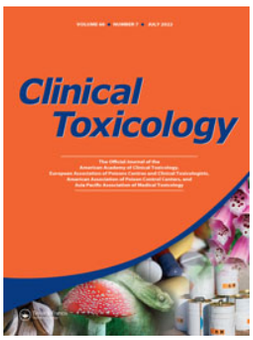

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REVIEW

Treating ethylene glycol poisoning with alcohol dehydrogenase inhibition, but without extracorporeal treatments: a systematic review

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ABSTRACT

Context: Ethylene glycol is metabolized to toxic metabolites that cause acute kidney injury, metabolic acidemia, and death. The treatment of patients with ethylene glycol poisoning includes competitively inhibiting alcohol dehydrogenase with ethanol or fomepizole to prevent the formation of toxic metabolites, and extracorporeal treatments such as hemodialysis to remove ethylene glycol and its metabolites. In the absence of significant metabolic acidemia or kidney injury, it is hypothesized that extracorporeal treatments may be obviated without adverse outcomes to the patient if alcohol dehydrogenase inhibitors are used.

Objectives: The objectives of this study are to: (1) identify indicators predicting ADH inhibitor failure in patients with ethylene glycol poisoning treated with either ethanol or fomepizole for whom extracorporeal treatment was not performed (aside from rescue therapy, see below) (*prognostic study*), and (2) validate if the anion gap, shown in a previous study to be the best surrogate for the glycolate concentration, is associated with acute kidney injury and mortality (*anion gap study*).

Methods: We conducted a systematic review to identify all reported patients with ethylene glycol poisoning treated without extracorporeal treatments but with either fomepizole (*fomepizole monotherapy*) or ethanol (*ethanol monotherapy*). Analyses were performed using both one case per patient and all cases (if multiple events were reported for a single patient). Data were compiled regarding poisoning, biochemistry, and outcomes. Treatment failure was defined as mortality, worsening of acid-base status, extracorporeal treatments used as rescue, or a worsening of kidney or neurological function after alcohol dehydrogenase inhibition was initiated. Also, we performed an analysis of previously described anion gap thresholds to determine if they were associated with outcomes such as acute kidney injury and mortality.

Results: Of 115 publications identified, 96 contained case-level data. A total of 180 cases were identified with ethanol monotherapy, and 231 with fomepizole monotherapy. Therapy failure was noted mostly when marked acidemia and/or acute kidney injury were present prior to therapy, although there were cases of failed ethanol monotherapy with minimal acidemia (suggesting that ethanol dosing and/or monitoring may not have been optimal). Ethylene glycol dose and ethylene glycol concentration were predictive of monotherapy failure for ethanol, but not for fomepizole. In the anion gap study (207 cases), death and progression of acute kidney injury were almost nonexistent when the anion gap was less than 24 mmol/L and mostly observed when the anion gap was greater than 28 mmol/L.

Conclusion: This review suggests that in patients with minimal metabolic acidemia (anion gap $<$28 mmol/L), fomepizole monotherapy without extracorporeal treatments is safe and effective regardless of the ethylene glycol concentration. Treatment failures were observed with ethanol monotherapy which may relate to transient subtherapeutic ethanol concentrations or very high ethylene glycol concentrations. The results are limited by the retrospective nature of the case reports and series reviewed in this study and require prospective validation.

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Introduction

Ethylene glycol is commonly used in many antifreeze products and each year is responsible for thousands of toxic exposures worldwide from intentional self-harm and other reasons [1,2,3]. Ethylene glycol itself causes little toxicity; however, its metabolites (glycolate, glyoxylate and oxalate) induce a wide anion gap metabolic acidemia and end-organ toxicity such as acute kidney injury (AKI), coma, seizures, cranial nerve defects, and death. In fact, ethylene glycol is the leading poisoning for which extracorporeal treatments are used in several countries [4].

In addition to supportive care, the mainstay of treatment for patients with ethylene glycol poisoning includes two other aspects: (1) competitive inhibition of alcohol dehydrogenase (ADH) with either ethanol or fomepizole, to prevent the production of toxic metabolites, and (2) extracorporeal treatments, such as hemodialysis and continuous kidney replacement therapy, to remove both ethylene glycol and its toxic metabolites.

Ethanol has an affinity approximately 100 times greater for ADH than ethylene glycol and was first used in humans in 1965 [5]. In fact, patients who co-ingest ethanol with ethylene glycol also generally experience less severe toxicity [6]. Fomepizole has a greater affinity for ADH than ethanol [7,8] and was first used in humans for ethylene glycol poisoning in 1986 [9,10]. Because of its simpler dosage, lack of CNS effects, cultural concerns for ethanol use, and non-requirement of a high-dependency unit or frequent blood tests, fomepizole has largely replaced ethanol in many regions, except where it is cost-prohibitive [11].

Hemodialysis is usually recommended in the presence of severe metabolic acidemia, kidney impairment, severe electrolyte imbalance, or deteriorating clinical conditions despite supportive measures [12,13]. If these are absent, proposed indications for hemodialysis in ethanol-treated patients include a serum ethylene glycol concentration greater than 8 mmol/L (50 mg/dL), while some authors have suggested that hemodialysis may be obviated if fomepizole is used [12,14,15]. However, there are no prospective trials to support this approach and, to our knowledge, a comprehensive review of data supporting the withholding of extracorporeal treatments under certain clinical circumstances has not been reported.

A prior review identified the prognostic value of the glycolate concentration, demonstrating that mortality was unlikely when the glycolate concentration was less than 8.3 mmol/L (negative predictive value = 100%) whereas a glycolate concentration exceeding 12.9 mmol/L predicted AKI (positive predictive value = 86%) [16]. Additionally, the anion gap was found to be the best surrogate marker for the glycolate concentration. However, extracorporeal treatment was used in 80% of cases from which these data were derived [16].

Objectives

The objectives of this study are to: (1) identify indicators predicting ADH inhibitor failure in patients with ethylene glycol poisoning treated with either ethanol or fomepizole for whom extracorporeal treatment was not performed (aside from rescue therapy, see below) (*prognostic study*), and (2) validate if the anion gap, shown in a previous study to be the best surrogate for the glycolate concentration [16], is associated with AKI and mortality (*anion gap study*).

