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Toxic Alcohols: Not Always A Clear-Cut Diagnosis

A 45-year-old woman with a history of depression is brought to the hospital by her family 2 to 3 hours after an intentional ingestion of windshield-washer fluid. Her family wants to know if she is going to be okay and when she can go home. Her initial triage vital signs include a heart rate of 88 beats per minute, a respiratory rate of 14 breaths per minute, and pulse oximetry of 100% on room air. Upon examination, she appears lethargic but neurologically intact and is ambulating without difficulty. As you order a serum osmolality, electrolytes, and serum ethanol, methanol, and ethylene glycol concentrations, you realize that you haven't taken care of a patient with a toxic alcohol ingestion in years. You wonder if you should begin treatment right away, whether hemodialysis is indicated, and how to interpret the labs once they are reported. A call is placed to the local poison control center.

The toxic alcohols that clinicians commonly encounter are ethylene glycol, methanol, and isopropanol. Adults ingest these either for suicidal intent or to achieve inebriation, since these substances are readily available and cheaper than alcohol. Definitive diagnosis of toxic alcohol poisoning requires measurement of a serum toxic alcohol concentration or detection in the serum of toxic alcohol metabolites. These required assays are not routinely performed in most hospital laboratories, making the diagnostic process a challenge. For this reason, clinicians often rely on osmolar and anion gap calculations to guide diagnosis and treatment, but published literature describes many pitfalls in relying solely on these values. Prompt diagnosis and treatment of toxic alcohol ingestions is critical, since

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Authors

Nilam Patil, DO
Emergency Medicine Physician, Saint Joseph's Regional Medical Center, Paterson, NJ

Melisa W. Lai Becker, MD, FACEP, FAAEM
Emergency Physician and Director, Division of Medical Toxicology, Cambridge Health Alliance, Cambridge, MA; Instructor in Medicine (Emergency Medicine), Harvard Medical School, Boston, MA

Michael Ganetskty, MD, FACEP
Clinical Director, Division of Medical Toxicology, Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA; Clinical Instructor, Harvard Medical School, Boston, MA

Peer Reviewers

Beth Y. Ginsburg, MD
Attending Physician, Department of Emergency Medicine, Division of Medical Toxicology, Elmhurst Hospital Center, Elmhurst, NY; Assistant Professor, Department of Emergency Medicine, Mount Sinai School of Medicine, New York, NY

Stephanie Hernandez, MD
Department of Emergency Medicine, Division of Medical Toxicology, Mount Sinai Medical Center; Assistant Professor, Mount Sinai School of Medicine, New York, NY

CME Objectives

Upon completion of this article, you should be able to:

1. Describe the pathophysiology and possible complications of methanol, ethylene glycol, and isopropanol ingestion.
2. Distinguish key physical examination findings based on the toxic alcohol ingested.
3. Know when to begin treatment with ADH inhibitors and/or hemodialysis.

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end-organ damage may be devastating, irreversible, and potentially fatal.

The American Association of Poison Control Centers' (AAPCC) 2008 Annual Report of the National Poisoning Database System (NPDS) cited 6395 exposures to ethylene glycol, 2272 exposures to methanol, and 17,220 exposures to isopropanol. Ethylene glycol exposures were a factor in 22 reported deaths and methanol in 9 deaths. None of the reported fatalities in 2008 resulted from pure isopropanol exposures.[1] Because not all states require that exposures or toxic alcohol ingestions be reported to poison control centers, these totals probably underestimate the actual number of toxic alcohol poisonings.

This issue of *Emergency Medicine Practice* focuses on the diagnostic approach to toxic alcohol poisoning, as well as the pathophysiology, management, and treatment specific to each of the toxic alcohols.

Critical Appraisal Of The Literature

A search of PubMed, Ovid MEDLINE®, the National Guideline Clearing House, and Cochrane Database of Systematic Reviews was carried out using the following combination of key words: *toxic alcohol, ethylene glycol, methanol, isopropyl alcohol, isopropanol, ethanol, fomepizole, 4-methylpyrazole, hemodialysis, AAPCC, osmolar gap,* and *anion gap.* This literature search focused on adults, children, and pregnant patients. Approximately 80 articles were found and served as the foundation of this evidence-based review article.

The literature regarding management of toxic alcohol ingestions is limited in many ways. First and foremost, current guidelines set forth by the American Academy of Clinical Toxicology (AACT) are based on the Methylpyrazole for Toxic Alcohols (META) trials, which were prospective studies.[2,3] In the META trial, only 19 patients were recruited for the ethylene glycol group and only 11 for the methanol group, and neither had a control group. In addition, no large prospective studies support these guidelines regarding the initiation of alcohol dehydrogenase (ADH) blockade and the end points of treatment. Finally, the AACT guidelines regarding when to begin treatment in the absence of a toxic alcohol concentration are based on anecdotal data.[4,5] Unfortunately, because of inherent difficulties in performing randomized, prospective trials involving poisoned patients, this is a common limitation of all the literature on toxicology management.

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Etiology And Pathophysiology

Isopropanol is the most commonly abused toxic alcohol because it is inebriating, readily available, and cheap; it is the least toxic in comparison to methanol and ethylene glycol. The critical distinction is that, unlike methanol and ethylene glycol, isopropanol does not cause metabolic acidosis. In each case, the parent compounds cause intoxication, but serious toxicity is caused by their metabolites. In order to better understand the treatment modalities for each of these agents, the pathophysiology and clinical effects of each toxic alcohol will be discussed separately.

Methanol

Methanol (methyl alcohol) is commonly found in windshield-wiper fluid and de-icing products. In addition, gas line antifreeze, gelled chafing fuel, paint removers, shoe dyes, and embalming fluid may contain varying amounts of methanol. The ingestion of "moonshine" contaminated with methanol, resulting in blindness, has been reported to have occurred several times in history.[6] Methanol toxicity is most commonly reported to be from ingestion, but inhalational and dermal exposures have also been reported.[7,8]

Methanol's pharmacokinetics are well-described and follow Michaelis–Menten kinetics. **(See Table 1.)** At low concentrations (10 mg/dL), methanol follows first-order kinetics and has a half-life

of 2.5 to 3 hours. At higher concentrations (100-200 mg/dL), methanol metabolism follows zero-order kinetics and has no half-life. With zero-order metabolism, the rate at which methanol is eliminated is 8.5 to 9 mg/dL/h.[9-11] When the patient is treated with fomepizole, methanol exhibits first-order kinetics and has a longer half-life (54 hours) than ethylene glycol.[2,12]

Methanol is hepatically metabolized by ADH to formaldehyde and then converted to formic acid by aldehyde dehydrogenase (ALDH). **(See Figure 1, page 4.)** Formic acid can be metabolized to water and carbon dioxide in the presence of folic acid; this minor metabolic pathway is dependent on folate stores. Acidosis occurs secondary to formic acid buildup and lactic acidosis. Formic acid is thought to be responsible for the optic and retinal toxicity seen in methanol poisoning.[13,14] In addition, formic acid inhibits cytochrome oxidase c in the mitochondria and shifts cellular metabolism from aerobic to anaerobic glycolysis, resulting in a lactic acidosis. Acidosis contributes to formate crossing the blood–brain barrier and results in the neurologic effects seen in methanol intoxication.[15,16] A small percentage (2.5%) of nonmetabolized methanol is excreted through the respiratory system.

Ethylene Glycol

Ethylene glycol, commonly present in radiator antifreeze, is also found in degreasing agents, foam stabilizers, and metal cleaners. It was initially synthesized in 1859 by Charles-Adolphe Wurtz, a French chemist, and was used as an engine coolant as early as World War I. It is an odorless, colorless, and sweet-tasting liquid. Peak concentrations of ethylene glycol have been reported 1 to 4 hours after ingestion. Approximately 80% undergoes hepatic metabolism and 20% is excreted unchanged in the urine. Ethylene glycol's elimination depends on renal function. When renal function is normal, it follows first-order metabolism and has a half-life of 8.5 hours.[17] In patients treated with fomepizole, it continues to follow first-order kinetics but has a half-life of 14 to 17 hours in patients with normal renal function and 49 hours in those with impaired renal function.[17-19] **(See discussion of fomepizole, page 8.)**

Similar to methanol, it is the metabolites of ethylene glycol that are responsible for toxicity rather than the parent compound itself. Ethylene glycol is hepatically oxidized to glycoaldehyde via ADH in the presence of oxidized nicotinamide adenine dinucleotide (NAD+). Once NAD+ is depleted, the citric acid cycle is inhibited and anaerobic metabolism is favored, causing the formation of lactate from pyruvate. Glycoaldehyde is converted to glycolic acid by ALDH. Glyoxylic acid formed from glycolic acid is then metabolized to oxalic acid. Oxalic acid combines with serum calcium to form calcium oxalate; these crystals deposit in the renal tubules and cause nephrotoxicity. The presence in the urine of monohydrate calcium oxalate crystals has been used to rapidly test for ethylene glycol toxicity; however, these crystals are not reliable indicators since they are often confused with hippuric acid crystals and do not always show up in the urine of patients with subsequently proven ethylene glycol ingestion.[3,20,21]

Thiamine and pyridoxine are cofactors for the production of nontoxic metabolites. In the presence of thiamine, glycolic acid is metabolized to alpha-hydroxy-beta-ketoadipate, while pyridoxine allows for the metabolism of glyoxylic acid to glycine.

