Toxic Alcohols

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POISONINGS BY THE TOXIC ALCOHOLS (METHANOL, ETHYLENE GLYCOL, ISO-propanol, diethylene glycol, and propylene glycol) can cause cellular dysfunction and death,[1] but symptoms may be nonspecific. Delays in diagnosis increase the risk of irreversible organ damage and death.[2] In this review, we discuss the mechanisms of toxicity, methods available for diagnosis, and current recommendations for therapy.

MECHANISMS OF TOXICITY

The toxic alcohols are inebriating but are not directly toxic, except for isopropanol. Their toxic effects result from their metabolites. A simplified schema depicting their primary metabolic pathways is shown in Figure 1A.

Alcohol dehydrogenase catalyzes the first oxidation of the toxic alcohols. The resulting aldehydes (except for acetone from isopropanol) undergo further oxidation by aldehyde dehydrogenase to form carboxylic acid metabolites: methanol is metabolized to formic acid,[3] ethylene glycol to oxalic and glycolic acid,[3] diethylene glycol to 2-hydroxyethoxyacetic acid and glycolic acid,[4] and propylene glycol to D-lactic and L-lactic acid.[5] Alcohol dehydrogenase is the critical enzyme that modulates the production of the toxic metabolites. Coingested ethanol, a competitive substrate for alcohol dehydrogenase, delays production of the toxic metabolites.[6] Increased production of lactic acid can result from exposure to the metabolites of methanol or ethylene glycol,[3,7] but spurious increments in blood lactate may occur with exposure to ethylene glycol metabolites as a result of interference of glycolate with the lactate measurement by point-of-care instruments.[8]

EPIDEMIOLOGIC FEATURES

The intoxications can occur through different means (Table 1). Methanol intoxication most commonly follows ingestion of automotive windshield-washer fluid, industrial products, or adulterated liquids,[9] but exposure can also occur through pulmonary and cutaneous routes.[10] Ethylene glycol is most commonly ingested by adults in antifreeze or in adulterated spirits in which ethylene glycol has been added in lieu of ethanol, in an attempt to commit suicide; in children, it is most commonly ingested unintentionally. Isopropanol intoxication usually results from ingestion of rubbing alcohol, hand sanitizer, and various industrial products, but intoxication can also be due to inhalation or absorption through dermal or rectal routes.[11]

Diethylene glycol intoxication results from ingestion of automotive brake fluids or industrial products, but it usually occurs in outbreaks in which consumer products or oral medications for children contain diethylene glycol in lieu of propylene glycol
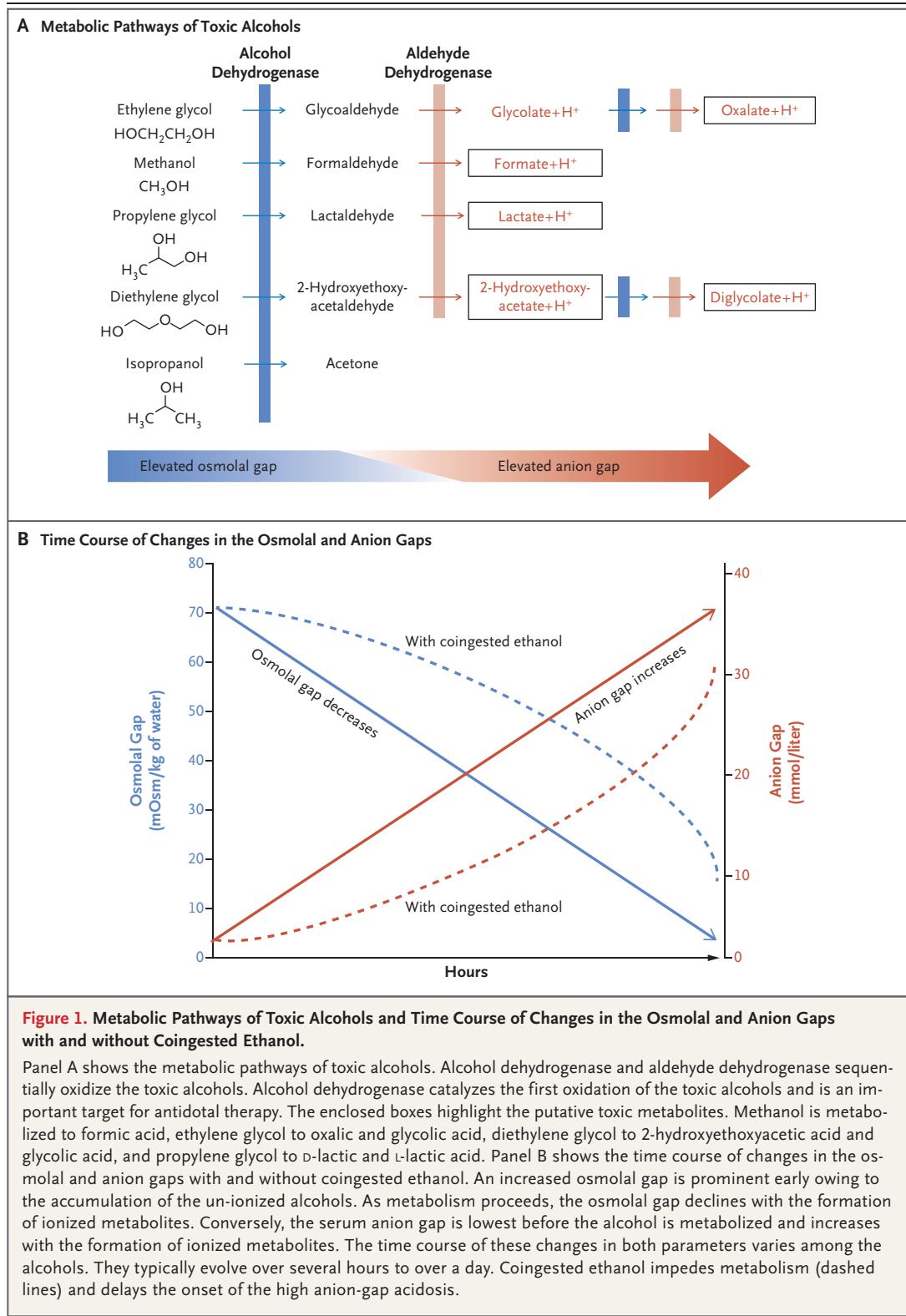
A Metabolic Pathways of Toxic Alcohols

B Time Course of Changes in the Osmolal and Anion Gaps

Figure 1. Metabolic Pathways of Toxic Alcohols and Time Course of Changes in the Osmolal and Anion Gaps with and without Coingested Ethanol.