Methods

Eligibility criteria

Types of studies

All study types that reported human ethylene glycol poisoning were considered eligible, including interventional trials, comparative studies, observational cohorts, and case reports. Reviews, editorials, book chapters, and commentaries were excluded if they contained no original data. *In vitro* and animal experiments were also excluded. Reference lists of all included and excluded articles were searched for other eligible publications. Only articles containing original case-level data were included. Cohorts without case-level data were presented in descriptive format only. For all cohorts and case series containing more than 8 patients, the authors were contacted for additional data.

Types of participants

Subjects of all ages and comorbidities with a diagnosis of ethylene glycol poisoning, confirmed from history or detectable ethylene glycol in blood, treated with ethanol and/or fomepizole without extracorporeal treatment initially were included. All types of exposures (acute, staggered, chronic) and all routes of exposure (ingestion, injection, inhalation) were eligible for inclusion. Multiple temporally separate cases in the same patient were considered as distinct cases due to variation in the amount taken, time to presentation, and treatment given. Cases were also evaluated by type of ADH inhibitor (i.e., ethanol or fomepizole) received.

Variable of interest

For the prognostic study, the following variables were analyzed to determine their influence on outcomes: dose (expressed as 100% ethylene glycol solution equivalent), time from exposure to health care presentation, ethanol co-ingestion, time from presentation to antidote administration, initial ethylene glycol concentration, kidney function, as well as acid-base parameters determined at the time ADH inhibition was initiated (anion gap, pH, bicarbonate concentration (HCO_3^-), base excess, glycolate concentration). For the anion gap study, the anion gap prior to the administration of ethanol or fomepizole was analyzed.

Outcomes

The outcome of interest in the prognostic portion of the analysis was "ADH inhibitor treatment failure". This was arbitrarily defined prior to data analysis as any of the following criteria ***after*** *the ADH inhibitor was started*:

1. Increase in anion gap greater than 5 mmol/L;
2. Decrease in HCO_3^- greater than 5 mmol/L or decrease in base excess by more than 5 mmol/L, or corresponding decrease in pH;
3. Increase in serum creatinine concentration greater than 1.0 mg/dL (88 μmol/L) or reported new onset oliguria;
4. Extracorporeal treatments performed as rescue treatment (e.g., for worsening of acidemia, AKI, complications of ADH inhibition);
5. All-cause inpatient mortality;
6. New onset or worsening of neurological symptoms attributed to ethylene glycol (seizures, altered consciousness, cranial nerve palsy).

For the anion gap study, the outcomes of interest were all-cause inpatient mortality and/or KDIGO (Kidney Disease Improving Global Outcomes) stage 2 or 3 AKI, i.e., serum creatinine concentration at least 2.0 times the baseline or reference value adjusted for age and gender. If the creatinine concentration was not reported, the presence of "anuria" or "AKI" or "acute renal failure" was accepted as indicators of significant AKI.

Case-level exclusion

Cases were excluded when any of the following were met:

1. They involved co-exposure with other toxic alcohols (methanol, diethylene glycol or propylene glycol) [17,18];
2. Ethylene glycol exposure could not be confirmed either by history or specific assay [19];
3. It was unclear if and when extracorporeal treatment was performed relative to ADH inhibition [20,21,22];
4. No ADH inhibitor was administered, isopropanol was administered, or it was unclear which ADH inhibitor was given [23,24,25,26,27];
5. The ethylene glycol concentration was undetectable, as there is no rationale for ADH inhibition in this context [28,29];
6. No outcomes of interest were presented [30,31,32,33,34,35,36,37];
7. Both ethanol and fomepizole were given as antidotes [38,39,40].

Search strategy

The following databases were searched from their inception: Medline/PubMed, EMBASE, and Cochrane library (Review and Central). Conference proceedings/meeting abstracts of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) and North American Congress of Clinical Toxicology (NACCT) annual scientific meetings were manually searched, each from 2002 to 2020.

The following search strategy was developed for Pubmed/MEDLINE and translated for the other databases:

1. (ethylene glycol*).af;
2. (monoethylene glycol*).af;
3. 1 or 2;
4. ethyl alcohol.af;
5. ethanol.af;
6. fomepizole.af;
7. antizol.af;
8. (methyl-pyrazole or methylpyrazole).af;
9. 4-MP;
10. or/4–9;
11. 3 and 10.

The search was performed on February 24th, 2021. To supplement the electronic searches, reviewers also manually searched reference lists of editorials, review articles, or similar literature for relevant research articles. No exclusions were made based on language or year of publication. Foreign language publications were all translated by native language speakers or professional translation services.

Study records

Selection process

Two reviewers (JB and MG) screened citations independently to determine eligibility for full-text assessment and subsequently screened the articles of the full text to select those meeting the inclusion criteria. Disagreement was resolved by consensus.

Data management and extraction

A standardized data extraction form was created and populated with data pertinent to the systematic review (Microsoft Excel). MG is responsible for the master copy. Two authors (JB, MG) extracted the data into Microsoft Excel software (version 2021); a methodologist (VL) reviewed all versions. Inconsistencies were resolved by consensus and data consolidated in one master flowsheet. The following data were extracted: baseline characteristics (age, gender), exposure (dose, route of exposure, percent ethylene glycol solution, time to presentation to a health care facility, ethanol co-ingestion, ethylene glycol concentration), clinical manifestations (altered mental status, seizures, hypotension, respiratory failure), laboratory values at the time ADH blockade was initiated and the worst value during hospitalization (pH, glycolate concentration, HCO_3^-, base excess, anion gap, creatinine concentration), treatment (ethanol, fomepizole, extracorporeal treatments, and their timing with relation to arrival at the healthcare facility), and clinical outcomes (death, AKI, seizures, altered mental status, or cranial nerve defect). The anion gap included in analyses was that incorporating potassium, i.e., $(Na^+ + K^+) - (Cl^- + HCO_3^-)$; if the anion gap was reported without potassium, 4 mmol/L (mid-range normal potassium concentration) was added to the reported number. If the method for calculating the anion gap was unknown, then 2 mmol/L was added to the reported anion gap. When parameters were described as "normal", values were reported as age-expected creatinine concentration, HCO_3^- = 25 mmol/L, anion gap = 14 mmol/L, base excess = 0 mmol/L, and pH = 7.40. Fomepizole or ethanol

monotherapy is defined as their use in addition to standard care which includes intravenous bicarbonate but excluded extracorporeal treatments.

