**Introduction**

Toxic alcohols refer to alcohol-containing compounds other than ethanol that can cause severe poisoning when ingested by humans. The most clinically significant toxic alcohols are methanol, ethylene glycol, and isopropanol. These substances have widespread industrial uses and are found in common household products, leading to thousands of exposures annually, both unintentional and intentional. While generally absorbed rapidly through ingestion, toxicity results not from the parent alcohols themselves, but from their toxic metabolic intermediates that cause a high anion gap metabolic acidosis and characteristic end-organ damage. As pharmacists, our role is crucial in promptly identifying possible toxic alcohol ingestions based on history and clinical presentation, assisting in interpretation of laboratory studies, and optimizing management through recommending appropriate antidotal therapy, adjuncts, and hemodialysis. This overview will discuss the pharmacology, pathophysiology, clinical features, diagnostic approach, and evidence-based treatment principles for toxic alcohol poisoning, equipping pharmacists to improve outcomes in this potentially devastating yet highly treatable condition. Recent focus has been on the ideal indications for hemodialysis versus antidotal therapy alone, use of oral ethanol formulations in resource-limited settings, and prevention of outbreaks through public health measures.

**Clinical Presentation**

The clinical manifestations of toxic alcohol ingestion depend on the specific agent, dose, and timing, but there are some common features:

* Central nervous system:
  + Early CNS depression, confusion, ataxia, seizures
  + Potential progression to coma

* Gastrointestinal:
  + Nausea, vomiting, abdominal pain from mucosal irritation
  + Hemorrhagic gastritis with isopropanol

* Ophthalmologic:
  + Blurred vision, snowy vision, blindness (methanol)
  + Optic disc swelling, optic atrophy

* Renal:
  + Flank pain, acute kidney injury (ethylene glycol)

* Cardiopulmonary:

* Tachycardia, hypotension, pulmonary edema
* Metabolic acidosis with elevated anion gap

Certain populations are at higher risk:

* Infants and young children - unintentional exposures, increased absorption
* Patients with alcohol use disorder - intentional ingestion, concomitant ethanol
* Older adults - impaired metabolism
* Patients on dialysis - decreased clearance
  + Methanol → formaldehyde → formic acid

Pitfalls include attributing initial CNS and GI effects to ethanol intoxication and missing the diagnosis of toxic alcohol ingestion entirely. A high index of suspicion is required based on history and clinical context. The manifestations change over time as the toxic metabolites accumulate. Repeated assessment and monitoring is key, as patients can rapidly deteriorate.

**Pathophysiology**

Toxic alcohols exert their deleterious effects not through the parent compounds themselves, but through toxic intermediate metabolites that accumulate as a result of hepatic metabolism.

The primary enzyme responsible for metabolism is alcohol dehydrogenase (ADH), which converts the parent alcohols into aldehydes, then aldehyde dehydrogenase (ALDH) further metabolizes them into organic acids.

**Methanol metabolism:**

* Accumulation of formic acid causes severe metabolic acidosis and end-organ damage
  + Ethylene glycol → glycoaldehyde → glycolic acid → glyoxylic acid → oxalic acid

**Ethylene glycol metabolism:**

* Glycolic acid is primarily responsible for metabolic acidosis
* Oxalic acid binds calcium, precipitating as crystals leading to kidney injury

**Isopropanol metabolism:**

* Isopropanol → acetone
* Acetone cannot be further metabolized, causing CNS depression, but not acidosis

The accumulated aldehyde and organic acid metabolites are directly toxic and are not readily eliminated from the body. The metabolic acidosis caused by these organic anions can be severe and life-threatening.

Additionally, the toxic effects of these metabolites manifest in certain susceptible end-organs:

Methanol: Formic acid targets the optic nerves and basal ganglia

Ethylene glycol: Oxalic acid precipitates as crystals damaging the kidneys

Isopropanol: Acetone causes CNS depression

Understanding this crucial concept that the parent alcohols require metabolism into toxic intermediates to cause poisoning sets the foundation for therapeutic approaches aimed at inhibiting the metabolic process through blocking alcohol dehydrogenase. This can prevent the downstream effects of the metabolites if implemented early enough in the course.