Panel A shows the metabolic pathways of toxic alcohols. Alcohol dehydrogenase and aldehyde dehydrogenase sequentially oxidize the toxic alcohols. Alcohol dehydrogenase catalyzes the first oxidation of the toxic alcohols and is an important target for antidotal therapy. The enclosed boxes highlight the putative toxic metabolites. Methanol is metabolized to formic acid, ethylene glycol to oxalic and glycolic acid, diethylene glycol to 2-hydroxyethoxyacetic acid and glycolic acid, and propylene glycol to D-lactic and L-lactic acid. Panel B shows the time course of changes in the osmolal and anion gaps with and without coingested ethanol. An increased osmolal gap is prominent early owing to the accumulation of the un-ionized alcohols. As metabolism proceeds, the osmolal gap declines with the formation of ionized metabolites. Conversely, the serum anion gap is lowest before the alcohol is metabolized and increases with the formation of ionized metabolites. The time course of these changes in both parameters varies among the alcohols. They typically evolve over several hours to over a day. Coingested ethanol impedes metabolism (dashed lines) and delays the onset of the high anion-gap acidosis.

Table 1. Clinical and Laboratory Features of the Toxic Alcohols.

Alcohol Type and Molecular Weight	Increase in Serum Osmolality per 10-mg/dl Increase in Serum Alcohol Concentration *mOsm/kg of water*	Common Sources	Common Clinical Features	Major Laboratory Features	Onset of Clinical and Laboratory Features* *hours after exposure*	
					Without Coingested Ethanol	With Coingested Ethanol
Ethylene glycol, 62.07	1.60	Automotive antifreeze, engine coolants, deicing fluids	Inebriation, acute kidney injury	Increased osmolal gap and high anion-gap metabolic acidosis, calcium oxalate crystalluria dihydrate (early) and monohydrate (late) and hypocalcemia, lactate gap (discrepancy between findings from a point-of-care analyzer and laboratory test)	12–24	48–72
Methanol, 32.04	3.09	Windshield-washer fluid, carburetor cleaner, octane boosters, racing fuels, camp stove fuel, adulterated ethanol ("moonshine")	Inebriation, abdominal pain, decreased vision with blindness, Parkinson-like features (rare)	Increased osmolal gap and high anion-gap metabolic acidosis, increased formate, lactic acidosis with cellular hypoxia, spurious increase in serum creatinine concentration	6–24	72–96
Propylene glycol, 76.09	1.31	Diluent in parenteral medications, automotive antifreeze (marketed as a safer alternative to ethylene glycol)	Hepatic and renal disease are uncommon but will predispose to more severe toxicity	Increased osmolal gap alone (most common finding), unexplained lactic acidosis, acute kidney injury (rare)	NA	NA
Diethylene glycol, 106.12	0.9	Automotive brake fluids, hydraulic brake fluids, adulterated liquid medications (e.g., inappropriate substitution for propylene glycol or glycerin) (most common source)	Abdominal pain, nausea and vomiting, acute pancreatitis, acute kidney injury	Increased osmolal gap and high anion-gap metabolic acidosis, acute kidney injury	24–48 (limited data available)	48–72 (limited data available)
Isopropanol, 60.02	1.66	Rubbing alcohol, hand sanitizers	Inebriation, depressed sensorium, abdominal pain	Increased osmolal gap, acetonemia, ketonuria	2–4	NA

* Without or with coingested ethanol indicates the impact of the simultaneous presence of ethanol in the patient. NA denotes not applicable.

as a diluent.[12,13] In rare cases, dermal absorption across nonintact skin may produce toxic effects.[12-14] Propylene glycol is present in numerous consumer products and in antifreeze, but intoxication is usually due to prolonged high-dose infusions of medications such as lorazepam that contain propylene glycol as a diluent.[5,15]

CLINICAL FINDINGS

The alcohols initially depress the sensorium and later produce organ dysfunction. Methanol is associated with decreased vision (in 29 to 72% of cases,[16] occasionally producing blindness), pulmonary dysfunction, abdominal pain, coma, and, rarely, Parkinson-like symptoms.[17] Clinical findings usually evolve over 6 to 24 hours but can be delayed as long as 72 to 96 hours if ethanol is coingested.[18] Neurologic sequelae may ensue days or weeks after exposure.[19]

Ethylene glycol poisoning leads to formation of oxalate crystals, which deposit in the lungs, heart, and kidney and produce organ dysfunction.[20,21] Cranial nerve damage, sometimes delayed for days, can also occur. Neurologic dysfunction develops in the first 12 hours, followed by cardiac and pulmonary dysfunction 12 to 24 hours after exposure and acute kidney injury 48 to 72 hours after exposure.[22] However, the organ dysfunction can occur concomitantly. Coingestion of ethanol can delay the appearance of clinical abnormalities.[20,22]

Isopropanol intoxication depresses the sensorium and can produce respiratory dysfunction, cardiovascular collapse, acute pancreatitis, hypotension, and lactic acidosis. Serum isopropanol concentrations above 500 mg per deciliter (83 mmol per liter) are clinically significant, and those greater than 1500 mg per deciliter (250 mmol per liter) produce deep coma.[23] Acetone can produce a spurious increase in serum creatinine concentration as a result of interference with laboratory measurement.[11]

Diethylene glycol poisoning can cause abdominal pain, nausea, vomiting, diarrhea, acute pancreatitis, altered mental status, hepatic disease, central and peripheral neuropathy (sometimes leading to quadriplegia), and acute kidney injury.[14] Acute kidney injury often appears 8 to 24 hours after exposure, can require dialysis, and is a major cause of death.[24,25] Coingestion of ethanol can delay toxicity by as long as 48 to 72 hours.[14] Cranial nerve palsies and other neurologic complications can appear 5 days or longer after exposure.

