

# Toxic Alcohol Ingestions: Clinical Features, Diagnosis, and Management

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Alcohol-related intoxications, including methanol, ethylene glycol, diethylene glycol, and propylene glycol, and alcoholic ketoacidosis can present with a high anion gap metabolic acidosis and increased serum osmolal gap, whereas isopropanol intoxication presents with hyperosmolality alone. The effects of these substances, except for isopropanol and possibly alcoholic ketoacidosis, are due to their metabolites, which can cause metabolic acidosis and cellular dysfunction. Accumulation of the alcohols in the blood can cause an increment in the osmolality, and accumulation of their metabolites can cause an increase in the anion gap and a decrease in serum bicarbonate concentration. The presence of both laboratory abnormalities concurrently is an important diagnostic clue, although either can be absent, depending on the time after exposure when blood is sampled. In addition to metabolic acidosis, acute renal failure and neurologic disease can occur in some of the intoxications. Dialysis to remove the unmetabolized alcohol and possibly the organic acid anion can be helpful in treatment of several of the alcohol-related intoxications. Administration of fomepizole or ethanol to inhibit alcohol dehydrogenase, a critical enzyme in metabolism of the alcohols, is beneficial in treatment of ethylene glycol and methanol intoxication and possibly diethylene glycol and propylene glycol intoxication. Given the potentially high morbidity and mortality of these intoxications, it is important for the clinician to have a high degree of suspicion for these disorders in cases of high anion gap metabolic acidosis, acute renal failure, or unexplained neurologic disease so that treatment can be initiated early.

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Lactic acidosis and diabetic ketoacidosis (DKA) are the most common causes of acute metabolic acidosis (1,2). Much less frequent but of great importance clinically are the alcohol intoxications shown in Table 1. Methanol, ethylene glycol, diethylene glycol, and propylene glycol intoxication and alcoholic ketoacidosis can produce hyperosmolality and metabolic acidosis (3–9). Isopropanol intoxication is usually associated with hyperosmolality alone (4,5). Importantly, several of these disorders can be fatal or produce irreversible tissue damage if they are not quickly recognized and treated appropriately (4–15).

## Effect of Alcohols on Serum Osmolality and the Osmolal Gap

The normal serum osmolality of 285 to 290 mOsm/L is due to sodium and its counterbalancing ions, bicarbonate and chloride, and glucose and urea. It can be calculated using the following equation:

Serum osmolality (mOsm/L) =  $2 \times \text{Na}^+$  + blood urea nitrogen (mg/dl)/2.8 + glucose (mg/dl)/18.

The serum osmolality measured by freezing point depression is usually within 10 mOsm/L of the calculated serum osmola-

lity (16). Accumulation of low molecular weight substances in the serum (such as each of the alcohols) will raise the measured serum osmolality above that of the calculated serum osmolality, producing an osmolal gap (4,5,16–18). The effect of each of the alcohols on serum osmolality is shown in Table 2. Methanol gives rise to the greatest increment in serum osmolality, followed by ethanol, isopropanol, ethylene glycol, propylene glycol, and diethylene glycol in that order (4,5,12,13,16,18–26).

An osmolal gap can also be found in some other disorders that might be considered in the differential diagnosis of alcohol-related intoxications, such as ketoacidosis, lactic acidosis, and renal failure and in critically ill patients with hyponatremia, but this osmolal gap is  $\leq 15$  to 20 mOsm/L (21,22,27). Thus, an osmolal gap  $>20$  mOsm/L indicates accumulation in the blood of one of the alcohols; however, the absence of an osmolal gap does not exclude an alcohol-related intoxication, because alcohol concentrations that are sufficient to produce clinical and laboratory abnormalities might not raise serum osmolality appreciably (12,13,23–25). A marked discrepancy between the serum osmolal gap and the severity of the clinical effects of these alcohols is not uncommon (6–8,23–25,28).

## Absorption, Distribution, Metabolism, and Elimination from the Body

Methanol, isopropanol, and propylene glycol are absorbed through normal skin (12,13,29–32), whereas ethylene glycol and diethylene glycol are absorbed in significant amounts only

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Table 1. Major alcohol intoxications<sup>a</sup>

Disorder	Substance(s) Causing Toxicity	Clinical and Laboratory Abnormalities	Comments
Alcoholic (ethanol) ketoacidosis	$\beta$ -hydroxybutyric acid Acetoacetic acid	Metabolic acidosis	May be most frequent alcohol-related disorder; mortality low relative to other alcohols; rapidly reversible with fluid administration; increase in SOsm inconsistent
Methanol intoxication	Formic acid Lactic acid Ketones	Metabolic acidosis, hyperosmolality, retinal damage with blindness, putaminal damage with neurologic dysfunction	Less frequent than ethylene glycol; hyperosmolality and high anion gap acidosis can be present alone or together; mortality can be high if not treated quickly
Ethylene glycol intoxication	Glycolic acid Calcium oxalate	Myocardial and cerebral damage and renal failure; metabolic acidosis, hyperosmolality, hypocalcemia	More frequent than methanol intoxication; important cause of intoxications in children; hyperosmolality and high anion gap acidosis can be present alone or together
Diethylene glycol intoxication	2-Hydroxyethoxyacetic acid	Neurological damage, renal failure, metabolic acidosis, hyperosmolality	Very high mortality possibly related to late recognition and treatment; most commonly results from ingestion in contaminated medications or commercial products; hyperosmolality may be less frequent than with other alcohols
Propylene glycol intoxication	Lactic acid	Metabolic acidosis, hyperosmolality	May be most frequent alcohol intoxication in ICU; minimal clinical abnormalities; stopping its administration is sufficient treatment in many cases
Isopropanol intoxication	Isopropanol	Coma, hypotension, hyperosmolality	Hyperosmolality without acidosis; positive nitroprusside reaction

<sup>a</sup>ICU, intensive care unit.

after the integrity of the skin is breached (33). Inhalation of methanol or topical absorption of ethylene glycol, propylene glycol, isopropanol, and diethylene glycol can produce intoxications (12,13,30–34), but most intoxications occur after their oral ingestion or, in the case of propylene glycol (4,5,12,13,35,36), after intravenous administration.

The volume of distribution, half-life, and route of elimination of the alcohols after oral ingestion are summarized in Table 3. Methanol, ethylene glycol, diethylene glycol, propylene glycol, ethanol, and isopropanol are rapidly absorbed from the gastrointestinal tract (4,5,12,13,37). Once absorbed, they have a volume of distribution similar to that of body water with peak

blood concentrations occurring within 30 to 60 min (12,13,37). Subsequently, they are metabolized in the liver or excreted primarily by the kidney. Figures 1 and 2 summarize the metabolic pathway of each of the alcohols.

Oxidation of the alcohols is first catalyzed by the liver enzyme alcohol dehydrogenase (ADH), this process being a critical step in their biotransformation (12,13,17,37–40): Methanol is metabolized to formaldehyde (6,12), ethylene glycol to glycoaldehyde (6,13), propylene glycol (present as DL isomers) to lactaldehyde (41), isopropanol to acetone (4), and ethanol to acetaldehyde (39). Formaldehyde is then metabolized *via* the enzyme formaldehyde dehydrogenase to formic acid, formate

Table 2. Effect of alcohols on serum osmolality

Compound	Molecular Weight	$\Delta$ SOsm (mOsm/L) per 10 mg/dl $\Delta$ Serum Alcohol Concentration
Methanol	32.04	3.09
Ethanol	46.07	2.12
Isopropanol	60.02	1.66
Ethylene glycol	62.07	1.60
Propylene glycol	76.09	1.31
Diethylene glycol	106.12	0.90

then being metabolized to CO<sub>2</sub> and H<sub>2</sub>O, a process that depends on liver tetrahydrofolate concentrations (12,15). This pathway is easily saturable, contributing to accumulation of formic acid in the blood.

Glycoaldehyde is converted to glycolic acid *via* aldehyde dehydrogenase (ALDH) and then to glyoxylic acid and oxalic acid (13,42,43). Glycolic acid can also be metabolized to  $\alpha$ -hydroxy- $\beta$ -keto adipate or glycine (13). Lactaldehyde is metabolized to L-lactic acid by ALDH or, alternatively, to methylglyoxal (41), but D-lactate can also be formed. L-Lactate enters the gluconeogenic pathways; D-Lactate is metabolized to pyruvate and CO<sub>2</sub>. Acetone is usually eliminated *via* the kidneys unchanged. Acetaldehyde is metabolized by ALDH to acetic acid, and the acetic acid is converted to acetyl CoA, which can enter the citric acid cycle. Diethylene glycol was postulated to be metabolized to glycolic acid and oxalate acid, but subsequent studies have shown that it is oxidized by ADH to 2-hydroxyethoxyacetaldehyde and then *via* ALDH to 2-hydroxyethoxyacetic acid (HEAA) (11,44–48); HEAA then is excreted by the kidneys. A certain proportion of each of the alcohols is excreted by the kidney: 50 to 70% of diethylene glycol, 25 to 45% of propylene glycol, 20% of ethylene glycol, 20% of isopropanol, 2 to 5% of ethanol, and 1 to 2% of methanol (12,13,37,47,49–51). Two to 3% of methanol is excreted by the lungs (12,50).