Table 1. Toxic Alcohol Pharmacokinetics

Toxic Alcohol	Volume of Distribution (L/kg)	Rate of Elimination		
		No Treatment	Treatment with Ethanol or Fomepizole	Treatment with Hemodialysis (at 225 mL/min)
Methanol	0.6-0.7	• Low serum concentration: First-order kinetics: Half-life = 2.5-3.0 h • High serum concentration: Zero-order kinetics: 8.5-9.0 mg/dL/h	First-order kinetics: Half-life = 54 h	First-order kinetics: Half-life = 2.5 h
Ethylene glycol	0.5-0.8	First-order kinetics: Half-life = 8.5 h with normal creatinine clearance	First-order kinetics: Half-life = 14-17 h with normal creatinine clearance, 49 h with decreased renal function	First-order kinetics: Half-life = 2.5 h
Isopropanol	0.6-0.7	First-order kinetics: Half-life = 2.5-3.5 h	NA	NA

Abbreviations: h, hours; NA, not applicable.

Isopropanol

Isopropanol is the most common toxic alcohol exposure in the United States.[1] It is commonly found in rubbing alcohol and other antiseptic products such as hand sanitizers. Unlike methanol and ethylene glycol, its metabolism does not result in an anion gap acidosis and its toxicity is much milder. Similar to methanol and ethylene glycol, it is hepatically metabolized by ADH. Its metabolite is acetone, which is a ketone. Because acetone does not undergo metabolism through ALDH, isopropanol is commonly known as the toxic alcohol that causes ketosis without acidosis. Peak serum concentrations of isopropanol occur within 30 to 60 minutes of ingestion; peak serum acetone levels occur at 4 hours.[22,23] Several case reports and studies confirm that isopropanol's half-life is less than that of acetone (2.5-16.2 h vs 7.6-26 h).[24,25]

Differential Diagnosis

Toxic alcohols should be part of the differential diagnosis of any patient with an elevated anion or osmolar gap, as well as any inebriated patient with a nondetectable serum ethanol concentration. **(See Table 2.)**

Prehospital Treatment

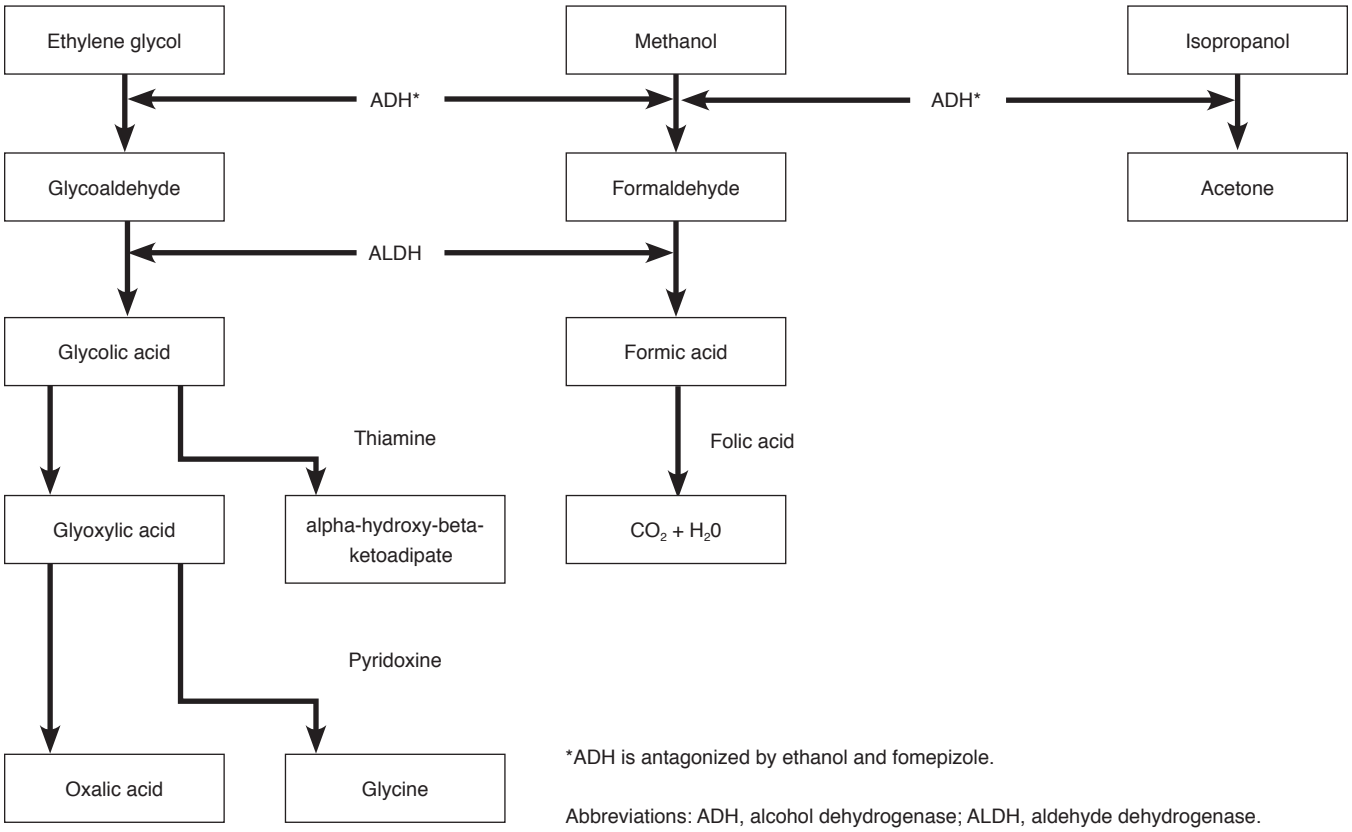
Prehospital management includes recognition of the life-threatening sequelae that can occur secondary to toxic alcohol ingestion, such as respiratory distress and hemodynamic instability from severe metabolic acidosis, traumatic injuries from intoxication, and hypoglycemia from concomitant ethanol ingestion. The key to efficiently diagnosing any type of toxic ingestion includes careful inspection of the scene and the questioning of family members and any other bystanders, if present, to identify any types of agents that the patient may have ingested. In addition, emergency medical services (EMS) personnel can often provide crucial historical information if they find empty containers at the scene. Due to associated QT prolongation from hypocalcemia related to ethylene glycol ingestion, EMS may be instructed to administer calcium carbonate to patients with ventricular dysrhythmias.

Emergency Department Evaluation

Methanol

Methanol toxicity commonly affects the neurological, ophthalmological, and gastrointestinal systems. Of the 3 toxic alcohols, methanol is the least ine-

Figure 1. Toxic Alcohol Metabolism



*ADH is antagonized by ethanol and fomepizole.

Abbreviations: ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase.

briating and does not produce the same degree of intoxication as ingestion of similar concentrations of isopropanol. Within the first 24 hours, central nervous system (CNS) depression, euphoria, and inebriation occur. This is followed by a latent period (between 6 and 30 hours) during which methanol is metabolized to formic acid, which ultimately leads to systemic effects.

Ophthalmologic symptoms can range from blurry vision, decreased visual acuity, and photophobia to blindness or the classic "snowstorm" vision. Initially, visual fields are not affected and patients may have a central scotoma (blind spot). These symptoms are followed by hyperemia of the optic nerve and edema of the disc margin and retina. If unrecognized and not appropriately treated, these changes will result in permanent blindness, absent papillary response, and permanent optic nerve atrophy.[4,12,22] During methanol ingestion epidemics, it has been reported that 25% to 33% of patients had permanent visual sequelae.[4,27]

Severe methanol intoxication can cause parkinsonian features, such as a masked facies, tremors, and muscle rigidity. Other neurologic symptoms reported in the literature include transverse myelitis, pseudobulbar palsy, cognitive deficits, and basal ganglia hemorrhages. Methanol toxicity causes gastrointestinal symptoms such as abdominal pain with or without evidence of pancreatitis and/or hepatotoxicity.[4,16,27-30]

Ethylene Glycol

Although several sources discuss the 3 stages of ethylene glycol toxicity, the emergency clinician should realize that not all patients will exhibit them. These stages are outlined in **Table 3.**

In severe cases, delayed cranial nerve deficits may occur 5 to 20 days after ingestion and can involve cranial nerves II, V, and VII to XII. Bilateral facial neuropathy has commonly been reported.[5,32]

Table 2. Differential Diagnosis For High Anion And/Or Osmolar Gap

Elevated Anion Gap	Elevated Osmolar Gap
• Methanol, metformin	• Acetone
• Uremia	• Ethanol, ethylene glycol, methanol
• Diabetic ketoacidosis	• Mannitol
• Alcoholic ketoacidosis	• Osmotic contrast dyes
• Paraldehyde, phenformin	• Propylene glycol
• Isoniazid, iron	• Isopropanol
• Lactic acidosis (cyanide, hydrogen sulfide, sodium azide)	
• Ethylene glycol	
• Salicylates, theophylline	
• Caffeine, seizures	
• Benzyl alcohol, acetaminophen	

Isopropanol

Isopropanol intoxication is primarily associated with gastrointestinal and neurologic effects. The emergency clinician may initially notice that the patient's breath has a fruity odor due to ketosis. Gastrointestinal signs include abdominal pain, nausea, vomiting, and hematemesis. Although hemorrhagic gastritis was initially thought to be due to direct irritation of the gastric mucosa by isopropanol itself, Dyer et al reported a case due to dermal absorption of isopropanol.[33] Neurologic manifestations include CNS depression (often more profound than that seen in ethanol toxicity in relation to comparable serum alcohol concentrations), nystagmus, ataxia, confusion, and coma. Acute renal failure, rhabdomyolysis, and myoglobinuria may occur secondary to prolonged "down time" prior to resuscitation and treatment.