Propylene glycol intoxication often produces only an increased osmolal gap,[22,23] but it can produce lactic acidosis and acute kidney injury. Preexisting hepatic disease, renal disease, or both are predisposing factors. Patients who receive a continuous infusion of high-dose lorazepam (>10 mg per hour) for more than 48 hours are at high risk.

DIAGNOSIS

Information from the medical history, physical examination, blood chemical profiles, and tests to identify the parent alcohol or its metabolites are helpful in diagnosis. History of exposure to one of the toxic alcohols is important, given the nonspecific clinical findings and the potential delay between exposure and their appearance.

BLOOD CHEMICAL PROFILES

Accumulation of the alcohol increases the serum osmolality and the osmolal gap (the difference between the serum osmolality measured by the freezing-point depression and the serum osmolarity estimated from the equation given below). Later, accumulation of organic acid anions increases the serum anion gap. The serum osmolality can be estimated with various formulae, but the formula that is acceptable for clinical purposes is as follows: estimated serum osmolality = $(2 \times Na^+$ [in millimoles per liter]) + (blood urea nitrogen [in milligrams per deciliter] ÷ 2.8) + (glucose [in milligrams per deciliter] ÷ 18).

The expected normal osmolal gap is 10 to 20 mOsm per kilogram of water.[26] Higher levels reflect accumulation of osmotically active substances such as the toxic alcohols. The increase in the serum osmolal gap depends on the serum concentration and the molecular weight of the alcohols (Table 1).

The basal serum osmolal gap can be less than 10 mOsm per kilogram of water or even negative.[27] A low basal serum osmolal gap might obscure any increase caused by accumulation of a toxic alcohol. A normal osmolal gap cannot be used to rule out toxic alcohol ingestion; in one study, some patients with toxic alcohol poisonings had osmolal gaps within the normal range.[28]

The osmolal gap varies during the course of intoxication (Fig. 1B).[29,30] Accumulation of the parent alcohol initially elevates the osmolal gap, but as metabolism progresses, the osmolal gap falls. Coingested ethanol (observed in 10 to 60% of cases of methanol and ethylene glycol intoxication)[31,32] will contribute to the increase in the osmolal gap (increase of 2.17 mOsm per kilogram of water per 10-mg-per-deciliter increase in serum alcohol concentration) and will also slow metabolism of the alcohols, prolonging the duration of an increased osmolal gap.[4]

The baseline value of the serum anion gap (i.e., before the accumulation of organic acid anions that results from metabolism of the alcohol) can vary by 10 mmol per liter from the lowest to the highest value.[33] If the baseline anion gap is low, it might not rise above the upper limit of normal despite considerable accumulation of organic acid anions.[33,34] Also, the anion gap rises as metabolism progresses (Fig. 1B). A poisoned patient can present with both a normal or high osmolal gap and a normal or elevated serum anion gap.[20,28,30,35]

An elevated osmolal or anion gap does not always indicate toxic alcohol poisoning. Lactic acidosis, ketoacidosis, chronic kidney disease, and the sick cell syndrome all may increase both gaps.[36] In one study, a minority of the patients with increased osmolal and anion gaps had toxic alcohol poisoning.[28] Some racing fuels containing methanol and nitromethane may falsely elevate creatinine concentration as a result of interference with laboratory testing by means of the Jaffe reaction.[37,38]

Ethylene glycol is metabolized to oxalic acid, which leads to crystalluria and, at times, severe acute kidney injury.[20,39] Dihydrate crystals appear early, and monohydrate crystals appear later. Coprecipitation of oxalate with calcium can occasionally produce hypocalcemia.[20,40] Acetone resulting from isopropanol metabolism can produce a positive nitroprusside reaction for acetoacetate at high concentrations.[11] Lactic acidosis due to accumulation of the L-isomer is most frequent in propylene poisoning, but D-lactic acidosis has occurred in some cases.[41] Because D-lactic acidosis will not be detected by the usual method for measuring lactate that detects only the L-isomer, the presence of D-lactic acidosis could be missed. Gas or liquid chromatography most accurately detects and quantifies the toxic alcohols in body

fluids but is laborious, expensive, and often unavailable.[42] Table 2 shows other methods to identify toxic alcohols that are either in use or in development.[27,43,46-48,50] Pitfalls in the interpretation of laboratory data include failure to recognize that concentrations may be expressed in milligrams per liter or milligrams per deciliter, with values higher than 200 mg per liter or 20 mg per deciliter indicating the need for treatment. Also, tests for volatile substances may detect methanol, ethanol, acetone, and isopropanol but not ethylene glycol or diethylene glycol.

TREATMENT

Delays in treating toxic alcohol poisonings lead to worse outcomes.[51] Therefore, therapy should commence expeditiously when there is a strong suspicion of toxic alcohol poisoning or when metabolic acidosis of unknown cause is present.[52] Although there will be variability in the approach to diagnosis and treatment of the toxic alcohol poisonings, an algorithm consistent with our experience and current literature is depicted in Figure 2.

METHANOL AND ETHYLENE GLYCOL

Gastrointestinal absorption of methanol or ethylene glycol is rapid, so gastric decontamination is usually not helpful. Treatment includes prevention of metabolism and removal of the alcohol and its metabolites from the body.[10,51,53-55]

Intravenous administration of base solution corrects metabolic acidosis and increases the ionization of formate, which facilitates its urinary excretion and reduces its penetration into the optic nerve.[56] Antidotal treatment should commence when the serum methanol or ethylene glycol concentration is higher than 20 mg per deciliter (methanol, 6 mmol per liter; and ethylene glycol, 3 mmol per liter) and the patient has a documented history of ingesting one of the alcohols or when there is strong suspicion that the patient ingested one of the alcohols and has an osmolal gap greater than 10 mOsm per kilogram of water or metabolic acidosis of unknown cause (in accordance with the guidelines from the American Academy of Clinical Toxicology [AACT]; Table S1 in Supplementary Appendix 1, available with the full text of this article at NEJM.org). Ethanol has a high affinity for alcohol dehydrogenase, and intravenous ethanol, although