## General Principles of Treatment

Basic principles underlying treatment of methanol, ethylene glycol, and diethylene glycol intoxications are summarized in

Table 4. Absorption from the gastrointestinal tract is rapid; therefore, gastric lavage, induced emesis, or use of activated charcoal must be initiated within 30 to 60 min of ingestion to be beneficial.

Administration of ethanol or fomepizole to attenuate the metabolism of the alcohols is an integral part of therapy. Although ethanol has never been approved by the Food and Drug Administration for this purpose, it has been used in the treatment of methanol and ethylene glycol intoxication for many years (6,12,13,52,53). Ethanol has 10 to 20 times greater affinity for ADH than the other alcohols; at a serum concentration of 100 mg/dl, it completely inhibits ADH (54). It is cleared by dialysis; therefore, the dosage has to be increased when patients undergo dialysis.

Fomepizole (4-methylpyrazole) Antizol (Jazz Pharmaceuticals, Palo Alto, CA) has approximately 500 to 1000 times greater affinity for ADH than ethanol and can completely inhibit ADH at a much lower serum concentration (12,55). Although it is effective when given orally, it is available only as an intravenous preparation in the United States (12,56). It has a volume of distribution of 0.6 to 1.0 L/kg and low protein binding. It is eliminated by hepatic metabolism and renal excretion. Studies in humans have confirmed its effectiveness in preventing metabolism of methanol and ethylene glycol to their toxic byproducts (12,13,56–58); as a result, it is approved for the treatment of both intoxications. Fomepizole has also been used off-label to treat diethylene glycol intoxication (17,44). It is cleared by dialysis; therefore, the dosage has to be increased in patients who undergo hemodialysis.

Table 5 summarizes advantages and disadvantages of fomepizole and ethanol in the treatment of the alcohol intoxications. Fomepizole does not cause the slowing of mentation noted with alcohol. The rate of its elimination from the body is more predictable, making monitoring of blood levels less necessary; therefore, patients do not have to be treated in the intensive care unit (13,40,50,53,55,58–60). Hypoglycemia that occasionally is found with ethanol is absent (12,53). Alcohol predisposes to lactic acid production and can also damage the liver; however, ethanol is easily obtained and is inexpensive, whereas fomepizole can cost as much as \$5000 for 48 h of therapy per patient and may not be available in all hospitals (12,54,58).

All of the alcohols have a low molecular weight, little or

Table 3. Volume of distribution, route of elimination, and elimination kinetics of major alcohols

Alcohol	Volume of Distribution (L/kg)	Half-Life (h) <sup>a</sup>		Route of Elimination (%)		
		Alone	With Ethanol	Liver	Lung	Renal
Ethanol	0.5	2 to 6		95	2	3
Methanol	0.6 to 0.7	14 to 30	43 to 96	97	2.5	1
Ethylene glycol	0.5 to 0.8	3 to 8	17 to 18	80	–	20
Diethylene glycol <sup>b</sup>	0.5	4 to 6	?	30 to 50	–	50 to 70
Propylene glycol	0.5	1.4 to 3.3	17	55 to 75	–	25 to 45
Isopropanol	0.5	2.5 to 6.4	?	80 - 90	–	10 to 20

<sup>a</sup>Half-life is longer at the higher blood concentration found with intoxications as a result of saturation of alcohol dehydrogenase.

<sup>b</sup>Elimination kinetics not elucidated in humans; data on route of elimination and byproducts from studies in rats and dogs.

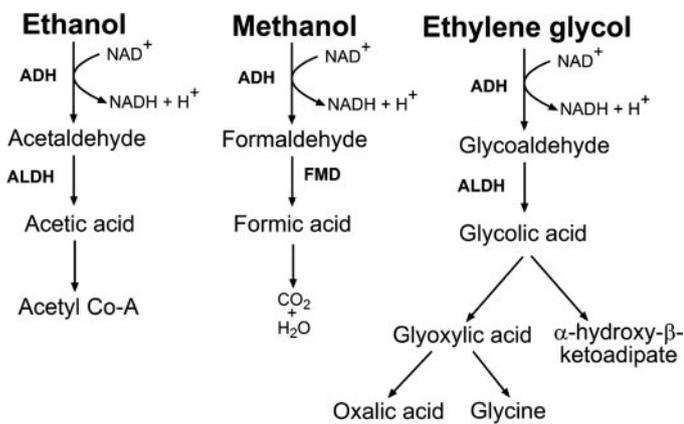


Figure 1. Metabolic pathways for ethanol, methanol, and ethylene glycol. Although, the metabolites for each alcohol differ, the initial metabolic step facilitated by the enzyme alcohol dehydrogenase (ADH) is an important determinant of generation of these products and serves as an important therapeutic target. Enzymes for only the first two steps of each pathway are shown. The conversion of formate to CO<sub>2</sub> and H<sub>2</sub>O depends on adequate folate concentrations. Pyridoxine promotes the metabolism of glyoxylate to glycine, and thiamine promotes metabolism of glycolic acid to α-hydroxy-β-ketoadipate. ALDH, aldehyde dehydrogenase; FMD, formaldehyde dehydrogenase.

absent protein binding, and a low volume of distribution and thus can be effectively removed by dialysis. Dialysis can also remove the organic acid anions such as formate, glycolate, and glyoxalate (15,28,43,61). Intermittent hemodialysis is the most efficient method of rapidly lowering serum alcohol levels or removing the organic acid anions (6,18,28,40,43), although continuous renal replacement therapy can also be used (40). Peritoneal dialysis is rarely used because of the low clearance of the alcohol or organic acid anion.

The response to dialysis can be evaluated by serial measurements of the alcohol. In the absence of these measurements, changes in serum osmolality can be used if it has been elevated (18,19,23,25,31). Serum formate and glycolate levels have been determined to assess the response to therapy in some clinical

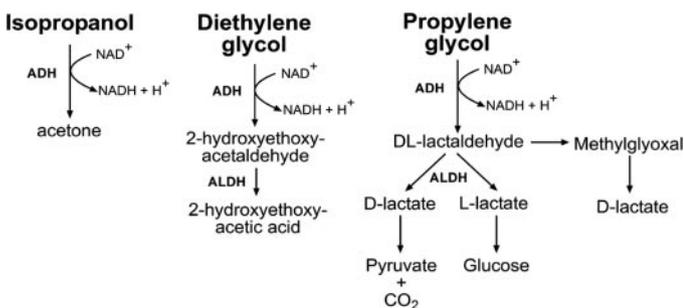


Figure 2. Metabolic pathways for isopropanol, diethylene glycol, and propylene glycol. Although the metabolites for each alcohol differ, the initial metabolic step facilitated by the enzyme ADH is an important determinant of generation of these products and serves as an important therapeutic target. Enzymes for only the first two steps of each pathway are shown.

Table 4. General principles in the treatment of alcohol intoxications<sup>a</sup>

Gastric lavage, induced emesis, or use of activated charcoal to remove alcohol from gastrointestinal tract needs to be initiated within 30 to 60 min after ingestion of alcohol

Administration of ethanol or fomepizole to delay or prevent generation of toxic metabolites needs to be initiated while sufficient alcohol remains unmetabolized measurement of blood alcohol concentrations and/or serum osmolality can be helpful

Dialysis<sup>b</sup> (hemodialysis > continuous renal replacement therapy > peritoneal dialysis) helpful in removing unmetabolized alcohol and possibly toxic metabolites and delivering base to patient to ameliorate metabolic acidosis

<sup>a</sup>Methods used in the treatment of methanol, ethylene glycol, and diethylene glycol intoxication. Methods may also be used for treatment of selected cases of severe propylene glycol intoxication.

<sup>b</sup>Dialysis can be used in treatment of severe isopropanol intoxication. Dialysis is effective in removal of ethanol but not usually used in treatment of alcoholic ketoacidosis.

studies of methanol and ethylene glycol intoxications (14,28,43,61,62). However, serum formate and or glycolate levels cannot be obtainable routinely in most clinical laboratories; therefore, in selected cases, examination of the serum anion gap can be used instead to determine the impact of treatment on the levels of these toxic metabolites (1,2,12,23).