Diagnostic Studies

Serum Chemistry Values And Serum Osmolality

Because most hospital laboratories cannot rapidly measure serum concentrations of toxic alcohols, the emergency clinician must rely on the basic serum chemistry profile and osmolality to implicate toxic alcohol ingestion. Serum electrolytes will allow the calculation of anion and osmolar gaps. To properly interpret these gaps, the following laboratory tests should be ordered at the same time and from the same blood sample: electrolytes, osmolality, ethanol level, and toxic alcohol concentrations. Arterial and venous blood gases are also useful for assessing the degree of intoxication and should be measured concurrent with other blood studies.

Table 3. Clinical Stages In Ethylene Glycol Toxicity[5,31]

Stage	Symptoms
1: Neurological (0.5-12 hours)	• Initial: intoxication, euphoria • After 4 to 12 hours, if ingestion is severe: CNS depression, seizures, meningismus, nystagmus, ataxia, ocular external muscle paralysis, hyperreflexia, muscle spasms, hypocalcemia
2: Cardiopulmonary (12-24 hours)	• Tachycardia, mild hypertension, hyperventilation (secondary to metabolic acidosis) • Acute respiratory distress syndrome, congestive heart failure, cardiac dysrhythmia (secondary to hypocalcemia and QTc prolongation)
3. Renal (24-72 hours)	• Oliguria, flank pain, acute renal failure • Renal failure (typically reversible) • Bone marrow suppression

Abbreviation: CNS, central nervous system.

Osmolarity indicates the total number of particles in solution per liter, while osmolality indicates the number of particles per kilogram of solvent. Serum osmolality should be measured by the freezing-point depression method rather than by the vapor-pressure method, since the latter technique will underestimate the concentrations of volatile alcohols (methanol, ethylene glycol, and isopropanol).[34,35] The following equations are used to determine the serum osmolality (Osmm) and osmolar gap (Osm_g) by using the calculated serum osmolarity (Osmc)[1]:

Equation 1: Determining Serum Osmolarity Calculated (Osmc)

$$Osmc = [2 \times (sodium)] + (BUN/2.8) + (glucose/18) + (ethanol/4.6)$$

Abbreviations: BUN, blood urea nitrogen; Osmc, calculated serum osmolarity.

Equation 2: Determining Osmolar Gap (Osm_g)

$$Osm_g = Osmm - Osmc$$

Abbreviations: Osmc, calculated serum osmolarity; Osm_g, osmolar gap; Osmm, measured serum osmolality.

The difference between the measured osmolality and calculated osmolarity is the osmolar gap. The osmolar gap typically ranges between −14 and +10 mOsm. Since the osmolar gap varies from person to person, its interpretation can often prove challenging.[36,37] There are no robust data on when to suspect toxic alcohol ingestion on the basis of the osmolar gap. Hovda et al proposed that an osmolar gap of greater than 25 mOsm in the setting of acidosis should suggest toxic alcohol ingestion.[38] Toxic alcohol concentrations (Equation 3) can be estimated based on the osmolar gap as calculated by Equation 2.

Equation 3: Estimating Toxic Alcohol Concentration

$$[Toxic\ alcohol\ (in\ mg/dL)] = Conversion\ factor^* \times Osm_g$$

*See Table 4 for conversion factors

The conversion factor **(see Table 4)** is based on the molecular weight of each substance.

The parent compound accounts for the osmolar gap. As methanol and ethylene glycol are metabolized to formic acid and glycolic acid, respectively, a metabolic acidosis develops, thus increasing the anion gap. These toxic intermediate compounds correlate with the degree of acidosis and with elevation of the anion gap.[38-40]

Table 4. Conversion Factors

Toxic Alcohol	Conversion Factor
Methanol	3.2
Ethanol	4.6
Isopropanol	6.0
Ethylene glycol	6.2

Anion Gap

The anion gap provides an estimate of unmeasured anions and is calculated as follows:

Equation 4: Estimating Anion Gap

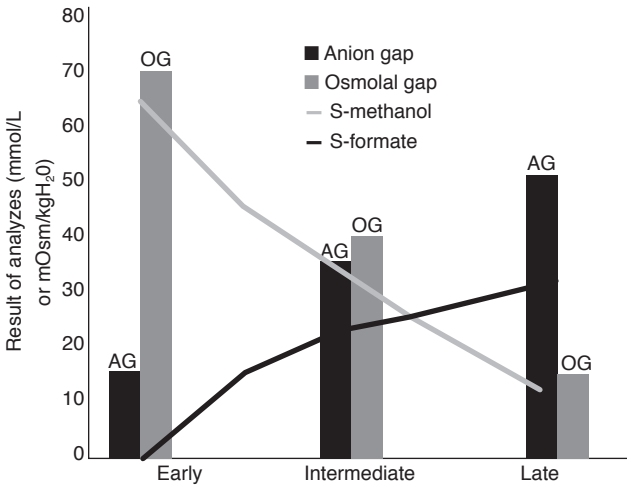
$$Anion\ gap = (sodium) - (chloride + bicarbonate)$$

What is considered to be a normal anion gap will vary among laboratories, but in most cases it is approximately 8 to 12 mmol/L. **Figure 2** shows the reciprocal relationship between the osmolar gap and the anion gap. Both of these gaps need to be interpreted in relation to the time of alcohol ingestion; early after ingestion, the anion gap may be normal, whereas late after ingestion, the osmolar gap may be normal.

Detection Of Metabolic Acidosis

In methanol and ethylene glycol toxicity, an arterial blood gas value may reveal a metabolic acidosis with a compensatory respiratory alkalosis. Isopropanol toxicity does not typically cause a metabolic acidosis unless it is due to hypoxia or hypotension. Metabolic acidosis in ethylene glycol or methanol intoxication is primarily due to their toxic metabo-

Figure 2. Relationship Between Osmolar And Anion Gaps[38]



Abbreviations: AG, anion gap; OG, osmolar gap.

Reproduced with kind permission from Springer Science+Business Media: *Intensive Care Medicine.* Anion and osmolal gaps in the diagnosis of methanol poisoning: clinical study in 28 patients. Volume 44, January 2004, pages 1842-1846, Hovda KE.

lites. In addition, lactic acid generated from anaerobic metabolism and hypotension (in very ill patients) contributes to the acidosis. A falsely elevated lactate level in ethylene glycol toxicity may occur on some assays, owing to the similarity in the structures of lactate and glycolic acid.[41,42]

Other Common Laboratory Abnormalities

Hypocalcemia and renal failure can be seen in patients with ethylene glycol toxicity. Oxalic acid chelates serum calcium to form calcium oxalate crystals that are deposited in the proximal renal tubule, resulting in nephrotoxicity.[43,44] **(See Table 5.)** Hypocalcemia can also cause QTc prolongation and lead to ventricular dysrhythmias. Falsely elevated creatinine can be seen in isopropanol intoxication. Acetone is known to interfere with colorimetric creatinine assay, specifically ones that use the Jaffe alkaline picrate reaction. The clinician should be aware that blood urea nitrogen (BUN) remains normal despite an elevated creatinine.[45-47]

Toxic Alcohol Concentrations

The definitive diagnosis for any toxic alcohol ingestion can be determined by measurement of the serum concentration for that specific alcohol. Turnaround and reporting times for results of these tests are typically prolonged because most hospital laboratories do not have the dedicated gas chromatography and mass spectrometry equipment necessary for this test. Since several hours may pass before a serum concentration can be obtained, the potential for increased morbidity and mortality is great if treatment decisions are delayed pending these results. In addition, because of the high volatility of these substances, toxic alcohol concentrations may be falsely low if the collecting tubes are not airtight.[48,49]

Urine Tests

Many sources discuss urinary microscopy and Wood's lamp fluorescence as useful diagnostic tests for ethylene glycol toxicity. These tests should be used as adjuncts; decisions to begin treatment should not be based solely on them. Calcium oxalate crystals can be detected in the urine within 4 to 8 hours and are excreted up to 40 hours after ingestion.[50] As seen in **Figure 3**, 2 forms of calcium oxalate crystals exist: monohydrate crystals, which are shaped like needles; and dihydrate crystals, which are shaped like envelopes. Jacobsen et al found that dihydrate crystals are seen within 5 hours after ingestion and monohydrate crystals within 7 hours after ingestion.[50] Monohydrate calcium oxalate stones in the urine were initially thought to be a reliable diagnostic test to rapidly help in diagnosing ethylene glycol toxicity; however, they are often confused with hippuric acid crystals and therefore are not reliable.[20,21] Crystals may be absent early in the course of the ingestion and do not reliably show up in the urine.[3]