Anion gap study

As mentioned, the glycolate concentration thresholds predicting clinical outcomes were found to be <8.3 mmol/L for survival and >12.9 mmol/L for AKI [16]. The anion gap cut-offs correlating to these glycolate concentrations were conservatively estimated to be 24 mmol/L and 28 mmol/L, respectively [16].

All cases identified from the systematic review outlined above were also used for the anion gap study if the anion gap prior to ADH blockade was reported. Three cohorts were analyzed: anion gap <24 mmol/L, anion gap 24–28 mmol/L, anion gap >28 mmol/L. Outcomes of interest were the presence of KDIGO stage 2 or 3 AKI or all-cause inpatient mortality. Cases were excluded if they reported a glycolate concentration, as these cases were already used to derive glycolate concentration cut-offs for AKI and mortality in the prior analysis [16].

Quality assessment

The risk for bias of each included study was assessed using the Quality In Prognosis Studies (QUIPS) tool, as applicable [41]. The quality of reports was evaluated using the CARE (CAse REport) guideline, but a systematic approach to assessing the risk of bias for the reports could not be performed due to the lack of a validated tool for case reports. Important limitations are described in the discussion.

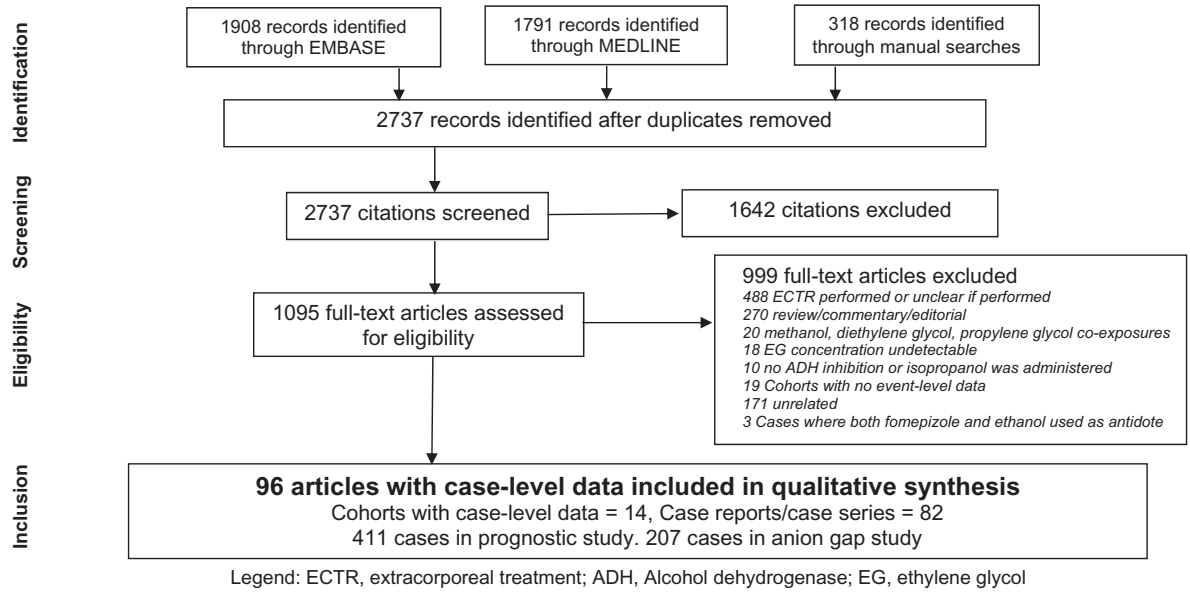
Data analysis and synthesis

Descriptive statistical analyses were conducted, in which nonparametric continuous data were expressed as median (interquartile range (IQR) and range), and the statistical difference was determined using the Mann-Whitney *U* test. A *p* value of <0.05 was considered statistically significant. All statistics were conducted using SPSS Software (Statistical Package for the Social Sciences; IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 25 Armonk, NY: IBM Corp). No meta-analysis of prognostic studies was planned due to the expected paucity and granularity of data.

This systematic review protocol is reported in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 Checklist. It was not registered to Prospero.

Results

After removal of duplicates, unrelated publications, and exclusions, 96 articles were included in the final analysis (Figure 1), including 14 cohorts with case-level data (authors provided individual case data when these were not reported in the article) [2,6,42,43,44,45,46,47,48,49,50,51,52,53], 82 case reports/case series [5,9,54–133]. A total of 411 cases were included, 347 of which were confirmed quantitatively by the presence of ethylene glycol in blood. The demographics, details of the poisoning, laboratory values and outcomes of included cases are presented in Table 1. When reported, all exposures were acute and all patients ingested ethylene glycol, except two who injected it subcutaneously [113]. One article [48] described a single patient admitted 154 times for ethylene glycol poisoning who received fomepizole monotherapy 63 times and ethanol monotherapy 16 times; case-level data were obtained. No comparative studies or randomized trials were identified. Nineteen cohorts containing no case-level data were excluded from analyses but are discussed [114,134–151].



Legend: ECTR, extracorporeal treatment; ADH, Alcohol dehydrogenase; EG, ethylene glycol

Figure 1. Flow diagram (February 24th, 2021). ECTR: extracorporeal treatment; ADH: Alcohol dehydrogenase; EG: ethylene glycol.

Table 1. Characteristics of included cases with case-level data.