Table 2. Diagnostic Tests for the Detection of Toxic Alcohols.*

Test	Comment
Wood's lamp to detect urine fluorescence	Detects fluorescein in antifreeze (ethylene glycol); false positives and false negatives occur frequently, which makes the test unreliable[43]
Alco-Screen (AlcoPro), a reagent strip containing alcohol oxidase	Ethanol and methanol are detected at low serum concentrations (5 mg/dl), but ethylene glycol is detected only at high concentrations (>300 mg/dl)[44]
Portable dry strip with enzyme formate dehydrogenase and formazan dye	Useful in the diagnosis of methanol poisoning[45]; serum methanol concentration is indirectly determined from assessment of serum formate concentration; positive results are detected by visual inspection and by means of a photometer
Modified rapid veterinary assay for the detection of ethylene glycol (Catachem)	An ethylene glycol assay that has been modified for use with automated clinical analyzers; good correlation with ethylene glycol concentrations measured by means of gas chromatography; also detects propylene glycol, so it could be used in suspected cases of this poisoning[46,47]
Liquid-based tests that use the enzymes alcohol oxidase or alcohol dehydrogenase or the oxidizing agents sodium periodate or potassium permanganate to detect toxic alcohols in saliva	Tests performed with the use of saliva that has been spiked with various toxic alcohols; detects concentrations of alcohols as low as 5 mg per deciliter[48]; requires confirmation of accuracy with the saliva from actual patients
Gas or liquid chromatography with flame-ionization detection	Most precise method to detect toxic alcohols; laborious and expensive; not available in most clinical laboratories[49]

* To convert the values for ethanol, methanol, and ethylene glycol to millimoles per liter, multiply by 0.2171 for ethanol, by 0.3121 for methanol, and by 0.1611 for ethylene glycol.

not approved by the Food and Drug Administration (FDA), is often used for treatment.[57] A serum ethanol concentration of 100 mg per deciliter (22 mmol per liter) provides competitive inhibition of the enzyme. Advantages include its ready availability and low cost. Disadvantages include the need for compounding by a pharmacist for intravenous use, the need for frequent monitoring of serum concentrations, its effect in blunting the sensorium, and the need for hospitalization in the intensive care unit.

Fomepizole (or 4-methylpyrazole) is a strong inhibitor of alcohol dehydrogenase (fomepizole has an affinity for alcohol dehydrogenase 8000 times that of ethanol) that received FDA approval for the treatment of ethylene glycol and methanol poisoning in 1997 and 2000, respectively,[52] but it is not approved for the treatment of the other toxic alcohol poisonings. Fomepizole is effective at low concentrations, has minimal side effects, and does not require monitoring in an intensive care unit.[58,59] For patients who are not undergoing dialysis, the loading dose is 15 mg per kilogram of body weight, followed by a maintenance dose of 10 mg per kilogram every 12 hours.[52] Because fomepizole may induce its own metabolism by cytochrome P-450 enzymes, after 48 hours the maintenance dose is increased to 15 mg per kilogram every 12 hours. The drug may be removed by dialysis, and therefore giving it immediately after dialysis is recommended. The package insert gives a more detailed schedule for patients who receive treatment with both fomepizole and hemodialysis (see Supplementary Appendix 1).[60]

In the United States, fomepizole is frequently used to treat methanol and ethylene glycol poisonings. In 2012 and 2015, fomepizole was used in 90 to 94% of cases, and ethanol was used in 5 to 6% of cases.[61] Outside the United States, fomepizole is less readily available and ethanol is used more frequently.[55,62,63] Oral ethanol is effective when intravenous ethanol is not available.[64] In 2013, the World Health Organization added fomepizole to the list of essential medications.[65]

A systematic review of the literature from 1974 through August 2010 showed that mortality among patients who ingested methanol or ethylene glycol and received treatment with ethanol was 21.8% and 18.1%, respectively.[59] Mortality among patients who ingested methanol or ethylene glycol and received treatment with fomepizole was 17.1% and 4.1%, respectively. Adverse events occurred more frequently with ethanol than with fomepizole (57% vs.
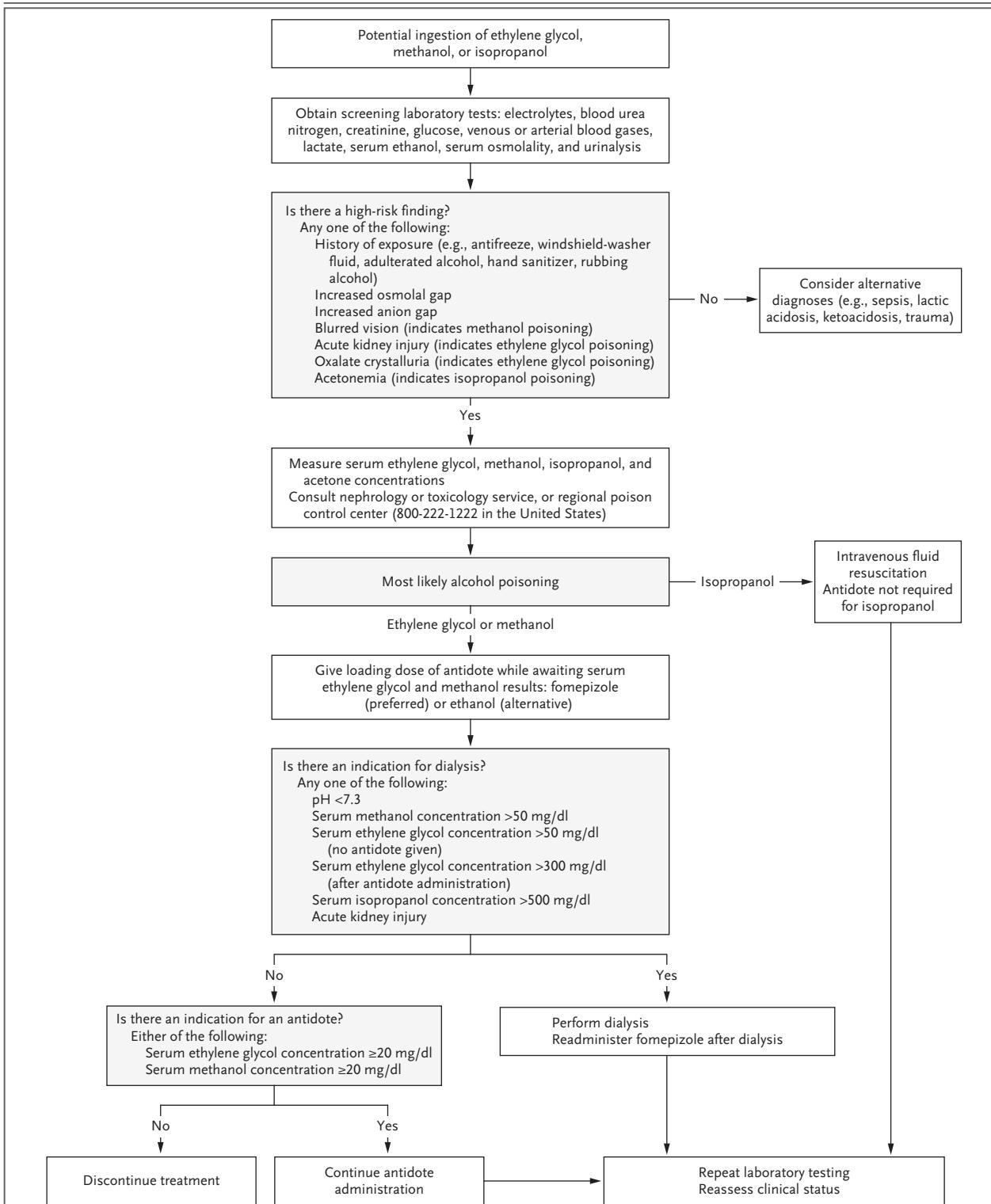
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┌─────────────────────────────────────┐
│ Potential ingestion of ethylene glycol,│
│      methanol, or isopropanol         │
└─────────────────────────────────────┘
                    │
                    ▼
┌─────────────────────────────────────┐
│ Obtain screening laboratory tests: electrolytes, blood urea │
│ nitrogen, creatinine, glucose, venous or arterial blood gases, │
│ lactate, serum ethanol, serum osmolality, and urinalysis │
└─────────────────────────────────────┘
                    │
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Is there a high-risk finding?
Any one of the following:
    History of exposure (e.g., antifreeze, windshield-washer
      fluid, adulterated alcohol, hand sanitizer, rubbing
      alcohol)
    Increased osmolal gap
    Increased anion gap
    Blurred vision (indicates methanol poisoning)
    Acute kidney injury (indicates ethylene glycol poisoning)
    Oxalate crystalluria (indicates ethylene glycol poisoning)
    Acetonemia (indicates isopropanol poisoning)