Using Wood's light to examine the urine has been used as an adjunctive test for detecting ethylene glycol. Sodium fluorescein, a component of many brands of antifreeze, is used by mechanics to detect coolant leaks. The Wood's lamp, a source of ultraviolet energy, excites sodium fluorescein and produces visible urine fluorescence. Many studies have shown that the finding of fluorescence with Wood's lamp is neither specific nor sensitive, since the confirmation of actual fluorescence may be operator-dependent and other medications and food products can also cause the urine to fluoresce.[51,52]

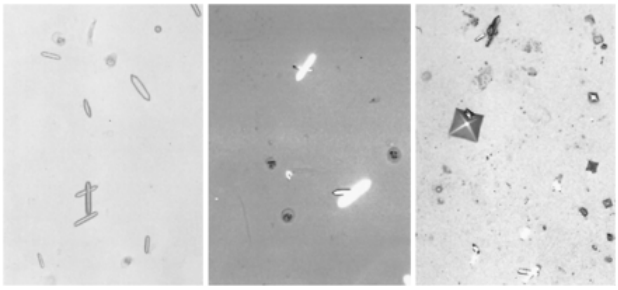
Imaging

Brain imaging may be useful in diagnosing possible methanol and ethylene glycol exposures. Following methanol exposure, findings on computed tomography (CT) of the brain — particularly within the first 24 hours — are usually normal. The most common finding is bilateral putamen necrosis, followed by necrosis of the caudate nucleus. Basal ganglia hemorrhages are also a common finding. Findings on magnetic resonance imaging (MRI) can include atrophy of the optic chiasma, prechiasmatic optic lesions,

Table 5. Common Laboratory Abnormalities

Toxic Alcohol	Anion Gap	Osmolar Gap	Other Laboratory Results
Ethylene glycol	+ (late)	+ (early)	Hypocalcemia, renal failure, low bicarbonate
Methanol	+ (late)	+ (early)	Low bicarbonate
Isopropanol	–	+	Falsely elevated creatinine

Figure 3. Calcium Oxalate Crystals



Left and center images show calcium oxalate crystals in the "needle" shape; the right image shows the crystals in the "envelope" shape.

occipital lesions, cerebral edema, and lesions of the subcortical white matter.[4,53-56] Because patients with methanol intoxication are at increased risk for basal ganglia hemorrhages, it is common practice to avoid heparinization of the circuit during hemodialysis.

Ethylene glycol exposures can cause cerebral edema, with compression of the supratentorial ventricular system. Abnormalities identified on CT may include reversible hypodensities in the thalamus, basal ganglia, pons, and temporal lobe that are consistent with meningoencephalitides.[5,57] Although cerebral edema often appears ominous on CT imaging, it can resolve rapidly upon treatment of the toxicity. Hemorrhagic necrosis of the putamen, globus pallidus, and thalamus have also been seen on MRI but are not very common.[29,57,58]

Treatment

Initial treatment in alcohol toxicity consists of addressing airway, breathing, and circulation issues and stabilizing patients with life-threatening events.

Gastrointestinal Decontamination

Methods for gastrointestinal decontamination after an ingestion of toxic alcohols have not been well studied. According to the AACT guidelines, toxic alcohols are rapidly absorbed, so such decontamination is of little value.[4,5] Activated charcoal should be administered if co-ingestions are suspected, provided that the patient has an intact airway. Anecdotal evidence supports the use of gastric aspiration if large amounts of alcohol have been ingested and the patient can be treated very quickly after the ingestion.[59] For more information on current guidelines on gastrointestinal decontamination, see the August 2010 issue of *EM Practice Guidelines Update,* "Current Guidelines For Gastrointestinal Decontamination In The Emergency Department."

Antidotes

Treatment with fomepizole or ethanol will inhibit the action of ADH and thus stop the conversion of the parent compounds, methanol and ethylene glycol, to their respective toxic metabolites.[2,3] **(See Figure 1, page 4.)** Treatment should begin as soon as possible, since this antidotal therapy is not helpful once the parent compound has already been metabolized. According to the AACT guidelines, fomepizole should be the first-line therapy.[4,5] Ethanol should be administered only if fomepizole is not available. Either treatment should begin when methanol or ethylene glycol concentrations exceed 20 mg/dL and should be continued until concentrations drop below this level. Note that ADH inhibitors are not used for isopropanol toxicity **(see section on Isopropanol Intoxication, page 12).** See **Table 6** for indications for beginning antidotal therapy.

Ethanol

Since the 1940s, ethanol has been used as an antidote for ethylene glycol and methanol despite never being approved by the U.S. Food and Drug Administration (FDA) for this indication.[60] Based on in vitro studies, ethanol's affinity for ADH is greater than that of ethylene glycol (by 67-fold) or of methanol (by 15-fold).[48] The intravenous (IV) loading dose is 0.6 to 0.8 g/kg of body weight in a 10% ethanol solution in dextrose in water (D5W) (volume/volume), followed by a maintenance dose of 80 to 130 mg/kg/h IV. Higher maintenance doses are used in patients with chronic alcoholism or during hemodialysis. If IV ethanol is not available, oral ethanol can be used. The oral loading dose is 0.8 g/kg in a 20% ethanol solution diluted in orange juice. The oral maintenance dose is 80 mg/kg/h and should be increased to maintain a serum ethanol concentration of 100 to 150 mg/dL. Chronic alcoholics should be placed on an oral maintenance dose of 150 mg/kg/h, while patients on hemodialysis should be placed on a oral maintenance dose of 250 mg/kg/h.

Standard recommendations are to maintain serum ethanol concentrations at 100 mg/dL; however, several cases suggest that lower serum levels are just as effective.[61-65] Side effects of ethanol treatment include hypoglycemia, CNS depression, intoxication, thrombophlebitis, and hypotension.[4,5,66] Cobaugh et al found that 90% of their patients had at least 1 episode of hypoglycemia (glucose less than 80 mg/dL) while receiving IV or oral ethanol.[66] In a retrospective study, Hantson et al studied 26 patients with ethylene glycol and methanol intoxication who were receiving ethanol infusions. They found that the infusion rate had to be changed an average of 12 times, most likely due to the fact that ethanol induces its own metabolism.[67] Due to these potential side effects, patients receiving an ethanol infusion are typically admitted to the intensive care unit for close monitoring.

Fomepizole

When compared with ethanol, fomepizole (4-methylpyrazole) has 8000 times the affinity for ADH.[17,18] The FDA approved fomepizole as treatment for ethylene glycol toxicity in 1997 and for methanol

Table 6. Indications To Start Antidotal Therapy For Methanol Or Ethylene Glycol Toxicity[4]

- Serum concentration of methanol or ethylene glycol > 20 mg/dL
- History or suspicion of methanol or ethylene glycol ingestion and 2 of the following:
  - Osmolal gap > 10 mOsm
  - Arterial pH < 7.3
  - Serum bicarbonate < 20 mmol/L
  - Presence of urinary oxalate crystals

toxicity in 2000. The evidence in support of fomepizole therapy comes from the 2 Methylpyrazole for Toxic Alcohols (META) trials that demonstrated its efficacy.[2,3] Its advantages over ethanol include easier dosing, more predictable kinetics, and fewer side effects.[11] Its primary and significant disadvantage is its high cost (about $1,000 per 1.0-g vial).

Lepik et al compared the adverse drug events associated with ethanol versus fomepizole therapy over a 10-year period.[11] This cohort study included 172 patients, 140 treated primarily with ethanol and 32 with fomepizole. Over half the ethanol-treated patients had an adverse drug event due to the therapy, in contrast to 12% of those treated with fomepizole. The predominant adverse effect was CNS toxicity (48% in the ethanol group vs 2% in the fomepizole group). Asymptomatic hypoglycemia (serum glucose 49-68 mg/dL) was found in 5 of the ethanol-treated patients but in none of the fomepizole-treated patients. This study reinforced the well-accepted safety profile of fomepizole compared with ethanol.

The current IV dosing regimen for fomepizole, based on preclinical studies and recommended by the AACT, is outlined in **Table 7**. After 48 hours, fomepizole induces its own metabolism, so the dose must be increased to 15 mg/kg. Its low volume of distribution (0.6-1.0 L/kg) and low degree of protein binding makes it amenable to patients receiving hemodialysis; therefore, it should be administered every 4 hours during dialysis treatments. **(See Table 8.)** Burning at the infusion site is the most common side effect, so diluting fomepizole in 100 mL of 0.9% normal saline or D5W with infusion over 30 minutes is recommended. Fomepizole is contraindicated in patients who are allergic to pyrazole derivatives.

Table 7. Fomepizole Dosing (Intravenous)[4,5]

Loading Dose	• 15 mg/kg
Maintenance Dose	• 10 mg/kg every 12 h (x 4 doses), then 15 mg/kg every 12 h

Table 8. Fomepizole Dosing In Patients On Hemodialysis

At the beginning of hemodialysis
- If < 6 hours since last dose, do not administer dose
- If ≥ 6 or more hours since last dose, administer next scheduled dose

During hemodialysis
- Administer dose every 4 hours

When hemodialysis is completed

If the time between the last dose and the end of hemodialysis is:
- < 1 hour: do not administer dose at the end of hemodialysis
- 1-3 hours: administer half of next scheduled dose
- > 3 hours: administer next scheduled dose

Maintenance dosing off hemodialysis
- Give next scheduled dose 12 hours from the last dose administered

Sodium Bicarbonate

With acidosis, the toxic metabolites penetrate end-organ tissues, and the severity of the acidosis correlates with overall outcome. Prospective trials have not explored how to administer sodium bicarbonate; however, according to AACT guidelines, an arterial pH less than 7.3 should be treated with sodium bicarbonate administration to keep the pH between 7.35 and 7.45.[4,5] The authors recommend adding 150 mEq of sodium bicarbonate to 1 L of D5W and infusing this solution at a rate of 150 to 200 mL/h in adults or 1.5 to 2 times the maintenance dose in children. When correcting acidosis in the setting of ethylene glycol toxicity, hypocalcemia may be exacerbated. In addition, hypokalemia may occur and should be replaced as needed.