Treatment of the metabolic acidosis with base has been recommended by most experts (12,13,28,52). Base administration has also been postulated to increase renal excretion of formate and glycolate (28,58,61,62). Base can be given intravenously or *via* dialysis. The delivery of base with dialysis might be preferred to lessen complications of base therapy (63). Folic acid to enhance the metabolism of formate (12) and pyridoxine or thiamine to promote the conversion of glyoxylate to glycine, and glycolic acid to α-hydroxy-β-ketoadipate, respectively has also been recommended (13).

## Methanol Intoxication

### Epidemiology

Methanol is used in industrial production and is also present in windshield wiper fluid, antifreeze, and model airplane fuel. It is also used in lieu of ethanol. It is colorless and has only a faint odor.

Methanol intoxication in the United States is uncommon with approximately 1000 to 2000 cases reported each year (approximately 1% of all poisonings) (10,12). It usually results from accidental ingestion of products containing methanol or ingestion as a method of attempting suicide or is taken in lieu of ethanol when the latter is in short supply (7,64,65).

The quantity of methanol that produces toxicity ranges from 15 to 500 ml of a 40% solution to 60 to 600 ml of pure methanol (6,12,52). The risk for methanol intoxication might be increased

Table 5. Comparison of fomepizole and ethanol in treatment of toxic alcohol ingestions<sup>a</sup>

Compound	Advantages	Disadvantages
Fomepizole	<ol style="list-style-type: none"> <li>1. High affinity for alcohol dehydrogenase (approximately 500 to 1000 times more than ethanol)</li> <li>2. Effective at relatively low serum concentrations</li> <li>3. Minimal adverse effects</li> <li>4. No effect of mentation that could confuse interpretation of clinical course</li> <li>5. Constant monitoring of blood levels not necessary</li> <li>6. Hospitalization in intensive care unit not necessary</li> <li>7. No increase in serum osmolality, allowing this to be used as surrogate for toxic alcohol levels in following response to treatment</li> </ol>	<ol style="list-style-type: none"> <li>1. Not available in all clinical settings</li> <li>2. Expensive, approximately \$5000 per 48-h course of therapy</li> <li>3. Intravenous preparation only available in United States</li> <li>4. Only formally approved by FDA for treatment of methanol and ethylene glycol intoxication</li> </ol>
Ethanol	<ol style="list-style-type: none"> <li>1. Inexpensive</li> <li>2. Available in most clinical settings</li> <li>3. Can be given intravenously or orally</li> </ol>	<ol style="list-style-type: none"> <li>1. Lower affinity for alcohol dehydrogenase than fomepizole</li> <li>2. Needs relatively high serum concentrations, approximately 100 mg/dl, to completely saturate the enzyme</li> <li>3. Requires constant monitoring of blood levels and possibly that of toxic alcohol</li> <li>4. Hospitalization in ICU necessary during treatment</li> <li>5. Increases serum osmolality, which can prevent effective use of serum osmolality to monitor response to therapy</li> <li>6. Impairs mentation, which can confuse interpretation of response to therapy</li> </ol>

<sup>a</sup>FDA, Food and Drug Administration.

in the presence of low hepatic tetrahydrofolate concentrations, which affects the rate of formate metabolism (6,12).

If left untreated or if treatment is begun after the full-blown syndrome has developed, then mortality of methanol intoxication can be high. Overall mortality in three studies totaling more than 400 patients varied between 8 and 36% but increased to 50 to 80% when serum bicarbonate concentration was <10 mEq/L and/or blood pH was <7.1 when treatment was begun (7,52,66).

#### Pathophysiology

Metabolic acidosis and visual problems, hallmarks of this disorder, are due to metabolites of methanol. One, formaldehyde, impairs retinal oxidative phosphorylation *in vitro* (67), but *in vivo*, it is rapidly metabolized to formate with a half-life in the blood of only 1 to 2 min. Formic acid (or formate) seems to be the major cause of clinical and laboratory abnormalities: Infu-

sion of formate causes damage to the optic disk in the absence of changes in pH (12,55,60), and the metabolic acidosis is directly correlated with blood formate concentrations (15,28,67).

#### Clinical Findings

The onset and severity of clinical and laboratory abnormalities depends largely on the generation of formic acid (6,12,23,28). Visual disturbances, including decreased visual acuity, photophobia, and blurred vision, and abdominal pain are the most common symptoms of methanol intoxication (7,64), one or both being found in 37 to 72% of patients (7,64). Hyperemia of the optic disks and a reduced papillary response to light may be present. The severity of the visual abnormalities is directly correlated with the severity of the metabolic acidosis (6,7,12). Although most patients will recover normal visual function,

permanent impairment of vision has been observed in from 11 to 18% of patients (7,64).

Abdominal pain can be present in both the presence and the absence of pancreatitis (7,12). Neurologic abnormalities including confusion, stupor, and coma are often present (52). The most severe neurologic dysfunctions are found in patients with the most severe metabolic acidosis (6,7,28,64).

A rare complication of methanol intoxication is putaminal necrosis, which presents with rigidity, tremor, masked faces, and monotonous speech (12). It has been attributed to reduced cerebral blood flow and/or accumulation of formic acid in the putamen (12). Although the syndrome often resolves, some neurologic abnormalities can persist. Kussmaul's breathing, impaired cardiac function, and hypotension as a result of acidemia can be present and are most profound when blood pH is  $\leq 7.2$  (63).

The clinical findings in methanol intoxication often develop in a characteristic manner. Changes in mentation as a result of methanol are present within the first 6 to 24 h but can be the only abnormality for as long as 72 to 96 h if patients have also ingested ethanol (6,7,12,23,52). The absence of more prominent signs or symptoms at this stage can delay recognition of this disorder. As methanol is metabolized to formic acid, visual and more severe neurologic abnormalities become prominent (6,7,12,55,67,68).

### Laboratory Findings

The serum osmolality can be increased or normal and is usually the greatest soon after ingestion of methanol. However, it can be only slightly perturbed even at this point (12,18,23,24), because an increment in serum osmolality of slightly more than 3 mOsm/L will be observed for every 10-mg/dl increase in its concentration. Thus, a methanol concentration of 50 mg/dl will increase serum osmolality by approximately 15 mOsm/L.

High anion gap metabolic acidosis (blood pH 6.8 to 7.3) primarily as a result of formic acid accumulation is often present (7,12,15,23,55,64,67,69). Lactic acidosis as a result of impairment of cellular respiration by formate or increased generation of NADH during the metabolism of methanol can also be present (6,12,23). In patients who also ingest ethanol, ketoacidosis can occur (52). Hyperchloremic metabolic acidosis noted with DKA has not been reported (70). However, the  $\Delta AG/\Delta HCO_3^-$  may be  $>1$  in some patients, reflecting either a concomitant metabolic alkalosis or a difference in the space of distribution of formate and  $HCO_3^-$  (2,7,15).

The serum anion gap may be minimally increased and serum  $HCO_3^-$  minimally reduced early in the course of the disorder, a time when the increment in serum osmolality is the greatest. Subsequently, as methanol metabolism proceeds, the serum  $HCO_3^-$  falls concomitant with a rise in the anion gap and fall in the serum osmolality. After the bulk of the methanol has been metabolized, little or no increase in serum osmolality will be present, whereas the serum anion gap can be strikingly increased and the serum  $HCO_3^-$  markedly depressed (7,12,18,23,24). In rare instances, patients may have ocular toxicity in the presence of normal serum osmolal and anion gaps (24). The different patterns of serum osmolality and serum

anion gap that can be observed with methanol and other intoxications are depicted in Figure 3.

When nitromethane (found in model airplane fuel) is ingested with methanol, the serum creatinine concentration determined using the Jaffe colorimetric method may be spuriously elevated (71). Correct determination of serum creatinine can be obtained using an enzymatic-based assay (71).

Measurement of methanol in blood is important to confirm the diagnosis of methanol intoxication and can be valuable in assessing the response to treatment. However, blood methanol is measured using gas chromatography in specialty laboratories, and the measurement can take many hours to a few days to complete. As noted previously, in the absence of measurements of methanol, assessment in changes of the serum osmolal gap can be useful in some cases, both in the diagnosis of methanol intoxication and for assessing the indication for and duration of treatment of this disorder.