**Diagnostic Approach**

The diagnosis of toxic alcohol ingestion requires a combination of clinical suspicion, laboratory studies, and identification of characteristic end-organ effects.

**Key Laboratory Tests**

* Serum electrolytes: identify anion gap metabolic acidosis
* Renal function: assess for ethylene glycol-related kidney injury
* Arterial blood gas: determine pH, lactate, bicarbonate
* Serum ethanol level: ethanol co-ingestion impacts metabolism
* Measured serum osmolality: calculate osmolal gap

* Toxic alcohol levels:
  + Methanol
  + Ethylene glycol
  + Isopropanol

* Metabolite levels:
  + Formic acid (methanol)
  + Glycolic acid (ethylene glycol)

* Urinalysis: assess for oxalate crystals (ethylene glycol)
* Urine fluorescence: may detect antifreeze (ethylene glycol)

**Characteristic End-Organ Effects**

* Optic nerve damage, blindness (methanol)
* Kidney injury - elevated creatinine, oliguria (ethylene glycol)
* CNS depression without acidosis (isopropanol)
* Hemorrhagic gastritis (isopropanol)

**Interpretation Caveats**

* Osmolal gap has limited sensitivity
* High anion gap nonspecific
* Normal gaps do not exclude significant ingestion
* End-organ findings may precede metabolic changes
* Co-ingestions and comorbidities confound the picture

In summary, diagnosis requires integration of multiple factors - history, exam findings, laboratory studies, and identification of characteristic end-organ effects. Targeted testing for toxic alcohols and metabolites is ideal when available. However, treatment should not be delayed for laboratory confirmation in symptomatic patients when there is sufficient clinical concern.

### Management Overview

General principles include:

* Stabilizing airway, breathing, circulation
* Gastrointestinal decontamination is not beneficial
* Inhibiting alcohol dehydrogenase with fomepizole or ethanol prevents metabolism to toxic products
* Hemodialysis removes parent compound and metabolites, corrects acidosis
* Sodium bicarbonate treats profound acidemia
* Supportive care for end-organ dysfunction:
  + Methanol: Folinic acid, vitamin replacement
  + Ethylene glycol: Thiamine, pyridoxine, monitor renal function

Disposition depends on severity, co-ingestions, and psychiatric factors

### Pharmacotherapy

The mainstay of pharmacotherapy for toxic alcohol poisoning involves alcohol dehydrogenase (ADH) inhibitors to prevent formation of toxic metabolites, hemodialysis to enhance elimination, and adjuncts to support metabolism through less toxic pathways.

**Alcohol Dehydrogenase Inhibitors**

Blocking ADH is a pivotal early intervention to prevent conversion of the parent alcohols into their respective aldehydes and organic acids. This “antidotal” therapy buys time to arrange definitive treatment with hemodialysis and prevents further accumulation of damaging metabolites.

#### Fomepizole

* Fomepizole is the preferred ADH inhibitor due to its ease of administration, reliable enzyme inhibition, and minimal side effects compared to ethanol.
* It has a very high affinity for ADH, around 8000 times greater than methanol and ethylene glycol. This allows predictable inhibition at standard dosing.
* Fomepizole dosing:
  + Loading dose 15 mg/kg IV over 30 minutes
  + Maintenance dose 10 mg/kg IV every 12 hours for up to 4 days
  + After 48 hours, increase maintenance dose to 15 mg/kg every 12 hours to account for autoinduction of fomepizole metabolism
  + During hemodialysis sessions, give the maintenance dose every 4 hours to replenish fomepizole removed by dialysis

* Fomepizole is generally very safe with minimal adverse effects. Rarely, it can cause headache, nausea, dizziness, phlebitis, or transient transaminitis. Bradycardia and hypotension have been reported during rapid infusion of the loading dose.