Hemodialysis

Methanol And Ethylene Glycol Intoxication

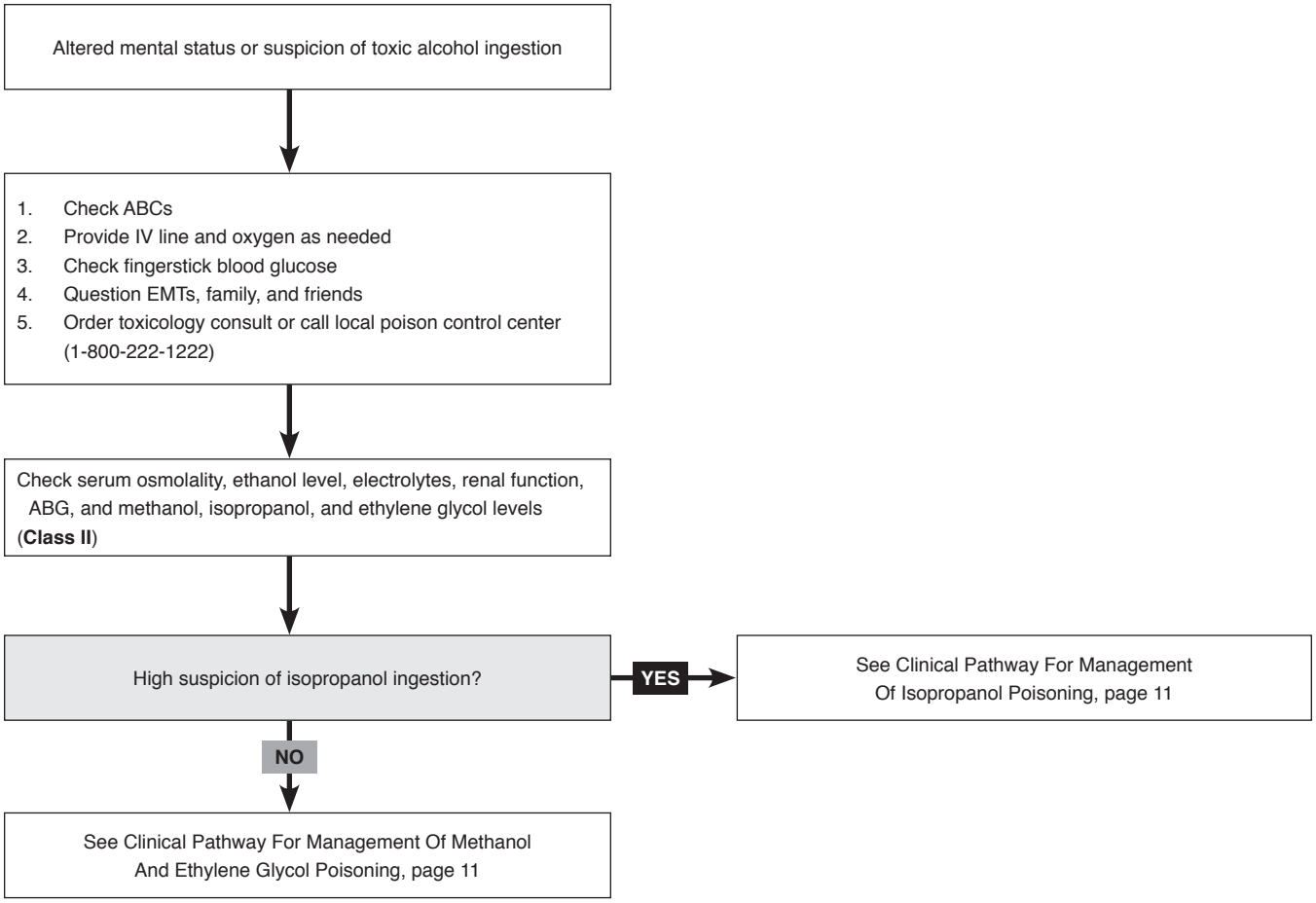
Hemodialysis is very efficient in increasing the elimination of both the parent compounds, methanol and ethylene glycol, and their toxic metabolites. AACT guidelines are outlined in **Table 9.**

Hemodialysis should be considered when these serum toxic alcohol concentrations exceed 50 mg/dL, regardless of renal functional status or the presence of acid-base abnormalities. Recent studies and case reports suggest that hemodialysis may not be needed if treatment with fomepizole is started early after ethylene glycol ingestion and there is no evidence of acidemia or alterations in renal function.[12,17,68,69] However, this practice will probably not be efficient for patients with methanol intoxication, since methanol's half-life can reach to 54 hours. Methanol is eliminated very slowly when ADH is inhibited; therefore, several weeks of treatment with fomepizole alone may be required if hemodialysis is never initiated. **(See Table 1, page 3).** Hemodialysis should be continued until acidemia resolves, signs of end-organ damage (eg, renal failure with ethylene glycol and visual disturbances with methanol) have

Table 9. Indications For Hemodialysis In Methanol And Ethylene Glycol Toxicity[4,5]

- Metabolic acidosis (pH < 7.25-7.30)
- Vision abnormalities
- Renal failure
- Electrolyte abnormalities not responsive to conventional treatment
- Hemodynamic instability refractory to intensive care treatment
- Serum concentration > 50 mg/dL

Clinical Pathway For Initial Evaluation Of Toxic Alcohol Poisoning



Abbreviations: ABCs, airway, breathing, circulation; ABG, arterial blood gas; EMT, emergency medical technician; IV, intravenous.

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

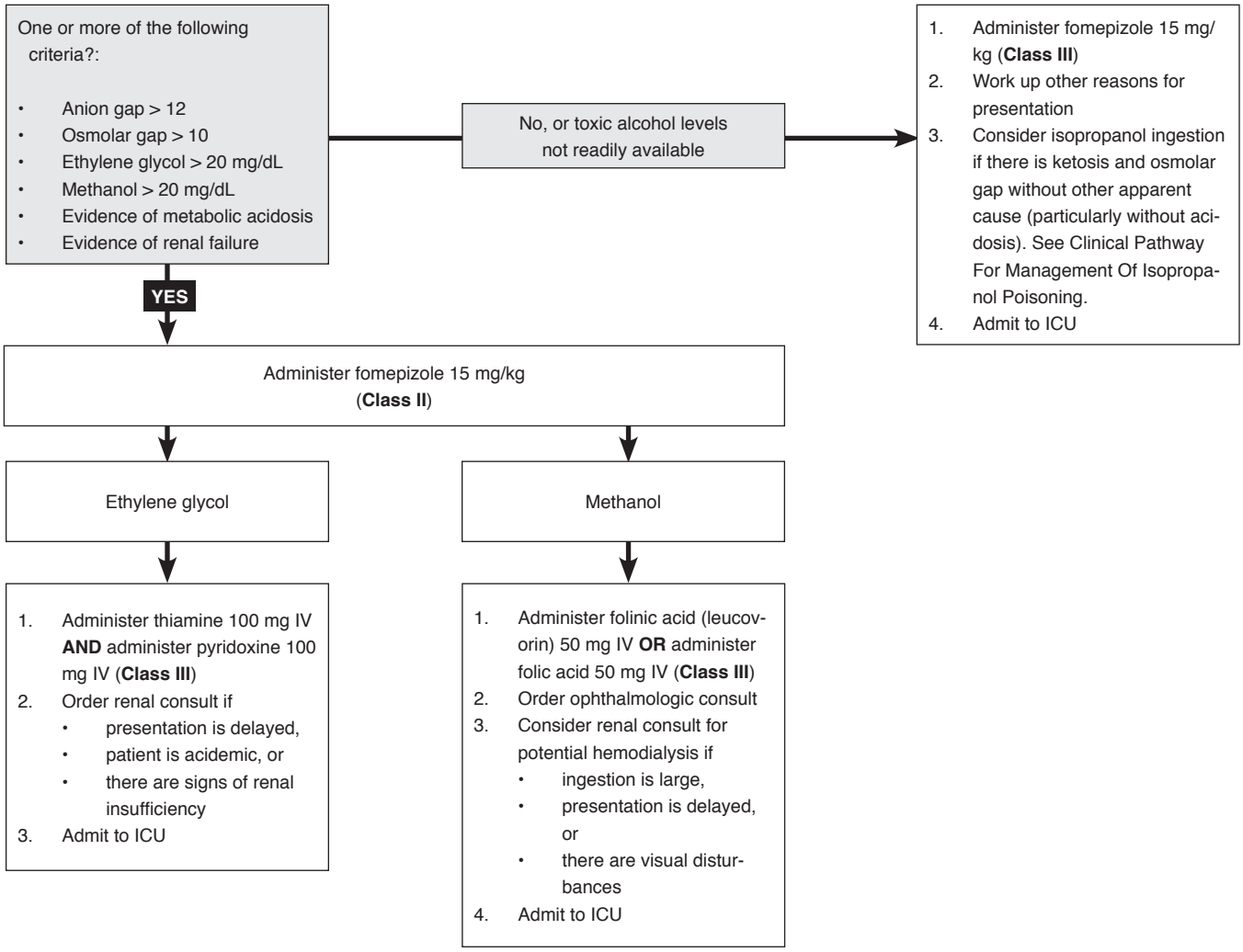
Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

