysis patients: metabolic effects of repletion. *Am J Clin Nutr.* 1980;33(7):1612–9.
325. Ramirez G, Chen M, Boyce HW Jr, Fuller SM, Ganguly R, Brueggemeyer CD, Butcher DE. Longitudinal follow-up of chronic hemodialysis patients without vitamin supplementation. *Kidney Int.* 1986;30(1):99–106.
326. Descombes E, Hanck AB, Fellay G. Water soluble vitamins in chronic hemodialysis patients and need for supplementation. *Kidney Int.* 1993;43(6):1319–28.
327. Zempleni J, Kibbler W. The utilization of intravenously infused pyridoxine in humans. *Clin Chim Acta.* 1994;229:27–36.
328. Kasama R, Koch T, Canals-Navas C, Pitone JM. Vitamin B6 and hemodialysis: the impact of high-flux/high-efficiency dialysis and review of the literature. *Am J Kidney Dis.* 1996;27(5):680–6.
329. Mydlik M, Derzsiova K, Zemberova E. Metabolism of vitamin B6 and its requirement in chronic renal failure. *Kidney Int Suppl.* 1997;62:S56–59.
330. Mydlik M, Derzsiova K, Svac J, Dlhopolcek P, Zemberova E. Peritoneal clearance and peritoneal transfer of oxalic acid, vitamin C, and vitamin B6 during continuous ambulatory peritoneal dialysis. *Artif Organs.* 1998;22(9):784–8.
331. Descombes E, Boulat O, Perriard F, Fellay G. Water-soluble vitamin levels in patients undergoing high-flux hemodialysis and receiving long-term oral postdialysis vitamin supplementation. *Artif Organs.* 2000;24(10):773–8.
332. Frank T, Bitsch R, Maiwald J, Stein G. High thiamine diphosphate concentrations in erythrocytes can be achieved in dialysis patients by oral administration of benfotiamine. *Eur J Clin Pharmacol.* 2000;56(3):251–7.
333. Moriwaki K, Kanno Y, Nakamoto H, Okada H, Suzuki H. Vitamin B6 deficiency in elderly patients on chronic peritoneal dialysis. *Adv Perit Dial.* 2000;16:308–12.
334. Okada H, Moriwaki K, Kanno Y, Sugahara S, Nakamoto H, Yoshizawa M, Suzuki H. Vitamin B6 supplementation can improve peripheral polyneuropathy in patients with chronic renal failure on high-flux haemodialysis and human recombinant erythropoietin. *Nephrol Dial Transplant.* 2000;15(9):1410–3.
335. Hung SC, Hung SH, Tarrg DC, Yang WC, Chen TW, Huang TP. Thiamine deficiency and unexplained encephalopathy in hemodialysis and peritoneal dialysis patients. *Am J Kidney Dis.* 2001;38(5):941–7.
336. Heinz J, Kropf S, Luley C, Dierkes J. Homocysteine as a risk factor for cardiovascular disease in patients treated by dialysis: a meta-analysis. *Am J Kidney Dis.* 2009;54(3):478–89.
337. Bukhari FJ, Moradi H, Gollapudi P, Ju Kim H, Vaziri ND, Said HM. Effect of chronic kidney disease on the expression of thiamin and folic acid transporters. *Nephrol Dial Transplant.* 2011;26(7):2137–44.
338. Clase CM, Ki V, Holden RM. Water-soluble vitamins in people with low glomerular filtration rate or on dialysis: a review. *Semin Dial.* 2013;26(5):546–67.
339. Kosmadakis G, Da Costa CE, Carceles O, Somba F, Aguilera D. Vitamins in dialysis: Who, when and how much? *Ren Fail.* 2014;36(4):638–50.
340. Jankowska M, Rudnicki-Velasquez P, Storoniak H, Rutkowski P, Rutkowski B, Krzymiński K, Dębska-Ślizień A. Thiamine diphosphate status and dialysis-related losses in end-stage kidney disease patients treated with hemodialysis. *Blood Purif.* 2017;44:294–300.
341. Harshman LA, Lee-Son K, Jetton JG. Vitamin and trace element deficiencies in the pediatric dialysis patient. *Pediatr Nephrol.* 2018;33(7):1133–43.
342. Jacobsen D, Bredesen JE, Eide I, Ostborg J. Anion and osmolal gaps in the diagnosis of methanol and ethylene glycol poisoning. *Acta Med Scand.* 1982;212(1–2):17–20.