	Cases identified					
	Either antidote		Ethanol alone		Fomepizole alone	
	All cases ($n = 411$)	Only 1 case per patient ($n = 333$)	All cases ($n = 180$)	Only 1 case per patient ($n = 165$)	All cases ($n = 231$)	Only 1 case per patient ($n = 168$)
Age (years)						
Median	30 [27,45]	37 [23, 48]	32 [23,47]	35 [22, 48]	29 [29, 43]	37 [25, 48]
Range	0.5 to 95	0.5 to 95	1 to 95	1 to 95	0.5 to 86	0.5 to 86
Sex (Male)	52%	67%	73%	80%	35%	52%
EG dose (mL, equivalent of 100% EG solution)						
Median	80 [30, 350]	73 [30, 205]	50 [30, 100]	50 [30, 100]	490 [139, 1000]	350 [100, 500]
Range	10 to 3800	10 to 3800	10 to 2250	10 to 2250	17 to 3800	17 to 3800
Time from exposure to health care facility arrival (hours)						
Median	3 [1, 7.5]	3 [1, 8]	2 [1, 6]	2 [1,6]	5 [3, 9]	5 [2.5, 10]
Range	0.3 to 120	0.3 to 120	0.3 to 60	0.3 to 60	0.5 to 120	0.5 to 120
Ethanol co-ingestion? (Yes)	32%	35%	35%	39%	30%	34%
Time from arrival to health care facility to antidote administration (hours)						
Median	2 [1, 4]	2 [1, 4]	2 [1, 4]	2 [1, 4]	2 [2, 4]	2 [2, 4]
Range	0 to 48	0 to 48	0 to 24	0 to 24	0 to 48	0 to 48
Initial EG concentration (mmol/L) $						
Median	13.9 [3.1, 42]	9.4 [2.3, 24]	4.7 [1.5, 13]	3.9 [1.5, 10]	22 [8.5, 56]	15 [5.7, 34]
Range	0.2 to 258	0.2 to 258	0.2 to 135	0.2 to 135	0.2 to 258	0.2 to 258
Blood pH*						
Median	7.34 [7.24,7.39]	7.35 [7.27, 7.40]	7.35 [7.24, 7.40]	7.35 [7.23, 7.40]	7.33 [7.26, 7.38]	7.35 [6.77, 7.47]
Range	6.60 to 7.54	6.60 to 7.54	6.60 to 7.54	6.60 to 7.54	6.77 to 7.49	6.77 to 7.47
Anion gap (mmol/L)*						
Median	21 [15, 28]	19 [15, 25]	22 [15, 31]	20 [14, 31]	21 [16, 27]	19 [15, 24]
Range	4 to 49	4 to 46	6 to 46	6 to 46	4 to 49	4 to 45
Serum HCO_3^- concentration (mmol/L)*						
Median	18 [10, 23]	20 [10, 24]	20 [10, 24]	21 [11, 24]	16 [10, 22]	18 [10, 23]
Range	1 to 35	1 to 35	2 to 35	2 to 35	1 to 31	1 to 31
Base excess (mmol/L)*						
Median	−14 [−7, −21]	−23 [−14, −29]	−18 [−7, −29]	−25 [−13, −30]	−11 [−7, −17]	−21 [−14, −26]
Range	0.9 to −39	0.9 to −39	0.9 to −39	0.9 to −39	0.8 to −28	−1 to −26
Serum creatinine concentration (μmol/L)*&						
Median	78 [65, 97]	80 [69, 97]	80 [70, 96]	80 [70, 97]	71 [62, 97]	79 [62, 97]
Range	18 to 298	18 to 298	24 to 298	24 to 298	18 to 235	18 to 235
Length of stay (days)						
Median	3 [2, 5]	4 [3, 6]	4 [2, 6]	4 [3, 10]	3 [2, 5]	4 [3, 6]
Range	1 to 28	1 to 28	1 to 28	1 to 28	1 to 18	1 to 18
Acute kidney injury (Yes)**	9.2%	11.4%	14.0%	15.3%	5.1%	7.2%
Received extracorporeal treatments as rescue therapy (Yes)	7.3%	9.2%	9.4%	10.6%	5.2%	7.8%
Neurological worsening (Yes)	6.2%	8.4%	15.8%	17.7%	2.8%	3.9%
Death (Yes)	4.9%	6.0%	9.4%	10.3%	1.3%	1.8%
Treatment failure (Yes)	12.2%	15.3%	16.7%	18.8%	8.7%	11.9%

*Value preceding the initiation of ADH inhibition.
**Defined as KDIGO stage 2 or 3 acute kidney injury (increase in serum creatinine concentration >2.0 times, urine output <0.5 mL/kg/h for ≥12 h).
$To convert ethylene glycol concentration from mmol/L to mg/dL, multiply by 6.2.
& To convert serum creatinine from μmol/L to mg/dL, divide by 88.4.
Medians are presented with first and third quartiles; EG: ethylene glycol.
When values were reported as "normal" they were interpreted as pH = 7.40, HCO_3^- concentration = 25 mmol/L, anion gap =14 mmol/L, age-expected creatinine concentration.

Prognostic study

Ethanol monotherapy

There were 180 cases reported with ethanol monotherapy, 30 of which failed (16.7%, Table 1). There were 17 deaths, 15 of which had marked acidemia (HCO_3^- <8 mmol/L or pH ≤7.0) prior to ethanol therapy [6,42,46,55,64,65,68,85,119,124]. One patient expired as extracorporeal treatment was not available [119]. Most of those who developed complications but survived also had significant kidney impairment or acidemia on arrival to the health care facility [5,63,70,81,98,108,112,127].

However, several cases with modest acidemia or kidney impairment failed ethanol therapy [56,67,73,89,123,132]. One patient had no AKI and pH 7.20 but died after a protracted course from AKI and cerebral edema following multiple seizures [67]. Another had a pH of 7.10 but developed progressive acidemia and AKI and died 6 days later despite subsequent peritoneal dialysis [91]. Failures were reported when serum ethanol monitoring was not performed [91] or subtherapeutic [67,89]. There were only eight cases with ethylene glycol ingestions larger than 1 L or a serum ethylene glycol concentration greater than 80 mmol/L (497 mg/dL) [2,46,48,76,80,89,111], all of which survived although one needed hemodialysis because of worsening acidemia and kidney function. [89].

Compared to cases that had no treatment failure, those that failed ethanol monotherapy had a significantly greater ethylene glycol dose (207 mL vs 30 mL, $p = 0.0002$), a longer time to the presentation (6 h vs 1.5 h, $p = 0.0002$), a higher ethylene glycol concentration (9.5 mmol/L (59 mg/dL) vs

Table 2A. Comparison of characteristics with or without ADH inhibitor treatment failure (all included cases).