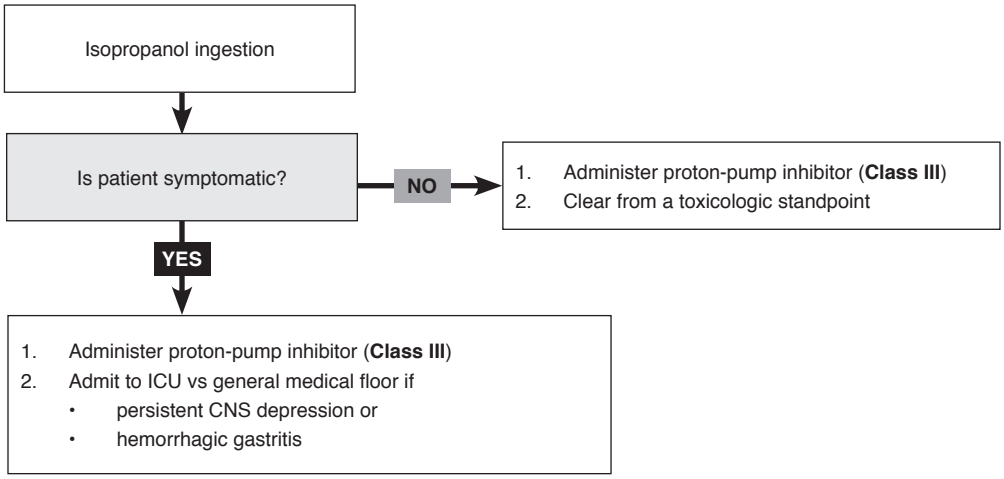
Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and representatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. *JAMA.* 1992;268(16):2289-2295.

Clinical Pathway For Management Of Methanol And Ethylene Glycol Poisoning



Clinical Pathway For Management Of Isopropanol Poisoning



See Class of Evidence Definitions, page 10.

Abbreviations: CNS, central nervous system; ICU, intensive care unit; IV, intravenous.

improved, and serum methanol and/or ethylene glycol concentrations drop below 20 mg/dL.

Cofactors

The administration of cofactors will promote the metabolism of intermediate metabolites into nontoxic metabolites, although substantial clinical evidence of their efficacy is not currently available. In ethylene glycol toxicity, pyridoxine and thiamine increase the metabolism of glycine and alpha-hydroxy-beta-ketoadipate, respectively. In methanol toxicity, either folinic acid (leucovorin) or folic acid promotes the metabolism of formic acid.[70,71] **(See Table 10.)**

Isopropanol Intoxication

Treatment for isopropanol intoxication is typically supportive. Treatment with ADH inhibitors is not indicated, since isopropanol's metabolite — acetone — is not as toxic as its parent compound.[72] Proton-pump inhibitors may be helpful, since hemorrhagic gastritis can occur. Hemodialysis is rarely indicated but has been reported when isopropanol levels exceed 150 to 400 mg/dL, and it can increase the rate of clearance of both isopropanol and acetone.[46] Hemodialysis should be considered if a patient is hemodynamically unstable or comatose.[73,74]

Special Circumstances

Pediatric Patients

Children who ingest more than a taste of ethylene glycol or any amount of methanol are referred by poison control centers to the ED for evaluation.[75] In children 18 months to 4.5 years of age, a mouthful is between 5 and 10 mL and could potentially result in concentrations that exceed 20 mg/dL of either toxic alcohol.[76] No guidelines are currently available from the AACT or the AAPCC for treating children with toxic alcohol ingestion. In addition, the FDA has not officially approved fomepizole for use in children. Several case studies and case series report the administration of fomepizole to pediatric patients.[77,78] Fomepizole is preferred over ethanol in children, since they are at risk for hypoglycemia (secondary to poor glycogen stores), hypothermia, and CNS depression.

Pregnancy

Limited data are available regarding the treatment of pregnant patients with toxic alcohol ingestion.

Table 10. Dosing Regimens For Cofactors

Ethylene glycol	Thiamine: 100 mg IV every 6 hours **AND** Pyridoxine: 100 mg IV every 6 hours
Methanol	Folinic acid (leucovorin):1-2 mg/kg (up to 50 mg) IV every 4 to 6 hours **OR** Folic acid: 50 mg IV every 4 to 6 hours

Fomepizole is a Category C drug. Several case reports have been published in which pregnant patients with methanol intoxication have been treated with ethanol or fomepizole.[7,79-81] Two case reports that describe chronic methanol inhalation during pregnancy found fetal cerebral infarcts, bilateral frontal cortical leukomalacia, and intraventricular hemorrhage.[7,79] One of these cases suggests that methanol crosses the placenta.[79] Ethanol should not be used in the treatment of pregnant patients, since it is teratogenic and can cause fetal alcohol syndrome.

Very few case reports have been published for ethylene glycol or isopropanol intoxication in pregnancy.

Controversies/Cutting Edge

Hemodialysis In Isopropanol Intoxication

Isopropanol ingestions are generally treated supportively. Clearance of isopropanol during hemodialysis was significantly increased according to a case report of a 61-year-old male who arrived comatose in the ED, was hypotensive (blood pressure 80/60 mm Hg), and had a serum isopropanol concentration of 309 mg/dL. Two hours after hemodialysis was initiated, this patient began responding to verbal commands.[74] Much of the literature cites this case in support of dialysis for patients with large isopropanol ingestions who are comatose or hypotensive or who have serum concentrations greater than 400 mg/dL. In addition, isopropanol is amenable to dialysis owing to its low volume of distribution, low protein binding, and low molecular weight. Contrary to this thinking, Trullas et al argue that no sequelae have been reported after these ingestions and therefore dialysis is not in order, even in life-threatening situations.[73]

Rapid Toxic Alcohol Test Kits

As mentioned previously, toxic alcohol concentrations are not readily available in the majority of hospitals, so appropriate treatment is often delayed. In an informal survey reported by the University of Maryland, the turnaround time for obtaining an isopropanol, methanol, or ethylene glycol level was 1 hour, not including the transport time.[82] In a prospective study based on data from the New York City Poison Control Center, the sensitivity and specificity of a rapid veterinary qualitative ethylene glycol kit were determined in humans.[83] Twenty-four samples were tested with this kit, and the results were compared with those of the traditional gas chromatography method. Sensitivity was 100%, while the specificity was 88.8%. Of the 24 samples, 15 were confirmed (by gas chromatography) for ethylene glycol, 5 for methanol, and 4 were negative for both of these alcohols. This kit qualitatively tested

Risk Management Pitfalls For Diagnosis And Management Of Toxic Alcohol Poisoning

1. **"The anion and osmolar gap were normal, so I didn't begin treatment."**
   Treatment with an ADH inhibitor should be initiated as soon as possible if there is significant suspicion of either methanol or ethylene glycol ingestion. At some point, both the anion and osmolar gaps may be within normal limits **(see Figure 2, page 6).** TIME = KIDNEY (for ethylene glycol) and EYES (for methanol).

2. **"He always comes in intoxicated, so I didn't even think of a toxic alcohol ingestion."**
   Chronic alcoholics are at risk for methanol, ethylene glycol, or isopropanol ingestion, since these substances are readily available. It can be challenging to identify a toxic alcohol ingestion in a chronic alcoholic, especially if routine serum ethanol concentrations are not checked. Frequent reevaluation of the intoxicated patient is required to ensure that clinical improvement is occurring.

3. **"The patient was not intoxicated, so I didn't think they actually ingested the toxic alcohol."**
   Patients vary in their degree of tolerance and may not exhibit inebriation at levels that are potentially toxic.

4. **"The methanol level was 10 mmol/L, so I didn't begin treatment."**
   The clinician should realize that treatment with fomepizole (or ethanol) should begin when levels of ethylene glycol or methanol are greater than 20 mg/dL. Laboratories may report these values in different SI units.

5. **"The child's mother stated that he drank only a mouthful of windshield-washer fluid."**
   A mouthful in a child is estimated anywhere between 5 and 10 mL and can potentially cause methanol levels to exceed 20 mg/dL. Failing to treat methanol toxicity can cause irreversible blindness.

6. **"I was waiting for the ethylene glycol and methanol levels to come back before I ordered fomepizole; then I found out it was a send-out test."**
   Requests for ethylene glycol and methanol levels are usually sent to outside laboratories, and results are often not quickly available. Fomepizole decreases the metabolism of each of these alcohols to their toxic metabolites and decreases the incidence of nephrotoxicity (ethylene glycol) and ophthalmologic (methanol) toxicity.