No → Consider alternative diagnoses (e.g., sepsis, lactic acidosis, ketoacidosis, trauma)

Yes
↓

Measure serum ethylene glycol, methanol, isopropanol, and
acetone concentrations
Consult nephrology or toxicology service, or regional poison
control center (800-222-1222 in the United States)

↓

Most likely alcohol poisoning → Isopropanol → Intravenous fluid resuscitation Antidote not required for isopropanol

Ethylene glycol or methanol
↓

Give loading dose of antidote while awaiting serum
ethylene glycol and methanol results: fomepizole
(preferred) or ethanol (alternative)

↓

Is there an indication for dialysis?
Any one of the following:
    pH <7.3
    Serum methanol concentration >50 mg/dl
    Serum ethylene glycol concentration >50 mg/dl
      (no antidote given)
    Serum ethylene glycol concentration >300 mg/dl
      (after antidote administration)
    Serum isopropanol concentration >500 mg/dl
    Acute kidney injury

No ←→ Yes

No:
Is there an indication for an antidote?
Either of the following:
    Serum ethylene glycol concentration ≥20 mg/dl
    Serum methanol concentration ≥20 mg/dl

No → Discontinue treatment

Yes → Continue antidote administration

Yes (dialysis): Perform dialysis
Readminister fomepizole after dialysis

→ Repeat laboratory testing
Reassess clinical status

Figure 2. Algorithm for the Diagnosis and Treatment of Methanol, Ethylene Glycol, and Isopropanol Intoxications.

This algorithm provides an approach to the diagnosis and treatment of the three most common poisonings. A similar approach might be useful for diethylene glycol poisoning, although this poisoning is rare. One criterion for dialysis (serum ethylene glycol concentration, >300 mg per deciliter after antidote administration) reflects the practice of the second author. To convert the values for methanol, ethylene glycol, and isopropanol to millimoles per liter, multiply by 0.3121 for methanol, by 0.1611 for ethylene glycol, and by 0.1664 for isopropanol.

12%).[66] The cost of fomepizole was often given as a reason to forgo its use. However, the introduction of generic forms has reduced the cost considerably.[58] Thus, fomepizole is preferable for treatment of these poisonings, but ethanol is effective when fomepizole is not available.[63,67]

The toxic alcohols and their metabolites are small and water soluble and are removed during hemodialysis. Guidelines for the use of hemodialysis in the treatment of methanol[51] or ethylene glycol[53] intoxication from the AACT and for treatment of methanol poisoning from the Extracorporeal Treatments in Poisoning Workgroup (EXTRIP)[35] are provided in Table S1 in Supplementary Appendix 1. In general, both guidelines recommend dialysis with severe metabolic acidosis, serum methanol and ethylene glycol concentrations higher than 50 mg per deciliter (methanol, 16 mmol per liter; ethylene glycol, 8 mmol per liter), deteriorating vital signs despite supportive care, and problems with vision (associated with methanol poisoning) or acute kidney injury. Intermittent hemodialysis (with a large-surface-area dialyzer and high-flux membrane) removes toxic alcohols more rapidly than continuous renal replacement therapy.[35,68,69]

Treatment of methanol or ethylene glycol intoxication with fomepizole alone (without hemodialysis) with no adverse consequences has been reported.[31,70-72] However, fomepizole prolongs the elimination half-lives of methanol and ethylene glycol to as high as 71 hours[31] and 16 hours,[58] respectively, as compared with 2.5 and 2.7 hours, respectively, with dialysis. A longer duration of exposure increases days of hospitalization and cost — reasons that are given by some experts to support the inclusion of hemodialysis.[73] The comparative costs of the two treatments will depend on several factors, including exposure dose, relative costs of the drug, cost of dialysis, and room costs, and should be factored in the decision about therapy.[74]

Treatment in children is similar to that in adults.[75] Further examination of the value and limitations of hemodialysis with or without an alcohol dehydrogenase inhibitor in the treatment of these intoxications is warranted. An interactive program to predict the duration of dialysis required to lead to reductions in the parent alcohol and metabolites to safe levels is shown in Supplementary Appendix 2, available at NEJM.org.[76] Body redistribution of the alcohol, metabolites, or both might require repeat dialysis.