	Ethanol					Fomepizole				
	Treatment failure ($n = 30$)		No treatment failure ($n = 150$)			Treatment failure ($n = 20$)		No treatment failure ($n = 211$)		
	N	Median, IQR	*n*	Median, IQR	*P*-value	*n*	Median, IQR	*N*	Median, IQR	*P*-value
Age (Years)	27	45 [29, 57]	136	31 [20, 44]	0.003	20	35 [16, 45]	205	29 [29, 43]	NS (1.0)
Gender (Male)	27	70%	135	73%	NS (0.8)	20	65%	203	32%	0.001
EG dose (mL equivalent of 100% EG solution)	11	207 [125, 425]	96	30 [30, 100]	0.0002	6	150 [94, 2288]	36	500 [184, 1000]	NS (0.6)
Time from EG exposure to presentation to health care facility (h)	19	6 [3.8, 8.5]	117	1.5 [1, 4.5]	0.0002	8	3 [3, 13]	88	5 [3, 9]	NS (0.7)
Ethanol co-ingestion? (Yes)	16	50%	64	31%	NS (0.1)	19	16%	156	32%	NS (0.2)
Time from presentation to antidote (h)	5	10 [6, 18]	12	1 [0.5, 2]	0.02	8	3.5 [1.7, 4.5]	31	2 [2, 4]	NS (0.6)
Initial EG concentration (mmol/L)$	16	9.5 [5.5, 22.3]	108	4.1 [1.4, 12.5]	0.04	19	12.4 [4.3, 37]	204	24.6 [9.3, 56]	NS (0.3)
Blood pH*	29	6.96 [6.73, 7.19]	134	7.37 [7.31, 7.40]	<0.00001	19	7.20 [7.01, 7.33]	159	7.34 [7.27, 7.38]	0.0008
Anion gap (mmol/L)*	11	34 [33, 37]	45	20 [13, 25]	0.0002	16	34 [22, 39]	152	20 [15, 25]	0.001
HCO_3^-, concentration (mmol/L)*	24	6 [3, 10]	102	22 [17, 24]	<0.00001	13	8 [4, 11]	116	17 [11, 22]	0.0004
Base excess (mmol/L)*	13	−32 [−25, −36]	29	−14 [−6, −21]	0.0006	7	−21 [−15, −25]	63	−11 [−7, −16]	0.004
Creatinine concentration (μmol/L)*&	18	130 [77, 180]	109	80 [69, 96]	0.0005	16	101 [77, 126]	154	71 [62, 90]	0.007

Table 2B. Comparison of characteristics with or without ADH inhibitor treatment failure (1 case per patient).

	Ethanol					Fomepizole				
	Treatment failure ($n = 30$)		No treatment failure ($n = 135$)			Treatment failure ($n = 20$)		No treatment failure ($n = 148$)		
	n	Median, IQR	*N*	Median, IQR	*P*-value	*n*	Median, IQR	*N*	Median, IQR	*P*-value
Age (Years)	27	45 [29, 57]	121	34 [17, 47]	0.005	20	35 [16, 45]	142	38 [26, 48]	NS (0.9)
Gender (Male)	27	70%	120	83%	NS (0.2)	20	65%	140	56%	NS (0.5)
EG dose (mL equivalent of 100% EG solution)	11	207 [125, 425]	88	30 [30, 100]	0.0001	6	150 [94, 2288]	29	400 [100, 500]	NS (0.8)
Time from EG exposure to presentation to health care facility (h)	19	6 [3.8, 8.5]	111	1.5 [1, 4.3]	0.0002	8	3 [3, 13]	73	5 [2.5, 10]	NS (0.7)
Ethanol co-ingestion? (Yes)	16	50%	56	34%	NS (0.3)	19	16%	140	36%	NS (0.1)
Time from presentation to antidote (h)	5	10 [6, 18]	12	1 [0.5, 2]	0.02	8	3.5 [1.7, 4.5]	31	2 [2, 4]	NS (0.6)
Initial EG concentration (mmol/L)	16	9.5 [5.5, 22.3]	95	2.7 [1.2, 8.3]	0.007	19	12.4 [4.3, 37]	145	16 [5.8, 34]	NS (0.9)
Blood pH*	29	6.96 [6.73, 7.19]	120	7.37 [7.32, 7.40]	<0.00001	19	7.20 [7.01, 7.33]	102	7.36 [7.31, 7.40]	0.0001
Anion gap (mmol/L)*	11	34 [33, 37]	36	17 [13, 22]	0.00008	16	34 [22, 39]	123	19 [15, 23]	0.0009
HCO_3^-, concentration (mmol/L)*	24	6 [3, 10]	89	23 [19, 25]	<0.00001	13	8 [4, 11]	56	20 [11, 25]	0.0002
Base excess (mmol/L)*	13	−32 [−25, −36]	15	−19 [−7, −29]	0.009	7	−21 [−15, −25]	4	−13 [−2, −24]	NA**
Creatinine concentration (μmol/L)*	18	130 [77, 180]	93	80 [70, 96]	0.0006	16	101 [77, 126]	107	75 [62, 97]	0.02

Medians are presented with first and third quartiles, EG, ethylene glycol.
*Prior to ADH inhibition.
$To convert ethylene glycol concentration from mmol/L to mg/dL, multiply by 6.2.
& To convert serum creatinine from μmol/L to mg/dL, divide by 88.4.
NA** Mann U-test not calculable since less than 5 observations in one group.

4.1 mmol/L (25.4 mg/dL), $p = 0.04$), and a longer time to antidote administration (10 h vs 1 h, $p = 0.02$). Those who failed ethanol monotherapy also had, on arrival to the healthcare facility, a significantly lower serum pH, a higher anion gap, a lower HCO_3^-, a lower base excess, and a higher creatinine concentration, which remained true when using 1 case per patient (Tables 2A and 2B). Among the cohorts with no case-level data, there were deaths reported in patients prior to receiving hemodialysis [134], and in patients considered too sick to receive extracorporeal treatment [137].

Fomepizole monotherapy

A total of 231 cases were reported with fomepizole monotherapy, 20 of which failed (8.7%, Table 1). Three patients died [52,53,120], all of whom had signs of late ethylene glycol toxicity and extremely elevated anion gap: one had an anion gap of 39 mmol/L [53], another had a pH of 6.77 and an anion gap of 41 mmol/L, remained acidemic and developed seizures despite hemodialysis starting 8 h after presentation [120], and a third had a pH of 6.88 and the family declined hemodialysis [52].

Seven cases were initially treated with fomepizole and needed subsequent extracorporeal treatment; six for progression of AKI (all had a serum HCO_3^- ≤8.0 mmol/L when fomepizole was started [72,84,102,117,126,128]), and one for worsening acidemia [121]. Other cases that failed fomepizole therapy had marked acidemia (serum HCO_3^- < 11 mmol/L or anion gap >28 mmol/L) on presentation. One patient experienced a seizure [110], five patients had modest worsening of acidemia or AKI during fomepizole therapy [49,52], and one patient developed osmotic diuresis from an extremely elevated ethylene glycol concentration (258 mmol/L; 1601 mg/dL) and subsequently experienced electrolyte abnormalities requiring hemodialysis [94]. One patient developed anaphylaxis from fomepizole that necessitated its cessation and extracorporeal treatment rescue [116]. Only two patients with minimal metabolic derangements or kidney impairment failed fomepizole: one patient had a decrease in HCO_3^- from 17 to 11 mmol/L but had an uneventful course [130] while the other developed an uncomplicated seizure but had a known seizure disorder [9].