### Treatment

The American Academy of Clinical Toxicology recommends ethanol or fomepizole be given to treat methanol intoxication based on the following criteria: Plasma methanol concentration  $>20$  mg/dl or recent history of ingestion of methanol with serum osmolal gap  $>10$  mOsm/L or strong clinical suspicion of methanol poisoning with at least two of the following: arterial

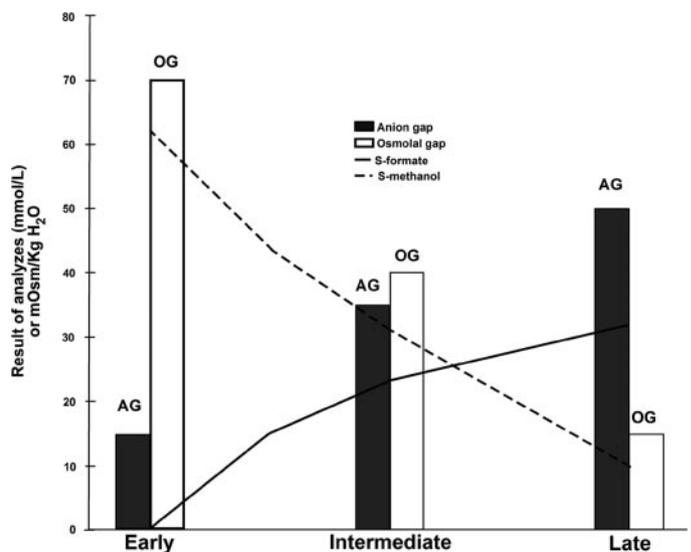


Figure 3. Evolution of changes in the serum osmolal and anion gaps during the course of methanol intoxication. Data from studies of methanol intoxication have revealed that early in the course of the disorder, the serum osmolal gap is the greatest and the serum anion gap the least. As metabolism of the parent alcohol proceeds, the serum osmolal gap and serum anion gap approximate each other. At later stages, the serum osmolal gap may return to baseline, whereas the serum anion gap continues to rise. Although it is presumed that a similar pattern would hold for many of the alcohol intoxications, sufficient data to confirm this are not available. Adapted from reference (23), with permission.

Table 6. Recommended dosage of ethanol for treatment of methanol or ethylene glycol intoxication<sup>a</sup>

Dose	Absolute Alcohol	Volume of 10% Solution
Loading	600 mg/kg	7.60 ml/kg
Maintenance, nondrinker with dialysis	66 mg/kg per h	0.83 ml/kg per h
	169 mg/kg per h	2.13 ml/kg per h
Maintenance, drinker with dialysis	154 mg/kg per h	1.96 ml/kg per h
	257 mg/kg per h	3.26 ml/kg per h

<sup>a</sup>Protocol theoretically can be used for treatment of other alcohol intoxications. Monitoring of ethanol levels is necessary to achieve values within recommended range. Reprinted from reference (12), with permission.

pH <7.3, serum  $\text{HCO}_3^-$  <20 mEq/L, and osmolal gap >20 mOsm/L (12,54).

One prescription for the quantity of ethanol to be given is shown in Table 6. If ethanol is present in the blood, then the quantity given will have to be reduced. Alternative prescriptions are designed to provide sufficient ethanol to maintain its concentration at approximately 100 mg/dl or a molar concentration of ethanol 25% of the methanol concentration (6,12). These latter methods require continual measurement of methanol and ethanol levels, which can be difficult to obtain in most hospital settings. If ethanol is given to patients who receive hemodialysis, then the quantity of ethanol will have to be increased.

Uncontrolled observational studies and individual case reports have demonstrated that fomepizole is safe and effective in the treatment of methanol intoxication (12,55,56,58). In a study of 11 patients who were treated with intravenous fomepizole (seven of whom also underwent hemodialysis), serum formic acid concentration fell markedly and both blood pH and visual acuity returned to normal (56). Nine of the 11 patients survived. Adverse effects included headache, nausea, dizziness, and dyspepsia. Hypotension, skin rash, and transient elevation in liver enzymes have been reported in other studies (12,56). Although randomized, controlled studies to compare ethanol and fomepizole have not been done, fomepizole is preferred by most experts (12,54,56,58). If fomepizole is not available, then ethanol is a reasonable alternative. Fomepizole should be given in sufficient concentrations to maintain serum concentrations in excess of 0.8 mg/L (10  $\mu\text{mol/L}$ ), a level that provides constant inhibition of ADH (55). As discussed next, patients may be treated with fomepizole and hemodialysis. Table 7 lists the recommended dosage of fomepizole with and without hemodialysis (12).

Hemodialysis has been used to remove methanol and formate and to correct the metabolic acidosis (12,15,28,58,67,72,73). A recent study (74) established a formula to determine the duration of dialysis necessary to achieve a serum methanol concentration (or that of other alcohols) of <5 mmol/L (approximately 16 mg/dl with methanol), based on the predialysis serum alcohol concentration, blood flow, gender, age, height, weight, and urea clearance of the dialyzer:

$$\text{Time (h)} = -V \ln (5/A)/0.06 \text{ k}$$

where V, the Watson estimate of total body water, is in liters; A is the initial alcohol concentration in mmol/L; and k is 80% of the manufacturer's specified urea clearance in ml/min.

The role of hemodialysis in formate removal is controversial. Kerns *et al.* (15) found that dialysis did not appreciably decrease the half-life for formate and concluded that dialysis might provide little benefit in the treatment of methanol intoxication if serum methanol were low. By contrast, Hovda *et al.* (75) found that it substantially accelerated the removal of formate and suggested that hemodialysis might be used to remove formate even if methanol levels were not elevated. In addition, they described a patient who had severe methanol intoxication and metabolic acidosis and whose formate half-life (usually 2.5 to 12.5 h) was prolonged to 77 h (28). Initiation of hemodialysis reduced it more than 20-fold to 2.9 h.

The American Academy of Clinical Toxicology recommends that hemodialysis be considered in the presence of metabolic acidosis (blood pH 7.25 to 7.30), visual abnormalities, renal failure, or electrolyte imbalance unresponsive to conventional therapy and/or serum methanol concentration of >50 mg/dl (12). However, fomepizole treatment of patients with methanol intoxication even with serum concentrations >50 mg/dl either eliminated completely the need for dialysis or allowed it to be done electively many hours after hospitalization (56,75,76).

Carefully controlled randomized studies would be useful to provide evidence-based guidelines for treatment at different stages of methanol intoxication. However, in their absence, hemodialysis in association preferably with fomepizole seems reasonable for the treatment of the majority of patients with methanol intoxication. Hemodialysis will result in rapid removal of methanol, probably will enhance formate removal, and will deliver base to correct the acidosis. Also, it is a relatively safe therapeutic procedure. This combination should reduce morbidity and mortality and decrease the duration of hospitalization. Other investigators, based on their clinical experience, have come to a similar conclusion (28,72). These treatment measures should be continued until methanol concentration is <16 mg/dl or undetectable, if possible, and blood pH is >7.3 (12,54,74).

It has been postulated that metabolism of formate is enhanced by folic acid, and given the lack of adverse effects, administration of folate as adjunctive therapy seems reasonable (12,15). Administration of base is recommended to treat the metabolic acidosis and promote the renal removal of formate (15,61). Criteria proposed for initiation of base therapy are not well established with recommendations to initiate it in the

**Table 7.** Recommended dosage of fomepizole for patients with methanol and ethylene glycol intoxication<sup>a</sup>

Without dialysis
Loading dose
15 mg/kg body wt
Maintenance dose
10 mg/kg body wt every 12 h for 4
15 mg/kg/ body wt every 12 h (if blood levels do not reach goal by 48 h)
With dialysis
Add 1 to 1.5 mg/kg body wt per h

<sup>a</sup>Dosage may have to be adjusted if <6 h from last dose. Protocol theoretically used for treatment of other intoxications. Reprinted from reference (12), with permission.

presence of any metabolic acidosis (pH <7.3) or only in the presence of severe acidemia (blood pH <7.1 to 7.2) (12,75).

## Ethylene Glycol Intoxication

### *Epidemiology*

Ethylene glycol is used in industrial production and is present in automobile coolants, heat transfer fluids, and runway deicers. It is colorless and odorless and has a sweet taste. Intoxication has resulted from topical applications of ethylene glycol-containing solutions to burns (77), but most intoxications result from oral ingestion of ethylene glycol-containing products (most frequently antifreeze), ethanol-based products containing ethylene glycol, or rarely contaminated drinking water (13). Ethylene glycol may be ingested as a cheap substitute for alcohol, taken in an attempt to commit suicide, or ingested accidentally. Ethylene glycol intoxication is more frequent than methanol intoxication. In 1999, the American Association of Poison Control Centers reported more than 5800 cases reflecting approximately 2% of the poisoning reported in that year in the United States (10). More than 600 of these cases (approximately 11%) occurred in children younger than 6 yr, and more than 800 (approximately 14%) occurred in children aged 6 to 19 yr (10).

The mortality of ethylene glycol intoxication is variable, ranging from 1 to 22% (8,10,78). The highest mortality is found in patients with the most severe metabolic acidosis and the longest duration between exposure and initiation of treatment: Either blood pH <7.1 or initiation of treatment >10 h after exposure (8,78). Although the lethal dosage of ethylene glycol has been reported to be 1.4 to 1.5 ml/kg body wt, death has been reported with lower amounts, and survival has been reported with much greater amounts (37). These observations could indicate some differences in susceptibility to the adverse effects of this alcohol.