343. Ghannoum M, Hoffman RS, Gosselin S, Nolin TD, Lavergne V, Roberts DM. Use of extracorporeal treatments in the management of poisonings. *Kidney Int.* 2018;94(4):682–8.
344. Fraser AD, MacNeil W. Colorimetric and gas chromatographic procedures for glycolic acid in serum: the major toxic metabolite of ethylene glycol. *J Toxicol Clin Toxicol.* 1993;31(3):397–405.
345. McMartin K, Brent J. Analysis of fomepizole elimination in methanol- and ethylene glycol-poisoned patients. *J Med Toxicol.* 2022;18(1):19–29.
346. Wildenauer R, Kobbe P, Waydhas C. Is the osmole gap a valuable indicator for the need of hemodialysis in severe ethanol intoxication? *Technol Health Care.* 2010;18(3):203–6.
347. Braden BR, Hurlbut KM, McMartin KE, Latimer B, Linas SL, Adebayo OO, Waldstein MM. Fomepizole clearance with continuous renal replacement therapy. *J Med Toxicol.* 2014;10(1):73–4.
348. Lao YE, Vartdal T, Froyshov S, Latimer B, Kvaerner C, Mataric M, Holm P, Foreid S, Jacobsen D, McMartin K et al. Fomepizole dosing during continuous renal replacement therapy—an observational study. *Clin Toxicol (Phila)* 2021;1–7.
349. Schweighauser A, Francey T. Ethylene glycol poisoning in three dogs: Importance of early diagnosis and role of hemodialysis as a treatment option. *Schweiz Arch Tierheilkd.* 2016;158(2):109–14.
350. Berstrand YM, Hermant A, Mahieu P, Roels J. Intracranial pressure changes in patients with head trauma during haemodialysis. *Intensive Care Med.* 1983;9(6):321–3.
351. Krane NK. Intracranial pressure measurement in a patient undergoing hemodialysis and peritoneal dialysis. *Am J Kidney Dis.* 1989;13(4):336–9.
352. Lin CM, Lin JW, Tsai JT, Ko CP, Hung KS, Hung CC, Su YK, Wei L, Chiu WT, Lee LM. Intracranial pressure fluctuation during hemodialysis in renal failure patients with intracranial hemorrhage. *Acta Neurochir Suppl.* 2008;101:141–4.
353. Lepik KJ, Pursell RA, Levy AR, Daws DE. Adverse reactions to hemodialysis in 72 cases of toxic alcohol poisoning. *Clin Toxicol* 2005;43(6):676.
354. Caparros-Lefebvre D, Pollicard J, Sengler C, Benabdallah E, Colombani S, Rigal M. Bipallidal haemorrhage after ethylene glycol intoxication. *Neuroradiology.* 2005;47(2):105–7.
355. Boyer EW, Mejia M, Woolf A, Shannon M. Severe ethylene glycol ingestion treated without hemodialysis. *Pediatrics.* 2001;107(1):172–3.
356. Luft FC. An acid-base conundrum for a rainy afternoon. *Nephrol Dial Transplant.* 1996;11(8):1653–5.
357. Nagesh IV, Koley KC, Sen S, Mohan S, Sahu S. Ethylene glycol poisoning. *Med J Armed Forces India.* 2015;71(Suppl 1):S36–38.
358. Beaulieu J, Roberts DM, Gosselin S, Hoffman RS, Lavergne V, Hovda KE, Megarbane B, Lung D, Thanacoody R, Ghannoum M. Treating ethylene glycol poisoning with alcohol dehydrogenase inhibition, but without extracorporeal treatments: a systematic review. *Clin Toxicol (Phila)* 2022:1–14.
359. Etchepare YM, Nauche P, Remize J, Sourzat C, Guindre O, Mage E. Mass acute ethylene glycol intoxication. *Urgences Medicales.* 1997;16(3):117–9.
360. Reess K, Chiang WK. Availability of serum methanol and ethylene glycol: a national survey. *Clin Toxicol.* 1997;35(5):509.
361. Cassidy N, Herbert JX, Tracey JA. The availability of toxicological analyses relating to the management of the poisoned patient in Ireland. *Clin Toxicol.* 2010;48(3):250.
362. Jacobsen D, McMartin KE. Methanol and ethylene glycol poisonings. Mechanism of toxicity, clinical course, diagnosis and treatment. *Med Toxicol* 1986;1(5):309–334.
363. Orozco BS, Engebretsen KM, Stellpflug SJ, Ellsworth H. Correlation of osmolal gap and ethylene glycol concentration during dialysis. *Clin Toxicol.* 2012;50:700–1.