Compared to patients who had no treatment failure, those who failed fomepizole monotherapy had a significantly lower serum pH, a higher anion gap, a lower HCO_3^-, a lower base excess, and a higher creatinine concentration (Table 2A and 2B). Neither the ethylene glycol dose, the time to presentation, nor the ethylene glycol concentration was predictive of treatment failure; thus there does not appear to be an ethylene glycol dose or ethylene glycol concentration cut-off above which toxicity was demonstrated if fomepizole is used. These include a benign evolution with a dose of ethylene glycol ≥1 L or ethylene glycol concentration >80 mmol/L (>497 mg/dL) [48,53,75,82,84,90,96,100,101,106,107,109,125]. Even for cases with ethylene glycol doses exceeding 3 L or serum ethylene glycol concentration >200 mmol/L (>1241 mg/dL), the outcomes were favorable [94,130], except in those who were already markedly acidemic (HCO_3^- ≤8 mmol/L) on presentation [117,120,128].

Published cohorts also reported good outcomes from fomepizole monotherapy (Table 3). There were, however, deaths reported, although the data regarding dose, antidote and timing of administration are lacking [147,150]. It is possible that in some cases, clinical markers on presentation were severe and/or extracorporeal treatment was not available. Another publication reports that no mortality or significant morbidity occurred in France in ethylene glycol-poisoned patients if treated within 24 h of exposure [10].

Anion gap study

There were 207 cases fulfilling inclusion criteria and included in this analysis (Table 4), 32% of which co-ingested ethanol. Twenty-two percent were treated with ethanol alone and 78% with fomepizole alone. Among the 132 cases with an anion gap < 24 mmol/L, none died, and two patients developed stage 2 or 3 AKI: one had anion gap of 15 mmol/L but significant AKI on presentation, although extracorporeal treatment was not needed and AKI resolved spontaneously [98]. One patient had an anion gap of 27 mmol/L on presentation, although the other acid-base parameters were extreme (pH 6.77, HCO_3^- 3 mmol/L, base excess −33 mmol/L), and later needed extracorporeal treatment for AKI [81]. Comparatively, 7.8% of patients with anion gap over 28 mmol/L died, and a quarter of patients had stage 2 or 3 AKI and/or needed extracorporeal treatment.

The relationship between the anion gap and the complications of AKI or death are shown in Figure 2. Here, there is a low risk of AKI for anion gaps less than 24 mmol/L, and of death for anion gaps less than 28 mmol/L, but the risks increase progressively with higher anion gaps.

Discussion

This systematic review presents cases in which fomepizole or ethanol was used without extracorporeal treatment as the sole treatment of ethylene glycol poisoning. Adverse outcomes and treatment failures from ethylene glycol poisoning were mostly described when severe metabolic acidemia and or Stage 2–3 AKI was present. When these two conditions were absent on presentation, only rare, minor, and reversible complications occurred when fomepizole is used as monotherapy [9,49,130]. This is consistent with the conclusions of other observational cohorts (Table 3) [114,142,145].

As suggested by prior reports, this study did not identify an ethylene glycol concentration over which fomepizole treatment is expected to fail, and several cases of benign outcomes were reported despite massive ethylene glycol ingestions treated with fomepizole [48,75,82,101,106,109,130]. There was only one reported case of treatment failure with a very high ethylene glycol concentration and a low anion gap on presentation; this patient had an ethylene glycol concentration of 258 mmol/L (1,601 mg/dL) and developed osmotic diuresis with electrolyte disturbances (hypernatremia) that necessitated hemodialysis [94], although the incidence of this phenomenon is unclear. One patient with repeated ethylene glycol ingestions was treated with antidote therapy alone on 81 occasions (highest ethylene glycol concentration was 112 mmol/L [695 mg/dL]) [48]. The only complication that she developed was mild and reversible AKI, with a peak creatinine concentration of 133 μmol/L (1.5 mg/dL).

Although fomepizole monotherapy appears safe in selected circumstances, this likely results in higher costs and prolonged length of stay compared to when extracorporeal treatment is also used [40,75,86,152,153,154,155,156]. The study was not designed to compare cost-benefit between extracorporeal treatment with ADH inhibitors and ADH inhibitors used alone.

Ethanol also appears efficient and safe when used as monotherapy in the absence of AKI and acidemia. However, there were several failures within the cutoffs identified above [56,67,73,89,123,132]. A subtherapeutic ethanol concentration (from reducing the ethanol infusion rate due to CNS effects) may have contributed to some of these failures [47,67,89,91]. Further evidence of the limitations of ethanol therapy is also demonstrated by patients presenting with end-organ injury despite having co-ingested ethanol and having a therapeutic

Table 3. Cohorts of patients receiving fomepizole or ethanol.