7. **"I thought isopropanol ingestion should be treated with fomepizole, like methanol and ethylene glycol."**
   Isopropanol's metabolite, acetone, does not cause an acidosis. Inhibiting ADH will prolong isopropanol's half-life as well as its CNS depressive effects.

8. **"Gastric lavage should be attempted in every poisoned patient."**
   Gastric lavage is not recommended for toxic alcohol ingestion unless the patient has ingested large amounts and presents immediately after ingestion. To properly perform gastric lavage, a 32-French gauge orogastric tube must be placed, which can often present a challenge. In addition, this procedure has the potential to cause aspiration and esophageal rupture.

9. **"My patient's methanol level was 100 mg/dL with no signs of acidemia, renal failure, or visual disturbances. The last time I took care of an ethylene glycol–intoxicated patient I used only fomepizole as treatment; hemodialysis didn't have to be initiated."**
   Methanol's long half-life results in a very long clearance time. Hemodialysis should be initiated in large methanol ingestions even in the absence of acidemia, visual disturbances, or renal failure.

10. **"I didn't think the poison control center was open so late at night."**
    Poison control centers in the U.S. are open 24 hours a day, 7 days a week. By calling 1-800-222-1222, you will be referred to your local poison control center. These centers have specialists trained in overdoses and have access to a toxicologist at all times.

positive for an ethylene glycol level as low as 27 mg/dL. The only discrepancy occurred in 1 sample, which was found to be a false positive.

Disposition

Patients can be cleared from a toxicologic standpoint if they do not have evidence of end-organ damage, are hemodynamically stable, and have a methanol or ethylene glycol concentration less than 20 mg/dL. Admission to the ICU is warranted in cases of acidemia or when signs of end-organ damage are evident. Patients who are not likely to have methanol or ethylene glycol ingestion, have normal anion and osmolar gaps, are not acidemic, and improve after several hours of observation can be cleared even if a toxic alcohol concentration is not readily available. Alcoholic ketoacidosis is often confused with toxic alcohol ingestion. If alcoholic ketoacidosis is suspected and if acidemia and the anion gap are improving with treatment (ie, fluids, dextrose, thiamine), the patient can be cleared if the toxic alcohol concentration is not readily available. Admission to ICU should be considered when there are signs of end-organ damage or acidemia. Finally, transfer to a tertiary care hospital is necessary if fomepizole or hemodialysis is not readily available.

Cost-Effective Strategies

1. If an ingestion of methanol or ethylene is suspected, fomepizole (or ethanol) should be administered as soon as possible. Delaying this treatment will increase the risk of end-organ damage and a prolonged ICU stay.
2. Treatment for large methanol ingestions should include a renal consult for hemodialysis even if there is no sign of acidosis. Methanol's long half-life (up to 30 hours) and Michaelis–Menten kinetics will result in a lengthy hospital course, requiring many doses of fomepizole.
3. At this time, treatment with fomepizole instead of ethanol is considered the standard of care for ethylene glycol or methanol intoxications. Ethanol's disadvantages include hypoglycemia, difficulties in appropriate administration, and thrombophlebitis. Fomepizole's only disadvantage is its high cost.
4. If hemodialysis and/or fomepizole is not readily available, the patient should be transferred to a tertiary care center that offers these treatment options.

Summary

Toxic alcohol ingestion is a challenging diagnosis in the ED. Asking the paramedics, family, and friends about the presence of containers at the scene is often the key to determining whether such an ingestion has occurred. Diagnostic tests such as osmolar and anion gaps can help support the diagnosis but should not be used to exclude this diagnosis. Ultimately, serum concentrations are necessary to guide treatment. Fomepizole therapy should be initiated as soon as possible for methanol or ethylene glycol ingestions to inhibit the conversion of these compounds to their toxic metabolites.

Case Conclusion

An IV line was placed, fomepizole was administered in a dose of 15mg/kg, and the patient was placed on fall precautions. Lab work revealed the following: an anion gap of 25, an arterial pH of 7.25, an osmolar gap of 30, and a BUN:creatinine ratio of 13:0.6. Her ethanol level was nondetectable. After another discussion with the local poison control center, you realized that most windshield-washer fluids contain methanol and some may contain ethylene glycol. You consulted nephrology regarding the need for hemodialysis and she was admitted to the ICU, at which time results of the methanol and ethylene glycol tests were still pending. A methanol concentration of 70 mg/dL was found 24 hours after admission, warranting fomepizole therapy until her methanol level was less than 20 mg/dL. Hemodialysis was initiated upon admission to the ICU and was discontinued once her acidemia resolved. Three days later, the patient was transferred to psychiatry, neurologically intact.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients involved, are included in bold type following each reference. In addition, the most informative references cited in this paper, as determined by the authors, are noted by an asterisk (*) next to the number of the reference.

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1. What is the most common toxic alcohol exposure in the United States, according to the AAPCC 2008 Report?
a. Methanol
b. Ethylene glycol
c. Isopropanol

2. Which of the following alcohols is a major ingredient in windshield-washer fluid?
a. Ethanol
b. Diethylene glycol
c. Methanol
d. Ethylene glycol

3. Which of the following toxic alcohols causes an anion gap and an osmolar gap?
a. Methanol and isopropanol
b. Ethylene glycol and isopropanol
c. Ethylene glycol, methanol, and isopropanol
d. Ethylene glycol and methanol

4. A child is brought in after his mother found him playing with a bottle of de-icer fluid. He arrives neurologically intact and hemodynamically stable. Which of the following is a potential complication of this ingestion?
a. Hepatotoxicity
b. Peripheral neuropathy
c. Parkinson-like symptoms
d. Hemorrhagic gastritis

5. Which of the following equations can be used to calculate serum osmolality?
a. (Na+) + (BUN/18) + (glucose/2.8)
b. 2 x (Na+) + (BUN/2.8) + (glucose/18)
c. 2 x (Na+) + (BUN/2.8) + (glucose/18) + (ethanol/4.6)
d. (Na+) + (BUN/2.8) + (glucose/18) + (ethanol/4.6)

6. Which of the following matches the correct toxic alcohol with its potential toxicity?
a. Methanol: nephrotoxicity
b. Ethylene glycol: ophthalmologic toxicity
c. Isopropanol: hemorrhagic gastritis
d. Methanol: hepatotoxicity

7. Which of the following ECG abnormalities can be seen in ethylene glycol intoxication?
a. Prolonged QTc
b. Shortened QTc
c. Prolonged QRS
d. Prolonged PR interval

8. Which of the following compounds is responsible for renal failure in ethylene glycol toxicity?
a. Formic acid
b. Glycoaldehyde
c. Calcium oxalate
d. Glycolic acid

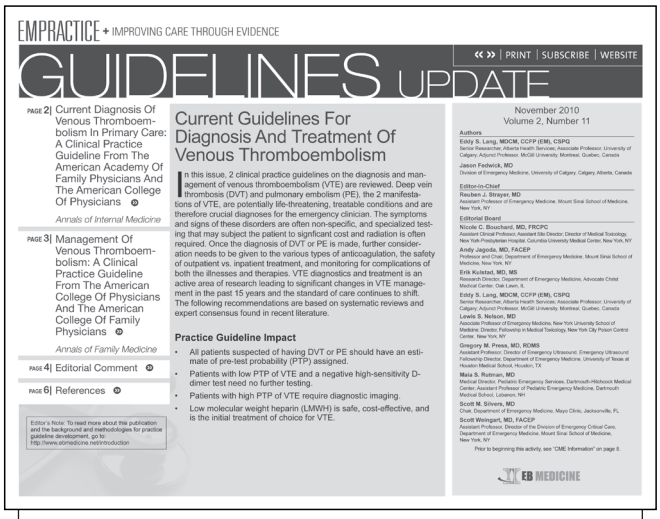
9. Detection of urine calcium oxalate crystals and urine fluorescence helps to verify which of the following toxic alcohol ingestions:
a. Ethylene glycol
b. Methanol
c. Isopropanol
d. Ethanol

10. What is fomepizole's mechanism of action?
a. Stimulates ADH
b. Stimulates ALDH
c. Inhibits ADH
d. Inhibits ALDH

11. Which of the following statements is correct when comparing fomepizole and ethanol?
a. Both inhibit the enzyme ADH
b. Ethanol has the potential to cause hyperglycemia
c. Fomepizole must be titrated more often than ethanol
d. Fomepizole has the potential to cause hypoglycemia

12. An elevated osmolar gap in the setting of a toxic alcohol ingestion is caused by which of the following?
a. The parent compounds methanol, ethylene glycol, and isopropanol
b. The metabolites of methanol, ethylene glycol, and isopropanol
c. The metabolites of methanol and ethylene glycol

13. Which of the following toxic alcohols has the longest elimination half-life?
a. Methanol
b. Ethylene glycol
c. Isopropanol



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GUIDELINES UPDATE

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PAGE 2| Current Diagnosis Of Venous Thromboembolism In Primary Care: A Clinical Practice Guideline From The American Academy Of Family Physicians And The American College Of Physicians

Annals of Internal Medicine

PAGE 3| Management Of Venous Thromboembolism: A Clinical Practice Guideline From The American College Of Physicians And The American College Of Family Physicians

Annals of Family Medicine

PAGE 4| Editorial Comment

PAGE 6| References

Editor's Note: To read more about this publication and the background and methodologies for practice guideline development, go to: http://www.acponline.net/introduction

Current Guidelines For Diagnosis And Treatment Of Venous Thromboembolism

In this issue, 2 clinical practice guidelines on the diagnosis and management of venous thromboembolism (VTE) are reviewed. Deep vein thrombosis (DVT) and pulmonary embolism (PE), the 2 manifestations of VTE, are potentially life-threatening, treatable conditions and are therefore crucial diagnoses for the emergency clinician. The symptoms and signs of these disorders are often non-specific, and specialized testing that may subject the patient to significant cost and radiation is often required. Once the diagnosis of DVT or PE is made, further consideration needs to be given to the various types of anticoagulation, the safety of outpatient vs. inpatient treatment, and monitoring for complications of both the illnesses and therapies. VTE diagnostics and treatment is an active area of research leading to significant changes in VTE management in the past 15 years and the standard of care continues to shift. The following recommendations are based on systematic reviews and expert consensus found in recent literature.