In methanol poisoning, 1 mg per kilogram of folic acid every 4 to 6 hours promotes the conversion of formic acid to carbon dioxide and water. In ethylene glycol poisoning, pyridoxine and thiamine promote the metabolism of glycolic acid to less toxic compounds.[56]

DIETHYLENE GLYCOL

Several experts recommend the use of alcohol dehydrogenase inhibitors in the treatment of diethylene glycol poisoning.[58,72] Fomepizole alone has been successful,[77] but because acute kidney injury is common, it seems reasonable to treat patients with both fomepizole and hemodialysis.[78]

ISOPROPANOL

Supportive measures are often sufficient, but hemodialysis may be necessary if the serum isopropanol concentration is 500 mg per deciliter (83 mmol per liter) or more or if hypotension or lactic acidosis is present.[11] Alcohol dehydrogenase inhibitors slow the removal of isopropanol and should not be used.[23]

PROPYLENE GLYCOL

In most cases, the elevated serum osmolality resolves with discontinuation of the drug containing propylene glycol.[5] There is no consensus regarding the use of fomepizole, but if lactic acidosis develops, hemodialysis has been recommended.[5,79]

MONITORING OF PATIENTS

Patients with severe poisoning or hemodynamic instability or those who are receiving ethanol therapy warrant care in an intensive care unit, but patients with less severe poisoning or hemodynamic stability or those who are receiving fomepizole therapy can safely be cared for outside the intensive care unit. Measurements of acid–base variables, electrolytes, renal function, and serum osmolality are necessary to assess the response to therapy. Measurement of serum concentrations of the toxic alcohols would be ideal to monitor treatment; however, obtaining serum concentrations in a timely fashion is not often feasible. In their absence, the serum concentration of the toxic alcohol can be estimated from the osmolal gap.[16,80] Therapy should continue until the serum concentration of ethylene glycol or methanol falls below 20 to 30 mg per deciliter

(ethylene glycol, 3 to 5 mmol per liter; methanol, 6 to 9 mmol per liter).[21,35]

CONCLUSIONS AND FUTURE DIRECTIONS

Methanol, ethylene glycol, and diethylene glycol poisoning can cause severe cellular dysfunction and high mortality if not recognized and treated quickly. Isopropanol frequently causes medical complications but has a lower risk of death. A high anion-gap metabolic acidosis, an increased serum osmolal gap, or both can suggest that one of the toxic alcohols is present in the blood, but these abnormal laboratory results are not always present. One of the poisonings should be strongly suspected in persons with the clinical findings described previously, in all obtunded patients, or in those with an unexplained high osmolal gap, high anion-gap metabolic acidosis, or both. Definitive tests such as high-pressure liquid chromatography are not always available, even in developed countries but especially in undeveloped countries. Therefore, there is an unmet need for tests that are accurate and can be completed rapidly.

Treatment with alcohol dehydrogenase inhibitors and the use of dialysis are effective, but both methods are not always available. Also, there is no consensus on when one or both methods should be used. Despite much progress in our understanding of the pathogenesis of reactions to these toxic alcohols and despite the development of effective treatments, much remains to be done to eliminate the severe clinical disturbances that result from exposure to these substances.

REFERENCES

1. Kraut JA, Kurtz I. Toxic alcohol ingestions: clinical features, diagnosis, and management. Clin J Am Soc Nephrol 2008; 3:208-25.
2. Mahieu P, Hassoun A, Lauwerys R. Predictors of methanol intoxication with unfavourable outcome. Hum Toxicol 1989; 8:135-7.
3. Jacobsen D, McMartin KE. Methanol and ethylene glycol poisonings: mechanism of toxicity, clinical course, diagnosis and treatment. Med Toxicol 1986;1:309-34.
4. Robinson CN, Latimer B, Abreo F, Broussard K, McMartin KE. In-vivo evidence of nephrotoxicity and altered hepatic function in rats following administration of diglycolic acid, a metabolite of diethylene glycol. Clin Toxicol (Phila) 2017;55:196-205.
5. Zar T, Graeber C, Perazella MA. Recognition, treatment, and prevention of propylene glycol toxicity. Semin Dial 2007;20:217-9.
6. Ammar KA, Heckerling PS. Ethylene glycol poisoning with a normal anion gap caused by concurrent ethanol ingestion: importance of the osmolal gap. Am J Kidney Dis 1996;27:130-3.
7. Latus J, Kimmel M, Alscher MD, Braun N. Ethylene glycol poisoning: a rare but life-threatening cause of metabolic acidosis — a single-centre experience. Clin Kidney J 2012;5:120-3.
8. Verelst S, Vermeersch P, Desmet K. Ethylene glycol poisoning presenting with a falsely elevated lactate level. Clin Toxicol (Phila) 2009;47:236-8.