Cohort	Full cohort (*n*)	EG patients treated with ethanol or fomepizole as monotherapy (*n*)	Co-exposure of ethanol	Antidote given	EG concentration (mmol/L)$	Acid-base status	Kidney function	Notes
[134]	14	3	NR	Ethanol	NR	NR	NR	1 died before receiving ECTR. 2 survived. No other details.
[135]	15	3	NR	Ethanol	NR	No acidemia	No AKI	Ingested $\leq$ 100 mL EG, symptoms were slight. No deaths
[136]	170 (only those ingesting concentrated EG)	58	NR	Ethanol	NR	NR	50% AKI	54/58 survived. 4 died while being prepared for ECTR. No data on these.
[137,167]	36	7	NR	Ethanol	19, 19, and 10 in 3 patients	NR	NR	2/7 patients died: 1 had poor clinical status that prevented hemodialysis and died within 24 h, the other within 48 h from therapy-resistant hypotension.
[138]	20 (symptomatic patients only)	20	NR	Ethanol	NR	NR	NR	No deaths
[139]	75	19	NR	Ethanol	<8.1	pH > 7.0	No AKI	All survived. All presented early and/or had small ingestions,
[140]	34	2	NR	Ethanol	NR	No acidemia	NR	Both survived
[141]	24 toxic alcohols (18 EG)	≥10	NR	Fomepizole	2.6 [1.0;11.3] Max 53.5	NR	NR	Results mixed with methanol cohort. Outcomes unclear. 1 patient died out of 24. Length of stay 2 [1–3] days in those with EG poisoning receiving oral fomepizole
[142]*	24	24	29%	88% fomepizole, 10% fomepizole + ethanol, 2% fomepizole and isopropanol	All over 8.1 Mean 22.2 ± 15.7 (range 8.4–69.1)	Mean pH 7.32 Mean HCO_3^- 22 mmol/L	Mean peak creatinine concentration = 123 μmol/L&	Good evolution in all patients, no progression of acidemia, no death
[143]	68	NR	NR	Fomepizole (all misdosed)	NR	NR	NR	No progression of acidemia in all
[144]*	14 (unintentional)	13	NR	46% fomepizole, 23% ethanol, 8% both	All <4.8	NR	NR	Good outcome
[145]*	29 toxic alcohols (mixed) al/< 18 y	18	0%	Fomepizole	<6.0	3 in whole cohort had *pH* = 7.30–7.34. 3 in whole cohort had AG = 20–23 mmol/L. Others normal	Normal in all	Favorable outcome in all
[146]	32	≤4	NR	Ethanol	NR	NR	NR	No deaths. Baseline characteristics of EG and methanol cases mixed together.
[147]	174	78	NR	Ethanol or fomepizole	NR	NR	NR	21 died. No other data on those 78 patients and why they were not dialyzed.
[114]	38 children (methanol and EG)	27	NR	Fomepizole	NR	NR	NR	No patient received ECTR. Outcome was favorable in all. No sequelae.
[148]	2	1	NR	Ethanol	NR	NR	NR	Discharged within 24 h. Good outcome. LOS = 1 day
[149]*	113 (all unintentional)	104	NR	67% fomepizole, 4% ethanol	All ≤6.8	NR	NR	No deaths, 12 moderate effect, 3 major effect
[150]*	56	28	NR	Unclear	NR	HCO_3^- <22 mmol/L	Creatinine concentration > 88 μmol/L&	8/28 died. No data presented. Unclear if patients were meant to be dialyzed. Death more likely if *pH* < 7.05, coma or AKI. No CKD in survivors
[151]	59	34	NR	All cohort: 90% fomepizole, 5% ethanol	Mean: 20.3, range 0.8–134.5	Mean 7.28 Range 6.60–7.52	Mean creatinine concentration: 109 μmol/L, range 26–431&	1 death. EG concentration = 42.9 mmol/L, unclear if received ECTR

*Conference abstract.
$To convert ethylene glycol concentration from mmol/L to mg/dL, multiply by 6.2.
& To convert serum creatinine from μmol/L to mg/dL, divide by 88.4.
AKI: Acute kidney injury; EG: Ethylene glycol; ECTR: Extracorporeal treatment; AG: Anion gap; LOS: Length of stay; NR: Not reported.

Table 4. Baseline features, treatment and outcomes relative to the admission anion gap.

	All		Anion gap < 24 mmol/L		Anion gap 24–28 mmol/L		Anion gap > 28 mmol/L	
	All cases (*n* = 207)	1 case/patient (*n* = 171)	All cases (*n* = 132)	1 case/patient (*n* = 119)	All cases (*n* = 24)	1 case/patient (*n* = 16)	All cases (*n* = 51)	1 case/patient (*n* = 36)
Age (years)	31 [27, 45]	35 [23, 48]	34 [27, 45]	37 [27, 46]	29 [26, 41]	28 [17, 52]	29 [28, 44]	35 [17, 51]
Sex (male)	44%	55%	50%	56%	18%	29%	43%	63%
EG dose (mL equivalent of 100% EG solution)	300 [100, 838]	207 [100, 500]	300 [100, 613]	300 [100, 613]	138 [69, 238]	138 [69, 238]	500 [200, 1125]	200 [175, 354]
Time from exposure to presentation (h)	4 [2, 7]	4 [2, 7]	3.5 [2, 6]	3.5 [1.5, 6.5]	4 [2.5, 6]	4 [2.3, 8]	6 [3.5, 10]	6 [3.3, 13]
Ethanol co-ingestion? (Yes)	32%	35%	39%	40%	12%	17%	20%	26%
Time from presentation to antidote (h)	2 [1, 4]	2 [1, 4]	2 [0.5, 3]	2 [0.5, 3]	3 [2, 4]	3 [2, 4]	4 [2, 8]	4 [2, 8]
Initial EG concentration (mmol/L)*$	19 [6.7, 56]	16 [4.8, 37]	17 [5.9, 45]	16 [4.4, 33]	33 [16, 56]	22 [12, 34]	25 [8.2, 59]	13 [3.1, 53]
Anion gap (mmol/L)*	21 [15, 28]	19 [15, 25]	18 [14, 20]	17 [14, 20]	26 [25, 27]	25 [24, 27]	33 [31, 39]	34 [31, 40]
Creatinine concentration (μmol/L)*&	79 [66, 97]	80 [68, 97]	74 [63, 90]	79 [65, 95]	74 [66, 84]	80 [70, 95]	91 [70, 114]	99 [72, 124]
Treated with ethanol alone (Yes)	22%	22%	20%	19%	25%	31%	25%	25%
Treated with fomepizole alone (Yes)	78%	78%	80%	81%	75%	69%	75%	75%
Death (Yes)	1.9%	2.3%	0.0%	0.0%	0.0%	0.0%	7.8%	11.1%
Stage 2 or 3 AKI (Yes)	7.2%	8.9%	1.6%	1.8%	4.2%	6.3%	23.4%	34.4%
Needed extracorporeal treatments as rescue therapy (Yes)	8.5%	10.9%	0.0%	0.0%	5.6%	10%	27.7%	40.6%

*Value preceding the initiation of ADH inhibition.
$To convert ethylene glycol concentration from mmol/L to mg/dL, multiply by 6.2.
& To convert serum creatinine from μmol/L to mg/dL, divide by 88.4.
AKI is defined as KDIGO stage 2 or 3 acute kidney injury (increase in serum creatinine concentration >2.0 times, urine output <0.5 ml/kg/h for ≥12 h).
Data are presented as medians with first and third quartiles.
N: number of cases; AKI: acute kidney injury; EG: ethylene glycol.