364. Greene HR, Krasowski MD. Correlation of osmolal gap with measured concentrations of acetone, ethylene glycol, isopropanol, methanol, and propylene glycol in patients at an academic medical center. *Toxicol Rep.* 2020;7:81–8.
365. Cohen ET, Su MK, Biary R, Hoffman RS. Distinguishing between toxic alcohol ingestion vs alcoholic ketoacidosis: How can we tell the difference? *Clin Toxicol (Phila)* 2021:1–9.
366. Krasowski MD, Wilcoxon RM, Miron J. A retrospective analysis of glycol and toxic alcohol ingestion: utility of anion and osmolal gaps. *BMC Clin Pathol.* 2012;12:1.
367. De Leacy EA, Moxon LN, Ellis VM, Van Dongen JM, Johnson LP, Doddrell DM, Cowley DM. A report of accidental ethylene glycol ingestion in 2 siblings. *Pathology.* 1995;27(3):273–6.
368. Lepeyre F, Ghannoum M, Ammann H, Madore F, Troyanov S, Goupil R, Bouchard J. Formulas for calculated osmolality and osmolal gap: a study of diagnostic accuracy. *Am J Kidney Dis.* 2017;70(3):347–56.



369. Aabakken L, Johansen KS, Rydningen EB, Bredesen JE, Ovrebø S, Jacobsen D. Osmolal and anion gaps in patients admitted to an emergency medical department. *Hum Exp Toxicol*. 1994;13(2):131–4.
370. Glaser DS. Utility of the serum osmolal gap in the diagnosis of methanol or ethylene glycol ingestion. *Ann Emerg Med*. 1996;27(3):343–6.
371. Pursell RA, Lynd LD, Koga Y. The use of the osmole gap as a screening test for the presence of exogenous substances. *Toxicol Rev*. 2004;23(3):189–202.
372. Lynd LD, Richardson KJ, Pursell RA, Abu-Laban RB, Brubacher JR, Lepik KJ, Sivilotti ML. An evaluation of the osmole gap as a screening test for toxic alcohol poisoning. *BMC Emerg Med*. 2008;8:5.
373. Waring WS, Ho C, Warner M. Significance of the osmolal gap in suspected ethylene glycol poisoning. *Clin Toxicol*. 2010;48(3):250.
374. Edelman IS, Leibman J, O'Meara MP, Birkenfeld LW. Interrelations between serum sodium concentration, serum osmolality and total exchangeable sodium, total exchangeable potassium and total body water. *J Clin Invest*. 1958;37(9):1236–56.
375. Hoffman RS, Smilkstein MJ, Howland MA, Goldfrank LR. Osmolal gaps revisited: normal values and limitations. *J Toxicol Clin Toxicol*. 1993;31(1):81–93.
376. Hložek T, Bursova M, Cabala R. Fast determination of ethylene glycol, 1,2-propylene glycol and glycolic acid in blood serum and urine for emergency and clinical toxicology by GC-FID. *Talanta*. 2014;130:470–4.
377. Soghoian S, Sinert R, Wiener SW, Hoffman RS. Ethylene glycol toxicity presenting with non-anion gap metabolic acidosis. *Basic Clin Pharmacol Toxicol*. 2009;104(1):22–6.
378. Heckerling PS. Ethylene glycol poisoning with a normal anion gap due to occult bromide intoxication. *Ann Emerg Med*. 1987;16(12):1384–6.
379. Leon M, Graeber C. Absence of high anion gap metabolic acidosis in severe ethylene glycol poisoning: a potential effect of simultaneous lithium carbonate ingestion. *Am J Kidney Dis*. 1994;23(2):313–6.
380. Chaudhry SD, Pandurangan M, Pinnell AE. Lactate gap and ethylene glycol poisoning. *Eur J Anaesthesiol*. 2008;25(6):511–3.
381. Cornes MP, Ford C, Gama R. The lactate gap revisited: variable interference with lactate analyses in ethylene glycol poisoning. *Br J Biomed Sci*. 2010;67(3):148–50.
382. 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):174–6.
383. Morgan TJ, Clark C, Clague A. Artifactual elevation of measured plasma L-lactate concentration in the presence of glycolate. *Crit Care Med*. 1999;27(10):2177–9.
384. Meng QH, Adeli K, Zello GA, Porter WH, Krahn J. Elevated lactate in ethylene glycol poisoning: True or false? *Clin Chim Acta*. 2010;411(7–8):601–4.