9. Bennett IL Jr, Cary FH, Mitchell GL Jr, Cooper MN. Acute methyl alcohol poisoning: a review based on experiences in an outbreak of 323 cases. Medicine (Baltimore) 1953;32:431-63.
10. 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;27:395-401.
11. Slaughter RJ, Mason RW, Beasley DM, Vale JA, Schep LJ. Isopropanol poisoning. Clin Toxicol (Phila) 2014;52:470-8.
12. Cantarell MC, Fort J, Camps J, Sans M, Piera L, Rodamilans M. Acute intoxication due to topical application of diethylene glycol. Ann Intern Med 1987;106:478-9.
13. Devoti E, Marta E, Belotti E, et al. Diethylene glycol poisoning from transcutaneous absorption. Am J Kidney Dis 2015;65:603-6.
14. Schep LJ, Slaughter RJ, Temple WA, Beasley DM. Diethylene glycol poisoning. Clin Toxicol (Phila) 2009;47:525-35.
15. Kapitein BS, Biesmans RS, van der Sijs HS, de Wildt SS. Propylene glycol-related delirium after esmolol infusion. Ann Pharmacother 2014;48:940-2.
16. Hovda KE, Hunderi OH, Tafjord AB, Dunlop O, Rudberg N, Jacobsen D. Methanol outbreak in Norway 2002-2004: epidemiology, clinical features and prognostic signs. J Intern Med 2005;258:181-90.
17. Karayel F, Turan AA, Sav A, Pakis I, Akyildiz EU, Ersoy G. Methanol intoxication: pathological changes of central ner-

vous system (17 cases). Am J Forensic Med Pathol 2010;31:34-6.
18. Haviv YS, Rubinger D, Zamir E, Safadi R. Pseudo-normal osmolal and anion gaps following simultaneous ethanol and methanol ingestion. Am J Nephrol 1998;18:436-8.
19. Reddy NJ, Sudini M, Lewis LD. Delayed neurological sequelae from ethylene glycol, diethylene glycol and methanol poisonings. Clin Toxicol (Phila) 2010;48:967-73.
20. Alhamad T, Blandon J, Meza AT, Bilbao JE, Hernandez GT. Acute kidney injury with oxalate deposition in a patient with a high anion gap metabolic acidosis and a normal osmolal gap. J Nephropathol 2013;2:139-43.
21. McMartin K. Are calcium oxalate crystals involved in the mechanism of acute renal failure in ethylene glycol poisoning? Clin Toxicol (Phila) 2009;47:859-69.
22. McQuade DJ, Dargan PI, Wood DM. Challenges in the diagnosis of ethylene glycol poisoning. Ann Clin Biochem 2014;51:167-78.
23. Pappas AA, Ackerman BH, Olsen KM, Taylor EH. Isopropanol ingestion: a report of six episodes with isopropanol and acetone serum concentration time data. J Toxicol Clin Toxicol 1991;29:11-21.
24. Sosa NR, Rodriguez GM, Schier JG, Sejvar JJ. Clinical, laboratory, diagnostic, and histopathologic features of diethylene glycol poisoning — Panama, 2006. Ann Emerg Med 2014;64:38-47.
25. Landry GM, Martin S, McMartin KE. Diglycolic acid is the nephrotoxic metabolite in diethylene glycol poisoning induc-

ing necrosis in human proximal tubule cells in vitro. Toxicol Sci 2011;124:35-44.

26. Dorwart WV, Chalmers L. Comparison of methods for calculating serum osmolality form chemical concentrations, and the prognostic value of such calculations. Clin Chem 1975;21:190-4.

27. Kraut JA. Diagnosis of toxic alcohols: limitations of present methods. Clin Toxicol (Phila) 2015;53:589-95.

28. 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.

29. Hovda KE, Hunderi OH, Rudberg N, Froyshov S, Jacobsen D. Anion and osmolal gaps in the diagnosis of methanol poisoning: clinical study in 28 patients. Intensive Care Med 2004;30:1842-6.

30. Ku E, Cheung EL, Khan A, Yu ASL. Anion and osmolal gaps after alcohol intoxication. Am J Kidney Dis 2009;54:385-8.

31. Hovda KE, Froyshov S, Gudmundsdottir H, Rudberg N, Jacobsen D. Fomepizole may change indication for hemodialysis in methanol poisoning: prospective study in seven cases. Clin Nephrol 2005; 64:190-7.

32. Brent J, McMartin K, Phillips S, et al. Fomepizole for the treatment of ethylene glycol poisoning. N Engl J Med 1999;340: 832-8.

33. Kraut JA, Nagami GT. The serum anion gap in the evaluation of acid-base disorders: what are its limitations and can its effectiveness be improved? Clin J Am Soc Nephrol 2013;8:2018-24.

34. Iberti TJ, Leibowitz AB, Papadakos PJ, Fischer EP. Low sensitivity of the anion gap as a screen to detect hyperlactatemia in critically ill patients. Crit Care Med 1990;18:275-7.

35. Roberts DM, Yates C, Megarbane B, et al. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. Crit Care Med 2015;43:461-72.

36. Kraut JA, Xing SX. Approach to the evaluation of a patient with an increased serum osmolal gap and high-anion-gap metabolic acidosis. Am J Kidney Dis 2011; 58:480-4.

37. Rastogi A, Itagaki B, Bajwa M, Kraut JA. Spurious elevation in serum creatinine caused by ingestion of nitromethane: implication for the diagnosis and treatment of methanol intoxication. Am J Kidney Dis 2008;52:181-7.

38. Mullins ME, Hammett-Stabler CA. Intoxication with nitromethane-containing fuels: don't be "fueled" by the creatinine. J Toxicol Clin Toxicol 1998;36:315-20.

39. Guo C, Cenac TA, Li Y, McMartin KE. Calcium oxalate, and not other metabolites, is responsible for the renal toxicity of ethylene glycol. Toxicol Lett 2007;173: 8-16.

40. Hodgman M, Marraffa JM, Wojcik S, Grant W. Serum calcium concentration in ethylene glycol poisoning. J Med Toxicol 2017;13:153-7.

41. Jorens PG, Demey HE, Schepens PJC, et al. Unusual D-lactic acid acidosis from propylene glycol metabolism in overdose. J Toxicol Clin Toxicol 2004;42:163-9.

42. Van Hee P, Neels H, De Doncker M, et al. Analysis of gamma-hydroxybutyric acid, DL-lactic acid, glycolic acid, ethylene glycol and other glycols in body fluids by a direct injection gas chromatography–mass spectrometry assay for wide. Clin Chem Lab Med 2004;42:1341-5.

43. Parsa T, Cunningham SJ, Wall SP, Almo SC, Crain EF. The usefulness of urine fluorescence for suspected antifreeze ingestion in children. Am J Emerg Med 2005;23:787-92.

44. Hack JB, Early J, Brewer KL. An alcohol oxidase dipstick rapidly detects methanol in the serum of mice. Acad Emerg Med 2007;14:1130-4.