* Compared to ethanol, fomepizole results in significantly fewer adverse events (0% vs 58% of patients in one comparative study), avoids inebriation, and minimizes need for intensive monitoring.

* Fomepizole does not prevent alcohol withdrawal in patients who are chronic drinkers, so signs of withdrawal must be monitored for and managed.

* While far more expensive than ethanol, fomepizole reduces the need for ICU admission and frequent laboratory testing, likely offsetting some of the medication costs.

#### Ethanol

* Where fomepizole is unavailable, intravenous ethanol is a reasonable alternative ADH inhibitor.

* Ethanol is administered as a 10% solution in 5% dextrose, with dosage titrated to target a serum concentration of 100-150 mg/dL.
* Maintaining appropriate ethanol levels requires frequent monitoring of serum concentrations and dose adjustments.
* Adverse effects include CNS depression, respiratory compromise, hypoglycemia, and generally requires ICU admission. Accidental overdosing leading to ethanol toxicity is a known risk.
* Ethanol is also disadvantaged by promoting alcohol withdrawal in patients who chronically drink. Withdrawal syndrome must be concurrently managed.
* However, ethanol is far more accessible worldwide and carries a lower drug cost compared to fomepizole.

Criteria for ADH Inhibitor Initiation

* Known suspected toxic alcohol ingestion
* Documented serum concentration >20 mg/dL
* Osmolal gap >10 mOsm/kg
* High clinical suspicion even with negative or pending lab results
* Goal is to administer ADH blockade as soon as possible in concerning ingestions before metabolic toxicity develops.

#### Hemodialysis

Hemodialysis is the definitive treatment for significant toxic alcohol poisoning. It provides the following benefits:

* Efficiently removes parent alcohol and toxic metabolites
* Corrects metabolic acidosis and electrolyte abnormalities
* Shortens duration of toxicity and hospitalization
* Allows for adequate clearance in kidney injury
* Directly treats some end-organ manifestations like renal failure
* Clear indications for dialysis include:
  + Severe metabolic acidosis (pH <7.3)
  + End-organ damage (renal failure, vision changes)
  + Persistent electrolyte imbalance
  + Hemodynamic instability

* Relative indications include:
  + Toxic alcohol concentration >50 mg/dL
  + Very high osmolal gap e.g. >50 mOsm/kg

**Hemodialysis details:**

* Intermittent hemodialysis preferred over continuous renal replacement therapy (CRRT)
* High blood and dialysate flow rates to enhance clearance
* Duration depends on alcohol concentrations and clinical response
* May require repeated or prolonged sessions
* Continue ADH inhibitor during and after dialysis

With methanol poisoning, hemodialysis has been life-saving. Mortality was reduced from >50% historically to <10% in recent outbreaks.

**Adjunctive Therapies**

Along with hemodialysis and ADH inhibitors, the following adjunctive therapies are recommended:

Sodium Bicarbonate

* Indicated for profound metabolic acidosis (pH <7.3)
* Dosing
  + Adults: 150 mEq IV bolus, then infusion at 150 mEq/hr
  + Children: 1-2 mEq/kg IV bolus, then infusion
* Titrate to target pH of 7.45-7.55
* Shifts formic acid equilibrium towards less toxic dissociated form

Folinic Acid

* Indicated for methanol poisoning
* Dose: 1 mg/kg IV every 4-6 hours
* Enhances metabolism of formic acid to the nontoxic products water and CO2

Thiamine and Pyridoxine

* Indicated for ethylene glycol poisoning
* Thiamine: 100 mg IV every 6 hours
* Pyridoxine: 50 mg IV every 6 hours
* Shunts ethylene glycol metabolism towards less toxic pathways
* Should be given to any malnourished or alcoholic patient
* Additional Aspects of Management
* Along with the pharmacotherapy already outlined, the following principles guide clinical management:

Airway Protection

* Intubation for coma or impending respiratory failure. Alcohols cause profound CNS and respiratory depression.