385. Moestue S, Akervik O, Svendsen J, Jacobsen D. Fomepizole treatment prevents renal failure in severe ethylene glycol poisoning: report of two cases. *Clin Toxicol*. 2002;40:269.
386. Antizol [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/020696s006lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020696s006lbl.pdf)
387. Harbon SCD, Thompson J. Successful use of fomepizole during second trimester of pregnancy. *Clin Toxicol*. 2014;52:314–5.
388. Piggott Z, Guinn A, Tenenbein M, Palatnick W. Recurrent inhalational methanol toxicity during pregnancy. *Clin Toxicol*. 2015;53(7):664.
389. Bouchard J, Lavergne V, Roberts DM, Cormier M, Morissette G, Ghannoum M. Availability and cost of extracorporeal treatments for poisonings and other emergency indications: a worldwide survey. *Nephrol Dial Transplant*. 2017;32(4):699–706.
390. Zakharov S, Pelclova D, Navratil T, Belacek J, Latta J, Pisar M, Rulisek J, Leps J, Zidek P, Kucera C, et al. Efficiency of acidemia correction on intermittent versus continuous hemodialysis in acute methanol poisoning. *Clin Toxicol*. 2017;55(2):123–32.
391. Rulisek J, Balik M, Polak F, Waldauf P, Pelclova D, Belohlavek J, Zakharov S. Cost-effectiveness of hospital treatment and outcomes of acute methanol poisoning during the Czech Republic mass poisoning outbreak. *J Crit Care*. 2017;39:190–8.
392. Lund A, Damholt MB, Wiis J, Kelsen J, Strange DG, Moller K. Intracranial pressure during hemodialysis in patients with acute brain injury. *Acta Anaesthesiol Scand*. 2019;63(4):493–9.
393. Walker JT, Keller MS, Katz SM. Computed tomographic and sonographic findings in acute ethylene glycol poisoning. *J Ultrasound Med*. 1983;2(9):429–31.
394. Roberts DM, Lea-Henry TN. Simplifying the hemodialysis prescription in patients with ethylene glycol poisoning. *Kidney Int*. 2017;92(2):291–3.
395. Walsh S, Abesamis M, Lynch M, Pizon AF. Severe ethylene glycol toxicity treated with single-dose fomepizole and hemodialysis. *Clin Toxicol*. 2011;49:539.
396. Summons G, Odedra P, Singer M. A case of raised anion gap metabolic acidosis: confirmed ethylene glycol poisoning with successful organ donation. *J Intensive Care Soc* 2018;19 (2 Supplement 1):49–50.
397. Corr P, Szolics M. Neuroimaging findings in acute ethylene glycol poisoning. *J Med Imaging Radiat Oncol*. 2012;56(4):442–4.
398. Wu AH, McKay C, Broussard LA, Hoffman RS, Kwong TC, Moyer TP, Otten EM, Welch SL, Wax P. National Academy of Clinical Biochemistry Laboratory M: 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):357–79.
399. Francis A, Taub ES, Howland MA, Su MK, Hoffman RS, Biary R. Diagnosing toxic alcohol poisoning: the cost of using the right tool for the job. *Clin Toxicol*. 2019;57(10):947.
400. Quinn N, Dulaney A, Beuhler M. The cost of toxic alcohol levels. *J Med Toxicol*. 2019;15(2):85.
401. Messiah JSNA, Hussein R, Mogri M, Thakur L. Unique survival story of hyperosmolar coma due to huge co-ingestion of ethylene glycol and ethanol. *Crit Care Med* 2016;44 (12 Supplement 1):564.
402. Frantz SW, Beskitt JL, Grosse CM, Tallant MJ, Dietz FK, Ballantyne B. Pharmacokinetics of ethylene glycol. I. Plasma disposition after single intravenous, peroral, or percutaneous doses in female Sprague-Dawley rats and CD-1 mice. *Drug Metab Dispos* 1996;24(8):911–921.
403. Corley RA, Bartels MJ, Carney EW, Weitz KK, Soelberg JJ, Gies RA, Thrall KD. Development of a physiologically based pharmacokinetic model for ethylene glycol and its metabolite, glycolic acid, in rats and humans. *Toxicol Sci*. 2005;85(1):476–90.
404. Harry P, Turcant A, Bouachour G, Houze P, Alquier P, Allain P. Efficacy of 4-methylpyrazole in ethylene glycol poisoning: clinical and toxicokinetic aspects. *Hum Exp Toxicol*. 1994;13(1):61–4.