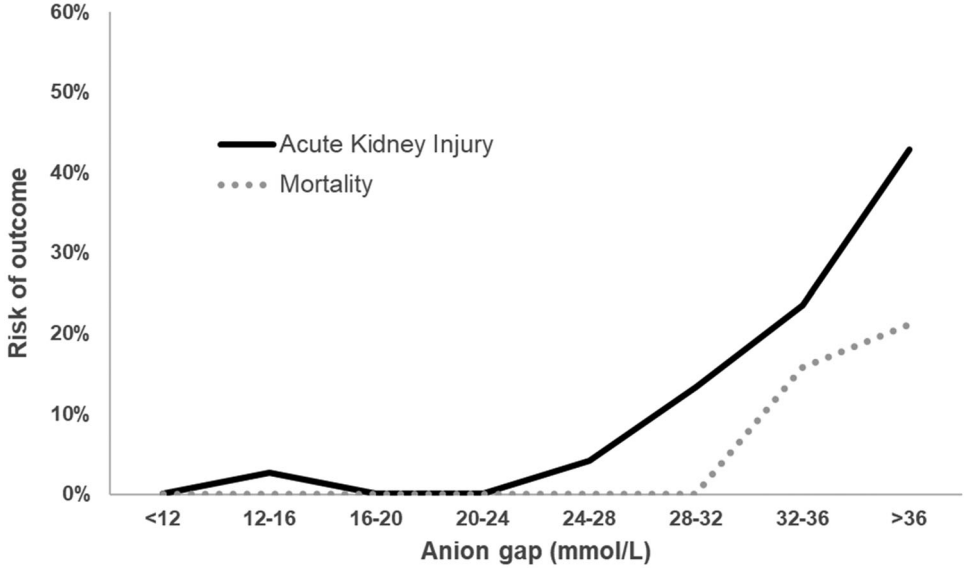


Figure 2. Relationship between anion gap and the risk of acute kidney injury or death in patients treated with ADH blockade but without extracorporeal treatments.

ethanol concentration on presentation. [157] Additionally, the ADH inhibition from ethanol is weaker than fomepizole [7,8]. Ethanol also carries risks, including altered mental status, hepatitis, pancreatitis and gastritis and hypoglycemia in children [45]. Contrary to fomepizole, the ethylene glycol dose and concentration appear predictive of ethanol failure (Tables 2A and 2B); this may reflect fomepizole's higher affinity or better efficiency compared to ethanol [158].

For these reasons, there are concerns that when the ethylene glycol concentration is >10 mmol/L (>62 mg/dL), ethanol therapy alone may be insufficient to prevent complications from ethylene glycol; this is not noted with fomepizole. There were 29 additional cases that were excluded because both ethanol and fomepizole were administered as antidotes [2,9,38,39,40,44,45,48,52,53,84]; the only reported failure developed AKI (peak creatinine 265 μmol/L; 3.0 mg/dL) although the patient survived without extracorporeal treatment or sequelae [2].

The anion gap is a good correlate for the glycolate concentration [6,16,48,159,160]. A prior analysis showed that

mortality did not occur if the glycolate concentration was <8 mmol/L, which is correlated to an anion gap of 24 mmol/L [16]. That same study showed that AKI was expected if the glycolate concentration was >12 mmol/L, which correlated to an anion gap over 28 mmol/L.

The present study reinforces the hypothesis that in patients who receive an ADH inhibitor but not extracorporeal treatment, an anion gap <28 mmol/L is associated with no mortality and a small likelihood of AKI. This confirms earlier findings [161] which were not unfortunately stratified for ADH inhibitor and extracorporeal treatment. A higher anion gap is also known to be associated with coma [162] and AKI [6]. These results can assist clinicians in the decision-making of the risk, costs and benefits of transferring patients to a facility with extracorporeal treatment.

This systematic review has several major limitations. The main case series and cohorts that were included [2,6,42,43,44,45,46,47,48,49,50,51,52,53] were considered at high risk of bias due to incomplete reporting (missing data). Publication bias is likely since most of the data consists of case reports and case series, including many conference abstracts. It is probable that good outcomes when extracorporeal treatment was not performed were preferentially reported. Better outcomes reported with fomepizole compared to ethanol could be explained by the older year of publication (and potentially inferior standard of care performed) in the latter group. One case series described a single patient with 79 presentations; however, it is unlikely that the inclusion of these cases skewed the analysis as results were very similar regardless of whether 1 case per patient or all cases was considered (Tables 2A and 2B).

Assumptions were required to normalize the anion gap data, although, these are unlikely to influence the analysis of patients with very elevated (>28 mmol/L) anion gaps. The retrospective nature of reports also limits the value of both analyses. There was extensive heterogeneity across the study types, treatments offered, differences in reported variables of interest and outcomes. Timing of extracorporeal treatment relative to ADH inhibition was not always reported, perhaps causing the non-inclusion of important case reports. The chosen criteria for failure of ADH inhibition were very sensitive: it is not clear that a 5 mmol/L decrease in HCO_3^- translates to poor clinical outcomes. We elected to take values at the time of ADH inhibition initiated rather than on arrival to the healthcare facility, to account for potential treatment delays and their impact on adverse outcomes. Finally, we acknowledge that the criterion of worsening kidney injury after ADH inhibition is controversial as kidney injury may have occurred prior to ADH inhibition but only manifested, from a serum creatinine standpoint, after ADH inhibition was initiated.

The study was not designed to compare the effectiveness of ethanol versus fomepizole; two systematic reviews failed to identify a superiority of fomepizole over ethanol [163,164]. Although other inhibitors of ADH have been studied in toxic alcohol poisonings, such as pyrazole [165], isopropanol [27], and abacavir [166], this systematic review only analyzed ethanol and fomepizole. This analysis did not address situations where antidotal therapy can be avoided (e.g., marginal ethylene glycol concentration).

Conclusions

This systematic review suggests that fomepizole monotherapy, without extracorporeal treatment, is an effective and safe treatment in patients with modest AKI and/or acidemia (anion gap <28 mmol/L), regardless of the ethylene glycol concentration. These cut-offs are not applicable to ethanol monotherapy, as more failures were reported (especially at higher ethylene glycol concentrations) which may reflect challenges in dosing and/or monitoring of ethanol therapy. These findings should be confirmed prospectively. Clinicians who encounter patients who fail these cut-offs are encouraged to report them. The cost-effectiveness of a strategy combining ADH inhibitors and extracorporeal treatment should be compared to that using ADH inhibitors alone.

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