Practice Guideline Impact

- All patients suspected of having DVT or PE should have an estimate of pre-test probability (PTP) assigned.
- Patients with low PTP of VTE and a negative high-sensitivity D-dimer test need no further testing.
- Patients with high PTP of VTE require diagnostic imaging.
- Low molecular weight heparin (LMWH) is safe, cost-effective, and is the initial treatment of choice for VTE.

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Authors

Eddy S. Lang, MDCM, CCFP (EM), CSPQ
Senior Researcher, Alberta Health Services; Associate Professor, University of Calgary; Adjunct Professor, McGill University, Montreal, Quebec, Canada

Jason Fedrick, MD
Division of Emergency Medicine, University of Calgary, Calgary, Alberta, Canada

Editor-in-Chief

Reuben J. Strayer, MD
Assistant Professor of Emergency Medicine, Mount Sinai School of Medicine, New York, NY

Editorial Board

Nicole C. Bouchard, MD, FRCPC
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Andy Jagoda, MD, FACEP
Professor and Chair, Department of Emergency Medicine, Mount Sinai School of Medicine, New York, NY

Erik Kulstad, MD, MS
Research Director, Department of Emergency Medicine, Advocate Christ Medical Center, Oak Lawn, IL

Eddy S. Lang, MDCM, CCFP (EM), CSPQ
Senior Researcher, Alberta Health Services; Associate Professor, University of Calgary; Adjunct Professor, McGill University, Montreal, Quebec, Canada

Lewis S. Nelson, MD
Associate Professor of Emergency Medicine, New York University School of Medicine; Director, Fellowship in Medical Toxicology, New York City Poison Control Center, New York, NY

Gregory M. Press, MD, ROMS
Assistant Professor; Director of Emergency Ultrasound, Emergency Ultrasound Fellowship Director, Department of Emergency Medicine, University of Texas at Houston Medical School, Houston, TX

Maia S. Rutman, MD
Medical Director, Pediatric Emergency Services, Dartmouth-Hitchcock Medical Center; Assistant Professor of Pediatric Emergency Medicine, Dartmouth Medical School, Lebanon, NH

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Chair, Department of Emergency Medicine, Mayo Clinic, Jacksonville, FL

Scott Weingart, MD, FACEP
Assistant Professor, Director of the Division of Emergency Critical Care, Department of Emergency Medicine, Mount Sinai School of Medicine, New York, NY

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September 2010
Volume 7, Number 9

Management Of Wounds In The Pediatric Emergency Department

The parents of a 13-year-old bring their son to the emergency department after the glass coffee table on which he was sitting broke under his weight, about a half-hour ago. The parents state that they were able to stop all bleeding both forearms. The parents state that they were able to stop all bleeding prior to coming to the ED, but they continue to maintain pressure over a larger cut on his right arm. You wonder how many of these lacerations are going to require closure. The boy's past medical history reveals that as a toddler he had several ear infections that were treated with uncomplicated bilateral tympanostomy tube placement under general anesthesia. He has also been under general anesthesia twice for dental procedures. There have been no hospitalizations or other surgeries, and he is immunocompetent. His developmental history reveals a diagnosis of autism at age 3. He is nonverbal and attends school in a highly structured classroom setting. His parents state that he can be "hard to handle" in strange or stressful situations. You immediately begin to run through various wound closure options in your mind while you ask yourself, "Will I be able to use routine sedation protocols, or will this child need something more?"

While you finish taking the boy's history from his parents, a medical student who is working with you arrives to let you know that a 5-year-old girl was just brought in by her parents. The girl tripped while running in the house and fell onto the stone fireplace. She has sustained a 2-cm laceration on her right cheek, just below the zygomatic process. "Must be a full moon," you mutter to the student. The student asks you if this is something routinely repaired by emergency clinicians and says, "I was taught that anything on the face should be

Authors

Paul J. Sagerman, MD
Associate Professor, Pediatrics, Wake Forest University Baptist Medical Center, Winston Salem, NC

Allison S. McBride, MD
Assistant Professor, Pediatrics and Emergency Medicine, Wake Forest University Baptist Medical Center, Winston Salem, NC

Elizabeth E. Halvorsen, MD
Resident, Pediatrics, Wake Forest University Baptist Medical Center, Winston Salem, NC

Peer Reviewers

Mona Bahrambeigi, PhD, APN, CWON, CWS
Wound Specialist Education & Research, James H. Quillen Veterans Affairs Medical Center, Johnson City, TN

Paula Wightman, MD
Attending Physician, Ruth and Harry Roman Emergency Department, Cedars-Sinai Medical Center, Los Angeles, CA; Director of Pediatric Emergency Services, Providence Tarzana Medical Center, Tarzana, CA

CME Objectives

Upon completion of this article, you should be able to:

1. Recognize the presentation and etiologies of pediatric wounds presenting to an emergency department.
2. Describe the steps in initial assessment and evaluation of patients who present with wounds.
3. Identify risk factors associated with wound repair complications or poor outcomes, which may warrant additional management decisions in wound care.
4. Describe the steps in wound closure by primary intention.
5. Recognize special circumstances which may warrant additional management decisions in wound care.

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Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals & Objectives: Upon completion of this article, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

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Toxic Alcohols: Not Always A Clear-Cut Diagnosis

Patil N, Lai Becker M, Ganetsky M. November 2010, Volume 12; Number 11

This issue of Emergency Medicine Practice *focuses on the diagnostic approach to methanol, ethylene glycol, and isopropanol poisoning, as well as the pathophysiology, mangagement, and treatment specific for each toxic alcohol. For a more detailed discussion of this topic, including figures and tables, clinical pathways, and other considerations not noted here, please see the complete issue on the EB Medicine website at www.ebmedicine.net/topics.*

Key Points	Comments
Flank pain or urinary complaints suggests ethylene glycol intoxication. Blurry vision, changes in vision, or blindness suggest methanol toxicity. Abdominal pain or hematemesis suggests isopropanol poisoning.	In each case, the parent compounds cause intoxication, but serious toxicity is caused by their metabolites. Toxic alcohols should be part of the differential diagnosis of any patient with an elevated anion or osmolar gap, as well as any inebriated patient with a nondetectable serum ethanol concentration.
Definitive diagnosis is verified by obtaining serum concentrations of methanol, ethylene glycol, or isopropyl alcohol. These levels are often not readily available and so the osmolar and anion gaps help in deciding treatment options. To properly interpret osmolar and anion gaps, these laboratory tests should be ordered at the same time and from the same blood sample: electrolytes, osmolality, ethanol level, and toxic alcohol concentrations.	Since the osmolar gap varies from person to person, its interpretation can often prove challenging.[36,37] There are no robust data on when to suspect toxic alcohol ingestion on the basis of the osmolar gap. Hovda et al proposed that an osmolar gap of greater than 25 mOsm in the setting of acidosis should suggest toxic alcohol ingestion.[38]
Decontamination methods are not recommended unless co-ingestions are suspected.	Methods for gastrointestinal decontamination after an ingestion of toxic alcohols have not been well studied. According to the AACT guidelines, toxic alcohols are rapidly absorbed, so such decontamination is of little value.[4,5]
Treatment for ethylene glycol and methanol intoxication includes an alcohol dehydrogenase inhibitor. Fomepizole (4-methylpyrazole) has a better safety profile than ethanol and has become the standard of care.	When compared with ethanol, fomepizole has 8000 times the affinity for ADH.[17,18] Its advantages over ethanol include easier dosing, more predictable kinetics, and fewer side effects.[11] Its primary and significant disadvantage is its high cost (about $1,000 per 1.0-g vial).
Hemodialysis should be considered when serum toxic alcohol concentrations exceed 50 mg/dL, regardless of renal functional status or the presence of acid-base abnormalities.	Recent studies and case reports suggest that hemodialysis may not be needed if treatment with fomepizole is started early after ethylene glycol ingestion and there is no evidence of acidemia or alterations in renal function.[12,17,68,69] However, this practice will probably not be efficient for patients with methanol intoxication, since methanol's half-life can reach to 54 hours.
Children who ingest more than a taste of ethylene glycol or any amount of methanol are referred by poison control centers to the ED for evaluation.[75]	In children 18 months to 4.5 years of age, a mouthful is between 5 and 10 mL and could potentially result in concentrations that exceed 20 mg/dL of either toxic alcohol.[76]

See reverse side for reference citations.

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