405. Carstens J, Csanady GA, Faller TH, Filser JG. Human inhalation exposure to ethylene glycol. *Arch Toxicol*. 2003;77(8):425–32.
406. Upadhyay S, Carstens J, Klein D, Faller TH, Halbach S, Kirchinger W, Kessler W, Csanady GA, Filser JG. Inhalation and epidermal exposure of volunteers to ethylene glycol: kinetics of absorption, urinary excretion, and metabolism to glycolate and oxalate. *Toxicol Lett*. 2008;178(2):131–41.
407. Arens AM, Gunsolus IL, Bartos E, Galliani C, Hillyer M, Hudson M, Kaczmarczyk C, Kloss J, Ulici A, Willhite LA, et al. Ethylene glycol elimination kinetics in an infant. *Clin Chem*. 2018;64(Supplement 1):S268–9.
408. Harry P, Jobard E, Briand M, Caubet A, Turcant A. Ethylene glycol poisoning in a child treated with 4-methylpyrazole. *Pediatrics*. 1998;102(3):E31.
409. Theurl A, Battista HJ, Fritzer W. Accidental glycol poisoning. *Wien Med Wochenschr*. 1989;139(17):390–5.
410. Stivrius TJ, Moore GF. Ethylene glycol ingestion in a retarded young adult—a case report. *Nebr Med J*. 1982;67(7):181–3.
411. Buchanan JA, Alhelail M, Cetaruk EW, Schaeffer TH, Palmer RB, Kulig K, Brent J. Massive ethylene glycol ingestion treated with fomepizole alone—a viable therapeutic option. *J Med Toxicol*. 2010;6(2):131–4.
412. Baud FJ, Bismuth C, Garnier R, Galliot M, Astier A, Maistre G, Soffer M. 4-Methylpyrazole may be an alternative to ethanol therapy for ethylene glycol intoxication in man. *J Toxicol Clin Toxicol*. 1986;24(6):463–83.
413. Hantson P, Hassoun A, Mahieu P. Ethylene glycol poisoning treated by intravenous 4-methylpyrazole. *Intensive Care Med*. 1998;24(7):736–9.
414. Baud FJ, Galliot M, Astier A, Bien DV, Garnier R, Likforman J, Bismuth C. Treatment of ethylene glycol poisoning with intravenous 4-methylpyrazole. *N Engl J Med*. 1988;319(2):97–100.
415. Demaille T, Wallemacq P, Clement de Cleyt S, Vanbinst R, Dembour G, Hantson P. Fomepizole alone for severe infant ethylene glycol poisoning. *Pediatr Crit Care Med*. 2004;5(5):490–1.
416. Velez LI, Shepherd G, Lee YC, Keyes DC. Ethylene glycol ingestion treated only with fomepizole. *J Med Toxicol*. 2007;3(3):125–8.

417. Levine M, Curry SC, Ruha AM, Pizon AF, Boyer E, Burns J, Bikin D, Gerkin RD. Ethylene glycol elimination kinetics and outcomes in patients managed without hemodialysis. *Ann Emerg Med*. 2012;59(6):527–31.
418. Bacis G, Cantu S, Rocchi L, Feruzzi M. Ethylene glycol poisoning in a child: efficacy and safety of fomepizole treatment. *Clin Toxicol*. 2003;41(4):478–9.
419. Caravati EM, Heileson HL, Jones M. Treatment of severe pediatric ethylene glycol intoxication without hemodialysis. *J Toxicol Clin Toxicol*. 2004;42(3):255–9.
420. Haggerty DA, Curtis J. Prolonged elimination of ethylene glycol in a patient receiving fomepizole with normal renal function. *Clin Toxicol*. 2010;48(6):620.
421. Spivak LA, Horowitz BZ. Treatment of severe ethylene glycol poisoning without hemodialysis. *Clin Toxicol*. 2005;43(6):691.
422. Holland MG, Stork CM, Hodgman MJ, Rosano T, Marraffa JM. Elevated glycolate levels after unintentional pediatric ethylene glycol ingestion. *Clin Toxicol*. 2009;47(7):737–8.
423. Sivilotti M, Burns M, McMartin KE, Brent J. Pharmacokinetics of ethylene glycol and methanol during fomepizole therapy: results of the meta trial. *Clin Toxicol*. 1998;36(5):451.
424. Marangella M, Petrarulo M, Vitale C, Cosseddu D, Linari F. Plasma and urine glycolate assays for differentiating the hyperoxaluria syndromes. *J Urol*. 1992;148(3 Pt 2):986–9.