### *Pathophysiology*

Metabolic acidosis and organ dysfunction primarily result from generation of glycolic and oxalic acid from metabolism of ethylene glycol (13,37,43,79). The accumulation of glycolic acid is

the primary cause of metabolic acidosis, but glycolate also impairs cellular respiration, and this effect can contribute to the development of lactic acidosis in some patients (6,37,43). Acute renal failure (ARF), myocardial dysfunction, neurologic function, and possibly pulmonary dysfunction result from deposition of oxalate with calcium in the kidney, heart, brain, and lung (8,13,37). Deposition of calcium oxalate in tissues also produces hypocalcemia, which depresses cardiac function and BP (13,37,80).

Because clinical and laboratory abnormalities are due to metabolites of ethylene glycol, co-ingestion of ethanol can delay their appearance by several hours (13,37,57). In the multicenter study examining the use of fomepizole in ethylene glycol intoxication (57), 12 (60%) of 19 had measurable blood ethanol levels, and four of the 12 had blood levels >100 mg/dl.

### *Clinical Findings*

The signs and symptoms of ethylene glycol have been reported to develop in three distinct stages: First there are neurologic abnormalities, followed by cardiopulmonary dysfunction, and finally renal dysfunction (13,37,57). However, it is not uncommon for neurologic, cardiopulmonary, and renal failure to be present together (37).

Initially, only mild confusion or stupor is present as a result of the effects of ethylene glycol. Within 12 to 24 h after ingestion (in the absence of ethanol), neurologic signs and symptoms can become more profound and focal signs may appear. Autopsy studies have revealed cerebral edema with calcium oxalate crystals in brain tissue at this point. Many of the deaths with ethylene intoxication have been reported to occur at this stage or shortly thereafter (37,80).

Cardiopulmonary signs and symptoms appear next and include shortness of breath associated with physical evidence of congestive heart failure. Myocarditis and pulmonary infiltrates with calcium oxalate crystal deposits in the myocardium or lungs have been found on autopsy examination (37). After 24 to 72 h, ARF, which can be oliguric or nonoliguric, develops (37,81). Rarely, ARF can be seen in the absence of other stigmata of ethylene glycol intoxication; therefore, this entity should be considered in the differential diagnosis of unexplained ARF (37). The appearance of cranial neuropathies, which are usually transient in nature, 8 to 15 d after ethylene glycol ingestion has been described (82). Signs and symptoms related to the presence of metabolic acidosis, such as Kussmaul breathing, and a predisposition to congestive heart failure or hypotension can be found at all stages and are most prominent in patients with blood pH <7.1 to 7.2.

### *Laboratory Findings*

The serum osmolality can be normal or elevated and is usually the highest within the first several hours after ingestion (13,24,37,38,43). As with methanol, even at this time it may be only slightly elevated. A serum concentration of 50 mg/dl will raise serum osmolality only approximately 9 mOsm/L. As ethylene glycol is metabolized to glycolic acid, a high anion gap metabolic acidosis will ensue. In this regard, approximately 86% of patients will be acidotic at the time of presentation

(13,37,83). Hyperchloremic acidosis at presentation or with treatment has not been reported.

It is postulated that glycolic and not oxalic acid is primarily responsible for the metabolic acidosis (14,38,43,78) based on a strong correlation between the measured glycolate concentration in the blood and the serum anion gap (13,43,78). However, the urinary excretion of oxalate and/or its deposition in tissues could result in an underestimation of its contribution to the metabolic acidosis.

The severity of the metabolic acidosis and level of glycolate in the blood are important prognostic signs: Patients with a serum  $\text{HCO}_3^- \leq 5$  mEq/L, blood pH <7.1, or serum glycolate level  $\geq 8$  to 10 mmol/L are more likely to die and/or develop ARF (14,78). In this regard, an important predictor of ARF and mortality is the time elapsed between ingestion of ethylene glycol and recognition of this intoxication, both being more frequent the longer it takes before a diagnosis is made and treatment is begun (13). Lactic acidosis can also be present and is more prominent in patients with the highest serum glycolate levels (37,43). However, serum lactate can be spuriously elevated if it is measured using a lactate oxidase-based method, because ethylene glycol is recognized by this enzyme (84).

An increase in the serum osmolal gap and high anion gap metabolic acidosis can be present simultaneously, but as more of ethylene glycol is metabolized, serum osmolality will fall, whereas the serum anion gap will stay elevated or rise further. In some cases, both serum osmolality and the serum bicarbonate and anion gap can be normal, the only remnant of the disorder being the finding of calcium oxalate crystals on pathologic examination of the tissues (37).

Four to 8 h after ingestion of ethylene glycol, calcium oxalate crystals will be present in the urine (38). Crystalluria can persist for as long as 40 h in the absence of renal failure and up to 4 d in its presence (37,38,81). The nature of the crystals can change with time: Within the first 4 to 5 h, envelope-shaped calcium oxalate dihydrate crystals are present; between 5 and 7 h, a mixture of monohydrate and dihydrate crystals are present; and after 7 h, only the needle-shaped monohydrate is present (37,38). Hypocalcemia, which is most profound many hours after ethylene glycol ingestion, is frequent at a time when oxalate crystalluria is prominent (13,37).

The diagnosis of ethylene glycol intoxication is confirmed by detection of elevated ethylene glycol levels as determined by gas chromatography (13,37,40,85). Falsely positive levels of ethylene glycol have been reported in the presence of both an elevated serum lactate dehydrogenase and lactate concentrations and with ketoacidosis (37,85). However, marked elevations in blood concentrations of ethylene glycol are unlikely to be caused by these abnormalities.

Sodium fluorescein is added to some brands of antifreeze at a final concentration of 20  $\mu\text{g}/\text{ml}$  (86,87). Examination of urine (collected in containers without intrinsic fluorescence) for visible fluorescence after exposure to ultraviolet light at a wavelength of approximately 360 nm with a Wood's lamp has been used as an additional diagnostic tool (86–89). There are several pitfalls with this test. A number of drugs, food products, toxins, and endogenous compounds can contribute to urine fluores-

cence, producing false-positive results (86,87,89,90). The urine fluorescence is often short lived because the half-life of sodium fluorescein is 4.25 h (86–89). Not every brand of antifreeze contains fluorescein. Also, the optimal excitation wavelength of fluorescein is approximately 494 nm (86,87). Thus, urine initially considered negative with a Wood's lamp demonstrated fluorescence when studied using a fluorimeter at this wavelength (86–89). Finally, fluorescence is pH dependent and will be minimal or absent at a urine pH  $\leq 4.5$  (86,87). Physicians, therefore, should be cautious about either excluding or confirming the diagnosis on the basis of this test, and decision about initiating treatment should never be made on its basis alone.

### Treatment

Volume expansion with or without mannitol and bicarbonate may increase the urinary excretion of ethylene glycol and its metabolites and theoretically help to forestall oxalate-induced ARF (37). Indications and prescription for the use of ethanol in treatment of ethylene glycol is similar to that for methanol.

The effectiveness of fomepizole in the treatment of ethylene glycol intoxication was first demonstrated in a small number of case reports (13,53,79). In 1999, Brent *et al.* (57) reported a multicenter, prospective, observational study of 19 patients who had ethylene glycol intoxication and metabolic acidosis (serum  $\text{HCO}_3^-$  4 to 28 mEq/L) and were treated with fomepizole (17 of whom also underwent hemodialysis). Within a few hours of fomepizole therapy, serum glycolate levels fell and acid-base parameters improved. With addition of dialysis, serum glycolate levels fell from a mean of 89.7 mg/dl to undetectable values, and acid-base parameters normalized within 24 h (57). Eighteen of the 19 survived. All patients without renal failure before treatment maintained normal renal function, and renal function returned to normal in six of nine patients with renal failure. Other studies confirmed the effectiveness of fomepizole in contributing to improvement of metabolic acidosis and avoidance or resolution of renal failure (58,59).

The American Academy of Clinical Toxicology recommends that ethanol or fomepizole be given in the presence of ethylene glycol level >20 mg/dl or a documented history of ingestion of potentially toxic amounts of ethylene glycol and serum osmolal gap >10 mOsm/L or history or strong clinical suspicion of ethylene glycol poisoning and two of the following abnormalities: Arterial pH <7.3, serum bicarbonate concentration <20 mEq/L, osmolal gap >10 mOsm/L, and the presence of oxalate crystals (13).

Hemodialysis is effective in rapidly lowering ethylene glycol levels and removing glycolate (43,62,78). The mean clearance rate of ethylene glycol is approximately 145 to 230 ml/min. The duration of hemodialysis necessary to reduce ethylene glycol concentrations can be estimated using the formula described by Hirsch *et al.* (74). Glycolate clearance is approximately 60% of urea clearance (43), and hemodialysis was shown to reduce its elimination half-life by more than four-fold (62).