45. Hovda KE, Urdal P, Jacobsen D. Increased serum formate in the diagnosis of methanol poisoning. J Anal Toxicol 2005; 29:586-8.

46. Juenke JM, Hardy L, McMillin GA, Horowitz GL. Rapid and specific quantification of ethylene glycol levels: adaptation of a commercial enzymatic assay to automated chemistry analyzers. Am J Clin Pathol 2011;136:318-24.

47. Rooney SL, Ehlers A, Morris C, et al. Use of a rapid ethylene glycol assay: a 4-year retrospective study at an academic medical center. J Med Toxicol 2016;12: 172-9.

48. Shin JM, Sachs G, Kraut JA. Simple diagnostic tests to detect toxic alcohol intoxications. Transl Res 2008;152:194-201.

49. Eder AF, McGrath CM, Dowdy YG, et al. Ethylene glycol poisoning: toxicokinetic and analytical factors affecting laboratory diagnosis. Clin Chem 1998;44:168-77.

50. Casavant MJ, Shah MN, Battels R. Does fluorescent urine indicate antifreeze ingestion by children? Pediatrics 2001; 107:113-4.

51. Barceloux DG, Bond GR, Krenzelok EP, Cooper H, Vale JA. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. J Toxicol Clin Toxicol 2002;40:415-46.

52. Brent J. Fomepizole for ethylene glycol and methanol poisoning. N Engl J Med 2009;360:2216-23.

53. Barceloux DG, Krenzelok EP, Olson K, Watson W. American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning. J Toxicol Clin Toxicol 1999;37:537-60.

54. Abramson S, Singh AK. Treatment of the alcohol intoxications: ethylene glycol, methanol and isopropanol. Curr Opin Nephrol Hypertens 2000;9:695-701.

55. Zakharov S, Pelclova D, Navratil T, et al. Fomepizole versus ethanol in the treatment of acute methanol poisoning: comparison of clinical effectiveness in a mass poisoning outbreak. Clin Toxicol (Phila) 2015;53:797-806.

56. Jacobsen D, Webb R, Collins TD, McMartin KE. Methanol and formate kinetics in late diagnosed methanol intoxication. Med Toxicol Adverse Drug Exp 1988;3:418-23.

57. Wacker WE, Haynes H, Druyan R, Fisher W, Coleman JE. Treatment of ethylene glycol poisoning with ethyl alcohol. JAMA 1965;194:1231-3.

58. McMartin K, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohols that form toxic metabolites. Br J Clin Pharmacol 2016;81:505-15.

59. 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.

60. Antizol (fomepizole): highlights of prescribing information. Montreal: Paladin Labs, 2009.

61. Mowry JB, Spyker DA, Brooks DE, Zimmerman A, Schauben JL. 2015 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 33rd Annual Report. Clin Toxicol (Phila) 2016;54:924-1109.

62. Thanacoody RH, Gilfillan C, Bradberry SM, et al. Management of poisoning with ethylene glycol and methanol in the UK: a prospective study conducted by the National Poisons Information Service (NPIS). Clin Toxicol (Phila) 2016;54:134-40.

63. Rietjens SJ, de Lange DW, Meulenbelt J. Ethylene glycol or methanol intoxication: which antidote should be used, fomepizole or ethanol? Neth J Med 2014;72:73-9.

64. Zakharov S, Pelclova D, Urban P, et al. Use of out-of-hospital ethanol administration to improve outcome in mass methanol outbreaks. Ann Emerg Med 2016;68: 52-61.

65. WHO model list of essential medicines: 18th list. Geneva: World Health Organization, 2013.

66. Lepik KJ, Levy AR, Sobolev BG, et al. 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.e10.

67. Anseeuw K, Sabbe MB, Legrand A. Methanol poisoning: the duality between 'fast and cheap' and 'slow and expensive.' Eur J Emerg Med 2008;15:107-9.

68. Zakharov S, Pelclova D, Navratil T, et al. Intermittent hemodialysis is superior to continuous veno-venous hemodialysis/hemodiafiltration to eliminate methanol and formate during treatment for methanol poisoning. Kidney Int 2014;86:199-207.

69. Peces R, Fernández R, Peces C, et al.

Effectiveness of pre-emptive hemodialysis with high-flux membranes for the treatment of life-threatening alcohol poisoning. Nefrologia 2008;28:413-8.

70. Borron SW, Mégarbane B, Baud FJ. Fomepizole in treatment of uncomplicated ethylene glycol poisoning. Lancet 1999; 354:831.

71. Mégarbane B, Borron SW, Trout H, et al. Treatment of acute methanol poisoning. Intensive Care Med 2001;27:1370-8.

72. Mégarbane B, Borron SW, Baud FJ. Current recommendations for treatment of severe toxic alcohol poisonings. Intensive Care Med 2005;31:189-95.

73. Hovda KE, Mundal H, Urdal P, McMartin K, Jacobsen D. Extremely slow formate elimination in severe methanol poisoning: a fatal case report. Clin Toxicol (Phila) 2007;45:516-21.

74. Wiles D, Tzeng J, Russell J, Casavant MJ. Comment on treatment methods for ethylene glycol intoxication. Neth J Med 2014;72:383-4.

75. Brent J. Fomepizole for the treatment of pediatric ethylene and diethylene glycol, butoxyethanol, and methanol poisonings. Clin Toxicol (Phila) 2010;48:401-6.

76. 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;60:2021-4.

77. Borron SW, Baud FJ, Garnier R. Intravenous 4-methylpyrazole as an antidote for diethylene glycol and triethylene glycol poisoning: a case report. Vet Hum Toxicol 1997;39:26-8.

78. Brophy PD, Tenenbein M, Gardner J, Bunchman TE, Smoyer WE. Childhood diethylene glycol poisoning treated with alcohol dehydrogenase inhibitor fomepizole and hemodialysis. Am J Kidney Dis 2000;35:958-62.

79. Pillai U, Hothi JC, Bhat ZY. Severe propylene glycol toxicity secondary to use of anti-epileptics. Am J Ther 2014;21(4): e106-e109.

80. Hunderi OH, Hovda KE, Jacobsen D. Use of the osmolal gap to guide the start and duration of dialysis in methanol poisoning. Scand J Urol Nephrol 2006;40: 70-4.

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