425. Knight J, Jiang J, Assimos DG, Holmes RP. Hydroxyproline ingestion and urinary oxalate and glycolate excretion. *Kidney Int*. 2006;70(11):1929–34.
426. Jacobsen D, Frederichsen PS, Knutsen KM. Clinical course in acute self-poisonings: a prospective study of 1125 consecutively hospitalised adults. *Hum Toxicol*. 1984;3(2):107–16.
427. Darracq MA, Cantrell FL. Hemodialysis and extracorporeal removal after pediatric and adolescent poisoning reported to a state poison center. *J Emerg Med*. 2013;44(6):1101–7.
428. Keeling T, Orozco B, Cole J, Nystrom P, Jouhari MT. Anaphylaxis following fomepizole for ethylene glycol poisoning. *Clin Toxicol*. 2014;52(7):751–2.
429. Thanacoody HKR, Weatherall I, Davies J, Thomas S. Treatment of severe toxic alcohol and glycol poisoning in the UK. *Clin Toxicol*. 2012;50:581.
430. Rasamison R, Besson H, Berleur MP, Schicchi A, Megarbane B. Analysis of fomepizole safety based on a 16-year post-marketing experience in France. *Clin Toxicol (Phila)*. 2020;58(7):742–7.
431. Lepik KJ, Levy AR, Sobolev BG, Pursell RA, DeWitt CR, Erhardt GD, Kennedy JR, Daws DE, Brignall JL. Adverse drug events associated with the antidotes for methanol and ethylene glycol poisoning: a comparison of ethanol and fomepizole. *Ann Emerg Med* 2009;53(4):439–450 e410.
432. Lepik KJ, Sobolev BG, Levy AR, Pursell RA, Dewitt CR, Erhardt GD, Baker JL, Kennedy JR, Daws DE. Medication errors associated with the use of ethanol and fomepizole as antidotes for methanol and ethylene glycol poisoning. *Clin Toxicol (Phila)*. 2011;49(5):391–401.
433. Roy M, Bailey B, Chalut D, Senecal PE, Gaudreault P. What are the adverse effects of ethanol used as an antidote in the treatment of suspected methanol poisoning in children? *J Toxicol Clin Toxicol*. 2003;41(2):155–61.
434. Brass P, Hellmich M, Kolodziej L, Schick G, Smith AF. Ultrasound guidance versus anatomical landmarks for subclavian or femoral vein catheterization. *Cochrane Database Syst Rev* 2015;1:CD011447.
435. Brass P, Hellmich M, Kolodziej L, Schick G, Smith AF. Ultrasound guidance versus anatomical landmarks for internal jugular vein catheterization. *Cochrane Database Syst Rev* 2015;1:CD006962.
436. Parienti JJ, Mongardon N, Megarbane B, Mira JP, Kalfon P, Gros A, Marque S, Thuong M, Pottier V, Ramakers M, et al. Intravascular complications of central venous catheterization by insertion site. *N Engl J Med*. 2015;373(13):1220–9.
437. Shin HJ, Na HS, Koh WU, Ro YJ, Lee JM, Choi YJ, Park S, Kim JH. Complications in internal jugular vs subclavian ultrasound-guided central venous catheterization: a comparative randomized trial. *Intensive Care Med*. 2019;45(7):968–76.
438. Bjorkander M, Bentzer P, Schott U, Broman ME, Kander T. Mechanical complications of central venous catheter insertions: a retrospective multicenter study of incidence and risks. *Acta Anaesthesiol Scand*. 2019;63(1):61–8.
439. Wong B, Zimmerman D, Reintjes F, Courtney M, Klarenbach S, Dowling G, Pauly RP. Procedure-related serious adverse events among home hemodialysis patients: a quality assurance perspective. *Am J Kidney Dis*. 2014;63(2):251–8.
440. Tennankore KK, d’Gama C, Faratro R, Fung S, Wong E, Chan CT. Adverse technical events in home hemodialysis. *Am J Kidney Dis*. 2015;65(1):116–21.
441. Yang X, Xin S, Zhang Y, Li T. Early hemoperfusion for emergency treatment of carbamazepine poisoning. *Am J Emerg Med*. 2018;36(6):926–30.
442. Shannon MW. Comparative efficacy of hemodialysis and hemoperfusion in severe theophylline intoxication. *Acad Emerg Med*. 1997;4(7):674–8.

## Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more [biomedcentral.com/submissions](https://biomedcentral.com/submissions)