Hemodialysis has been recommended for the treatment of ethylene glycol intoxication in the presence of severe metabolic

acidosis that is unresponsive to therapy (blood pH <7.25), the presence of renal failure particularly if severe, and ethylene glycol levels >50 mg/dl (13). Because the serum concentration of glycolic acid has been shown by some to be an important prognostic sign, hemodialysis is also recommended if concentrations are >8 to 10 mmol/L (78).

Some investigators have found that hemodialysis is not necessary even in the face of very high ethylene glycol levels (79,91). In a retrospective study, eight of 11 patients with ethylene glycol intoxication were treated only with fomepizole without dialysis (79). Twenty-one percent of the patients were comatose, 34% had severe metabolic acidosis, and 11% had significant renal failure. Patients without renal failure recovered without developing renal failure or other complications, and only one of the 11 died.

Similar to methanol intoxication, given the relative safety of hemodialysis, its effectiveness in removing the alcohols and potentially toxic metabolites and the difficulty of obtaining rapid measurements of ethylene glycol or glycolate levels, consideration should be given to initiation of hemodialysis in concert with fomepizole in the majority of suspected or documented cases of ethylene glycol intoxication to prevent calcium oxalate deposition and renal failure and to reduce the cost of hospitalization. However, controlled, prospective studies would be useful in developing evidence-based guidelines, and a comparison of fomepizole alone *versus* dialysis with fomepizole is indicated.

Administration of thiamine may promote metabolism of glycolic acid to  $\alpha$ -hydroxyl- $\beta$ -keto adipate, whereas administration of pyridoxine will promote metabolism of glyoxylate to glycine (13,40). Treatment with these compounds could be of value therefore in promoting the breakdown of the organic acids to less injurious products, although this has not been proved. Conversely, their administration is associated with little morbidity. Base administration to treat metabolic acidosis and perhaps augment urinary excretion of organic acid anions has been recommended by most experts (13).

## Diethylene Glycol Intoxication

### *Epidemiology*

Diethylene glycol is used in industrial production, is present in brake fluid, and is used as an illegal adulterant in ethanol spirits or in medication (17,46). Sporadic cases of accidental poisoning or its use as a means of attempting suicide have been described (17,44,92). However, this intoxication has primarily been reported in outbreaks in which the diethylene glycol was used as a solvent for medications (46,93–96).

The first reported cases of diethylene glycol intoxication in the United States in 1937 were directly responsible for the passage of the Federal Food Drug and Cosmetic Act in 1938 (46). Since then, outbreaks have occurred in China, Haiti, India, Bangladesh, and Latin America (9,46,95). In four of the outbreaks, only children were affected (9,46,93,96). This has been attributed to the smaller size of children. Importantly, the mortality approached 90% in some instances (9,93,96). The high mortality could be the result of late recognition of the disorder. All of these cases described resulted from oral ingestion of

diethylene glycol. A single case of diethylene glycol from topical application has been reported (33). The toxic dose of diethylene glycol has been estimated at 0.14 mg/kg body wt and the lethal dose at 1 to 1.63 g/kg body wt (11,17). However, there is great variability in susceptibility to diethylene glycol, suggesting that individual risk factors are important (11,93).

### *Pathophysiology*

Metabolic acidosis and organ dysfunction initially attributed to generation of glycolic acid and oxalic acid is presently postulated to result from the generation of HEAA from the metabolism of diethylene glycol (11,46,47,92,93,97–99). The mechanism by which HEAA produces cellular dysfunction remains unclear.

### *Clinical Findings*

The time from ingestion of diethylene glycol until the onset of clinical findings has not been well established because, in most cases, several days had elapsed until the diagnosis of diethylene glycol intoxication was made (9,11,46,96). However, in one study of five patients who presented within 24 h after the ingestion (92), clinical findings were similar to those noted in patients who were seen several days after ingestion.

Acute oliguric and nonoliguric renal failure is frequent (9,92,93,96). In patients who survived, irreversible renal failure has been reported; however, the factors that contribute to irreversibility of the renal failure are not clear (92,93). Hepatitis, pancreatitis, and neurologic abnormalities are seen, and patients commonly present with abdominal pain, diarrhea, headache, and altered mental status (9,17,46,92,93,96). Physical examination at the time can demonstrate hepatomegaly and jaundice. Although rare, cranial neuropathies and bulbar palsy appearing 10 to 14 d after the ingestion have been reported, even though patients had been treated with ethanol infusion and hemodialysis (92). Signs and symptoms related to the presence of metabolic acidosis described previously are often prominent.

### *Laboratory Findings*

Serum osmolality can be high or normal (17,92). The molecular weight of diethylene glycol is relatively high (106); therefore, hyperosmolality is less frequent than with the other alcohols. Metabolic acidosis ranging from mild to severe is usually present if patients are seen  $\geq 24$  h after ingestion (11,17,92,96). Elevations in blood amylase and liver enzymes reflect the presence of both pancreatic and hepatic injury. Blood urea nitrogen, serum creatinine, and potassium concentration are elevated as a result of renal failure.

Serum diethylene glycol concentration is measured using gas chromatography in a specialized laboratory (17). Documentation of high levels in contaminated medication has been reported, and this may be a valuable method of confirming exposure in large outbreaks.

### *Treatment*

Administration of inhibitors of ADH and ALDH to rats given diethylene glycol completely prevented production of HEAA

(47), and a young girl with known ingestion of diethylene glycol intoxication but without metabolic acidosis or renal failure was treated successfully with fomepizole without dialysis (44). Dialysis with or without fomepizole or ethanol has been used in the treatment of most patients (9,17,92,93). In part, the use of dialysis resulted from the high prevalence of renal failure in these patients (9,93,94,96); however, because diethylene glycol and possibly HEAA are theoretically dialyzable, use of dialysis even in the absence of renal failure seems logical. Two case reports of children who did not have renal failure and were treated with ADH inhibitors and/or dialysis have been reported, both of whom recovered (17,44). Similarly, five patients with diethylene glycol intoxication were treated with ethanol and dialysis with complete recovery in two (92); one of the patients died, and two others developed irreversible renal failure.

The clearance of diethylene glycol is not known. In one case in which diethylene glycol levels in blood were measured before and after dialysis, the predialysis levels were extremely low and those obtained after dialysis were undetectable (17). However, given its relatively small molecular weight, its clearance should be not too dissimilar from that of the other alcohols. No studies examining the dialysis of its major metabolite HEAA have been published.

Given the high mortality and the risk for irreversible renal failure, treatment of suspected patients with fomepizole and hemodialysis is warranted. Clearly, documentation of a cohort of patients, particularly children, presenting with ARF and metabolic acidosis should arouse the suspicion of the clinician (9,11,46,93,94,96). Because other diagnostic clues such as an increment in serum osmolality are inconsistent, the clinician may be forced to initiate treatment before confirmation of the diagnosis.

## Propylene Glycol

### *Epidemiology*

Propylene glycol is used as a solvent for intravenous, oral, and topical pharmaceutical products (29,100–105) and as a major ingredient of some antifreeze and hydraulic fluids (49). Drugs in which it is present include etomidate, phenytoin, diazepam, lorazepam, phenobarbital, nitroglycerin, digoxin, hydralazine, and trimethoprim-sulfamethoxazole. Cases of intoxication have been reported after topical administration for treatment for burns (31) and with oral ingestion (49), but the majority of reported cases have resulted from intravenous administration (36,100,101,104,105). In this regard, propylene glycol is used as a diluent in benzodiazepines (lorazepam concentration, vol/vol 0.8), which commonly are administered to patients who have seizures, are undergoing alcoholic withdrawal, or are intubated (36). The exact prevalence is not known, but a study of 21 patients receiving benzodiazepines in the intensive care unit revealed that four (19%) had either an increased serum anion gap or a fall in serum bicarbonate concentration consistent with propylene glycol toxicity (36).

The serum propylene glycol concentration associated with toxicity has ranged from 12 to 520 mg/dl, but toxicity is most likely to occur at blood concentration in excess of 100 mg/dl

(19,106,107). Patients with impaired liver or kidney function are said to be at increased risk for developing toxicity (107). In contrast to methanol, ethylene glycol, and diethylene glycol, the mortality of propylene glycol is low, despite its administration to patients with multiple organ dysfunction (19,36,49,100,104–107).

### *Pathophysiology*

Metabolic acidosis associated with propylene glycol has been attributed to generation of lactic acid during its metabolism (49,108–111). Both L- and D-lactic acidosis have been described (109–111). Renal failure has been described in some patients, and proximal tubular cell injury has been reported in cultured renal cells exposed to propylene glycol, but the pathogenic mechanisms of renal toxicity are unclear (110,111).

### *Clinical Findings*

Clinical findings attributable to propylene glycol intoxication other than those associated with renal failure or metabolic acidosis are limited. After intravenous administration with benzodiazepines, central nervous system depression may occur, but this is an expected result of the medication rather than due to propylene glycol (29,104,107,109).

### *Laboratory Findings*

Laboratory abnormalities are the most common evidence of propylene glycol intoxication. Serum osmolality can be normal or high (26,36,105,107,109,111), and an increased serum osmolality may be the only evidence of abnormal blood concentrations. Because its half-life in blood is short, once the intravenous infusion is discontinued, serum osmolality will return rapidly to baseline. As a result, several clinicians have recommended using the serum osmolal gap as a surrogate for propylene glycol concentrations to evaluate the response to treatment (19,105,106,111).

Mild L-lactic acidosis with serum lactate concentration in the range of 2 to 6 mEq/L can be found, but more severe lactic acidosis is infrequent (36,104,109). Rare cases of D-lactic acidosis have been reported (110).

Renal dysfunction has been described in a small percentage of patients, some of whom had pathologic evidence of tubular necrosis (36,106,107,109–111). However, this is not common. In one carefully controlled observational study, renal function, as assessed by measurement of serum creatinine concentration, was not reduced, although serum propylene glycol concentrations were at levels at which other evidence of propylene glycol toxicity has been described (36).

### *Treatment*

Because this disorder is iatrogenic, prevention by limiting the dosage of propylene glycol that is given to patients in the intensive care unit may be the best treatment. Zar *et al.* (111) recommended that propylene glycol be given in doses not to exceed 2.9 g/h (<69 mg/d). Based on the concentration of propylene glycol in lorazepam for example, this could be achieved by limiting lorazepam to <166 mg/d. This dosage

might have to be reduced further in patients with significant risk factors.

The metabolic acidosis is usually mild to moderate in degree, and discontinuation of medication containing propylene glycol can lead to correction of the acidosis in  $\leq 24$  h in most patients (36). In the face of extremely high blood concentrations, hemodialysis is extremely effective in rapidly reducing serum propylene glycol levels (107). Therefore, in the face of renal failure, extremely high serum propylene glycol levels, or severe metabolic acidosis, early institution of dialysis is warranted (35,107,111). Although theoretically fomepizole should be beneficial, its use has not been reported. However, a patient with a serum propylene glycol concentration of 470 mg/dl, the highest reported blood level, was treated with ethanol infusion alone. He was discharged after 48 h having had only minimal lactic acidosis and no sequelae (49). Thus, in cases of propylene glycol intoxication with very high blood concentrations and lactic acidosis, administration of fomepizole along with dialysis is warranted. If severe lactic acidosis is present and dialysis is not done, then base might be given, although this remains controversial (63).

## Alcoholic Ketoacidosis

### Epidemiology

The syndrome of alcoholic ketoacidosis (AKA) is uncommon in patients with acute ethanol intoxication, being found in  $<10\%$  of patients (112–114). It is most frequent in patients who have long-term ethanol intake and liver disease and develop the syndrome after a period of binge drinking (39,112) and is associated with reduced food intake and episodes of vomiting; the latter might explain the concurrence of metabolic alkalosis noted in some patients (39,112,115,116).

A large number of patients with methanol or ethylene glycol intoxication have developed these intoxications after ingesting contaminated ethanol-based products, and, in these cases, serum ethanol levels are high (55,57). In this regard, increased levels of ketones in the blood or urine have been found in from 2 to 20% of patients with methanol intoxication (52,56), consistent with AKA. Although AKA often occurs in patients with significant comorbid conditions, the mortality is often low: In a study of 74 patients with AKA, only 1% died (39).

### Pathophysiology

Although oxidation of ethanol in the liver generates acetaldehyde, which is converted to acetate and acetyl CoA, a precursor of ketone bodies, the ketogenesis has been primarily attributed to stimulation of lipolysis and free fatty acids generation from the low insulin levels and development of increased levels of counterregulatory hormones such as epinephrine, cortisol, and glucagon in these patients (115). Excess production of acetoacetic acid and  $\beta$ -hydroxybutyric acid underlies the metabolic acidosis, with increased NADH favoring production of  $\beta$ -hydroxybutyrate compared with acetoacetate (115), the ratio of these ketones rising from the normal value of 3:1 to more than 9:1 (112–115). The increased NADH also favors increased lactic acid production; therefore, concomitant lactic acidosis even in the absence of impaired tissue perfusion is not uncommon

(39,112,115). However, the increase in lactic acid production is small, and severe lactic acidosis in the absence of sepsis or hypotension is rare (39,112,114,115).

### Clinical Findings

Because this disorder is most frequent in chronic alcoholic patients with acute and chronic liver and pancreatic disorders, it may be difficult to distinguish clinical findings that are due to AKA from those that are due to liver or pancreatic disease (39,112,117). Abdominal pain, nausea and vomiting, and altered mental status are the most prominent symptoms, being found in approximately 25 to 37% of patients (39). Changes in mental status without focal neurologic signs are frequent. Abdominal tenderness on palpation and enlargement of the liver and occasionally the spleen may reflect the presence of acute or chronic liver disease. Nonspecific symptoms and signs related to the presence of metabolic acidosis can be observed.

### Laboratory Findings

Metabolic acidosis alone is common, but more frequently there are mixed acid-base disorders, including respiratory alkalosis and metabolic acidosis, metabolic acidosis associated with metabolic alkalosis, or triple disturbances including respiratory and metabolic derangements (3,39,112,116,117). The metabolic acidosis is usually of the high anion gap variety. Hyperchloremic acidosis, described in patients with DKA is uncommon, even after treatment with saline (115). Hyponatremia, hypokalemia and/or hyperkalemia, and hypophosphatemia are also commonly found (39,112,117).

The serum osmolality is often normal, because AKA is often found after most of the ethanol has been metabolized (39,112,115). However, serum osmolality can be elevated as a result of an elevated serum concentration of either ethanol or ketones (21,22,39,112,118–120). In some patients, the increased serum osmolality is due to substances other than ketones or ethanol. Braden *et al.* (118) reported an increase in the serum osmolal gap in a patient with alcohol intoxication but undetectable ethanol levels. Serum concentrations of glycerol, acetone, and the acetone metabolites acetol and 1,2-propanediol were increased, accounting for 92% of the osmolal gap.

Theoretically, the diagnosis of alcohol ketoacidosis is confirmed by detection of elevated ethanol levels. However, serum ethanol concentrations are often undetectable (39,112,117,119,120). Therefore, the clinician will often have to rely on a history of alcohol ingestion and the absence of stigmata of diabetes in making the diagnosis of AKA. Ketones in body fluids are detected by the nitroprusside reaction. This test detects acetoacetate but not  $\beta$ -hydroxybutyrate. Therefore, the nitroprusside test of urine or blood may revealed a trace positive reading (112,114,115,119,120). Negative readings, although they can occur, are uncommon: Only 10 of 74 patients with AKA had a negative test for ketones. (39).

Blood glucose can be low normal or high (39,112,114,115,119–121). Hypoglycemia has been attributed to the presence of depleted glycogen stores and reduced gluconeogenesis. If hyperglycemia is present, then it can make the distinction from DKA difficult.

### Treatment

Resolution of AKA occurs after administration of dextrose and/or saline; however, the metabolic acidosis resolves more quickly and  $\beta$ -hydroxybutyrate levels fall more rapidly when both are administered together (121,122). Saline administration alone, although effective in restoring volume deficits, could also theoretically convert the metabolic acidosis to a hyperchloremic form, as described for DKA (70). However, none of the patients who had AKA and were given saline developed hyperchloremic acidosis, whereas >50% of the patients with DKA did (115). Resolution of AKA after fluid administration is often more rapid than DKA (mean time 6 versus 16 h) (115).

At present, it is recommended that both dextrose and saline be administered in a patient with AKA to restore volume deficits and provide glucose to prevent hypoglycemia. Insulin is not routinely recommended. However, if significant hyperglycemia or life-threatening acidemia is present, then insulin may be indicated (122). Base administration is not usually

required given the rapid resolution of acid-base abnormalities once appropriate therapy is initiated.

## Isopropanol

### Epidemiology

Isopropanol is used in various industrial products, as a cleaning agent, deicer, and in rubbing alcohol. Isopropanol intoxication results from its accidental ingestion or its use in suicide attempts or when used in lieu of ethanol (4,5). In 1997, 1999, and 2004, a total of almost 27,000 exposures (most of them minor) were reported to poison control centers; one third were in children who were younger than 6 y (10,123,124). Mortality is often less than with methanol or ethylene glycol intoxication (0.1% in 2004) (124).

Some investigators had suggested that isopropanol concentrations >150 mg/dl produce coma and hypotension and levels >200 mg/dl are said to be incompatible with life (4,125). By contrast, Lacouture *et al.* (126) found that severe hypotension

Table 8. Epidemiology, diagnostic clues, poor prognostic factors, and recommendations for treatment of toxic alcohol ingestions<sup>a</sup>

Disorder	Epidemiology	Diagnostic Clues <sup>b</sup>	Poor Prognostic Factors
Methanol intoxication	Accidental or intentional ingestion of adulterated alcohol or products with methanol; rare cases of inhalation of methanol	Osmolal gap with HAGA <sup>c</sup> Visual difficulties with optic papillitis	Blood pH <7.1; LA; severe coma; severe hypotension; serum methanol >50 to 100 mg/dl
Ethylene glycol intoxication	Accidental or intentional ingestion of antifreeze, alcohol adulterated with ethylene glycol, or products with ethylene glycol	Osmolal gap with HAGA <sup>c</sup> ARF with osmolal gap Calcium oxalate crystals in urine, monohydrate or dihydrate	Blood pH <7.1; glycolate level >8 to 10 mmol/L; ARF requiring HD; diagnosis >10 h after ingestion; serum ethylene glycol >50 to 100 mg/dl
Diethylene glycol intoxication	Ingestion of contaminated medication or products with diethylene glycol	Osmolal gap with HAGA <sup>c</sup> Osmolal gap with ARF Osmolal gap with coma	Blood pH <7.1; ARF requiring HD; severe coma; ingestion of >1.34 mg/kg body wt
Propylene glycol intoxication	Intravenous administration of medication with propylene glycol; rare ingestion of products with propylene glycol	Osmolal gap with or without LA	Severe LA; serum propylene glycol level >400 to 500 mg/dl
Isopropanol intoxication	Accidental or intentional ingestion of rubbing alcohol	Osmolal gap without HAGA	Severe LA; hypotension; serum isopropanol level $\geq$ 200 to 400 mg/dl
Alcoholic ketoacidosis	Binge drinking often in alcoholic patients associated with starvation and often vomiting	HAGA, trace positive or negative nitroprusside reaction with increase with H <sub>2</sub> O <sub>2</sub> ; hypoglycemia; osmolal gap	Blood pH <7.0; severe comorbid conditions

<sup>a</sup>ARF, acute renal failure; HAGA, high anion gap metabolic acidosis; HD, hemodialysis; LA, lactic acidosis.

<sup>b</sup>Clues present in descending order of usefulness.

<sup>c</sup>Presence of serum osmolal gap and HAGA will depend largely on time after ingestion when blood is sampled. Presence of osmolal gap and HAGA together are important diagnostic clues.

with coma was found only with serum isopropanol levels >400 mg/dl.

#### Pathophysiology

Although isopropanol is metabolized to acetone, which itself might be toxic, the cause of the clinical and laboratory abnormalities seem to be due to the effects of isopropanol on organ function (4,5,125–128).

#### Clinical Findings

Clinical findings usually appear within 30 to 60 min after ingestion, although they can take as long as 3 to 4 h to develop (4,5,126,128). Abdominal pain, nausea, vomiting, diarrhea, and changes in mentation are the most common findings. Hypotension can be present in the face of very high isopropanol levels.

#### Laboratory Findings

The most common laboratory abnormality is an increase in the serum osmolality (4,5,126,127). Metabolic acidosis is usually

absent, unless hypotension is sufficient to produce lactic acidosis (126–128). Because one of the major metabolites of isopropanol is acetone, the nitroprusside reaction will be positive (4,126). The triad of normal acid-base parameters, hyperosmolality, and a positive nitroprusside reaction of urine and/or blood should suggest this diagnosis.

Isopropanol levels will usually be elevated. Serum creatinine, if measured with the colorimetric method, can be elevated in the absence of renal failure as a result of the interference of acetone with the creatinine determination (4).

#### Treatment

Supportive measures are often sufficient if the patient is not comatose and/or hypotensive. If hypotension is present along with coma, then initiation of hemodialysis has been recommended (4,126–128). The blood level of isopropanol at which dialysis should be initiated is not clear. Correlations between the severity of the clinical outcome and the blood levels of

Table 9. Recommendations for treatment of toxic alcohol ingestions<sup>a</sup>

Disorder	Treatment <sup>b</sup>
Methanol intoxication	Initiate fomepizole (alcohol if fomepizole not available) and HD with methanol >20 mg/dl, in presence of HAGA with osmolal gap and high suspicion of ingestion. Initiate HD alone if HAGA present and methanol levels <10 mg/dl or no osmolal gap but strong suspicion of ingestion. Give folinic or folic acid. Give base with severe acidosis if patient not undergoing HD. Discontinue treatment when pH normalized and methanol levels <10 to 15 mg/dl or undetectable. If measurement of methanol not available use return of blood pH and serum osmolality to normal as goals of therapy.
Ethylene glycol intoxication	Initiate fomepizole (alcohol if fomepizole not available) and HD with ethylene glycol levels >20 mg/dl or in presence of HAGA with osmolal gap and high suspicion of ingestion. Initiate HD alone if HAGA present and ethylene glycol level <10 mg/dl or no osmolal gap but strong suspicion of ingestion. Give base with severe acidosis if patient not undergoing HD. Give thiamine and pyridoxine. Discontinue treatment when pH normalized and ethylene glycol levels <10 to 15 mg/dl or undetectable. If measurement of ethylene glycol not available use return of blood pH and serum osmolality to normal as goals of therapy.
Diethylene glycol intoxication	Initiate HD with osmolal gap, HAGA, and ARF or with high suspicion of ingestion because of cohort of cases ingesting contaminated medication. Administration of fomepizole not approved but recommended in addition to dialysis. Discontinuation of treatment with recovery of renal function, normalization of acid-base parameters and osmolal gap.
Propylene glycol intoxication	Discontinue medication containing propylene glycol which will be effective alone in most cases. Initiate dialysis and/or fomepizole with severe LA or very high serum concentrations >400 mg/dl and evidence of severe clinical abnormalities.
Isopropanol intoxication	Supportive therapy usually sufficient. Initiate HD with serum level 200 to 400 mg/dl or in presence of marked hypotension or coma. <sup>c</sup>
Alcoholic ketoacidosis	Administer intravenous fluids including dextrose and NaCl; base rarely needed, might be considered with blood pH <6.9 to 7.0; consider administering insulin with marked hyperglycemia

<sup>a</sup>ARF, acute renal failure; HAGA, high anion gap metabolic acidosis; HD, hemodialysis; LA, lactic acidosis.

<sup>b</sup>Indications for treatment may differ from those of the American Academy of Clinical Toxicology particularly with recommendation for early initiation of HD (see text).

<sup>c</sup>Estimate of serum level to initiate HD not established.

isopropanol have revealed conflicting results (126–128). Some studies have suggested blood levels of 150 to 200 mg/dl can be associated with increased mortality (125,128), whereas, in others, only blood concentrations of approximately 400 mg/dl were associated with a poor outcome (126). Given the effectiveness of dialysis in removing isopropanol and the safety of this procedure, it seems reasonable to initiate hemodialysis in the presence of severe coma, hypotension, or serum isopropanol levels >200 mg/dl.

## Conclusions and Future Considerations

Several of the alcohol intoxications can produce severe cellular dysfunction, which can be irreversible, and if they are untreated or treatment is initiated late in their course, then they can be associated with a very high mortality. Therefore, a high index of suspicion for these disorders should be maintained in the presence of unexplained metabolic acidosis or hyperosmolality, unexplained ARF, or neurologic dysfunction. Recent reports of contamination of medication with diethylene glycol further emphasize the importance of these disorders (94,95).

Given the absence of inexpensive and rapid diagnostic tools in common use to detect these intoxications, early treatment including fomepizole and/or dialysis might have to be initiated before a definitive diagnosis is made, particularly in the cases of methanol, ethylene glycol, and diethylene glycol intoxications. In this regard, a high priority should be given for developing methods to diagnose these disorders rapidly and thereby facilitate the initiation of appropriate therapy (129).

Table 8 summarizes salient epidemiologic aspects, key clinical and laboratory findings listed in the order of their usefulness for diagnosis, and important indicators of a poor prognosis. Table 9 summarizes the authors' recommendations for indications and timing of initiation and duration of specific therapy for each of the disorders. In regard to treatment, as has been emphasized before, controlled studies are not available to evaluate the usefulness of many of the various therapies. Therefore these recommendations represent conclusions gleaned from the authors' analysis of the literature and may differ from those of the American Academy of Clinical Toxicology, particularly with recommendations for the early initiation of hemodialysis for several of the disorders. Randomized, controlled studies of all modalities of treatment would be valuable to facilitate the development of evidence-based guidelines for therapy, particularly of methanol, ethylene glycol, diethylene glycol, and isopropanol, the disorders with potentially the highest mortality.

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None.

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