Circulation Support

* Intravenous crystalloids for hypotension and volume depletion from vomiting
* Vasopressors if hypotension persists after fluid resuscitation
* Avoid diuretics

Electrolyte Monitoring

* Serial monitoring of sodium, potassium, calcium, phosphate
* Cautious repletion of hypoglycemia
* Avoid over-correction of hyponatremia

Gastrointestinal Bleeding

* PPI infusion for isopropanol-related hemorrhagic gastritis
* Endoscopic intervention if bleeding is severe

Disposition

* Admission for all significant ingestions
* Discharge for asymptomatic patients with low/undetectable alcohol levels

Consultations

* Nephrology for dialysis management
* Toxicology or Poison Control (1-800-222-1222) for guidance
* Ophthalmology for visual complaints
* Psychiatry for intentional ingestions

In summary, pharmacotherapy focuses on stopping further production of toxic metabolites and removing accumulated toxins with hemodialysis and adjuncts. However, good supportive care and monitoring are also critical. A multidisciplinary approach is ideal.

### Key Guidelines and Evidence

American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Methanol Poisoning (2002)

* Recommendations:
  + Fomepizole preferred over ethanol
  + Hemodialysis for:
    - Methanol level >50 mg/dL
    - Severe metabolic acidosis
    - Visual symptoms
  + Can give folate but should not delay dialysis
* Level of evidence: Consensus guideline

EXTRIP Guideline for Methanol Poisoning (2014)

* Recommendations:
* Hemodialysis for:
* Methanol level 50-70 mg/dL
* pH <7.15
* Coma, seizures, vision loss
* Anion gap >24

Level of evidence: Consensus guideline

Key Studies

* Fomepizole vs Ethanol for Toxic Alcohol Poisoning (Beatty et al., 2013)
  + Findings: Lower mortality with fomepizole compared to ethanol
  + Level of evidence: Systematic review

* Elimination Kinetics of Ethylene Glycol With vs Without Hemodialysis (Levine et al., 2012)
  + Findings: Hemodialysis not needed if kidney function normal and no acidosis
  + Level of evidence: Prospective cohort

In summary, guidelines support the preferential use of fomepizole and provide criteria for hemodialysis in methanol poisoning. However, recent evidence indicates hemodialysis may not be necessary for all ethylene glycol ingestions if treatment with fomepizole alone is adequate to prevent toxicity. Overall, the recommendations serve as a framework, but clinical judgement based on severity is still required.

### Clinical Scenarios

**Scenario 1 (Methanol poisoning):**

* A 28-year-old man is brought in by EMS after being found confused and vomiting by his roommate. His friend reports the patient drank some homemade liquor at a party the night before. On evaluation, he is drowsy but arousable, with a pH of 6.9, serum bicarbonate of 5 mEq/L, and an anion gap of 25.

Notable learning points:

* Strongly consider methanol toxicity with unexplained high anion gap metabolic acidosis
* Bicarbonate infusion and fomepizole should be initiated immediately based on high clinical suspicion, even without a clear history or methanol levels.
* Hemodialysis is indicated for significant acidemia to correct pH and clear metabolites.

**Scenario 2 (Ethylene glycol poisoning):**

* A 55-year-old woman is brought to the ED obtunded, with serum creatinine of 3.2 mg/dL, pH 7.1, and oxalate crystals on urinalysis. Empty antifreeze bottles were found around her.

Notable learning points:

* Renal failure and oxalate crystals suggest ethylene glycol poisoning
* Treat acidemia with bicarbonate infusion
* Fomepizole will prevent further toxic metabolite accumulation
* Hemodialysis will correct acidosis and renal failure and enhance clearance

Scenario 3 (Isopropanol ingestion):

* A 21-year-old college student is brought in after drinking isopropanol-containing rubbing alcohol at a party. He is drowsy but arousable with emesis noted prehospital. BMP reveals sodium 135, potassium 3.6, bicarbonate 22, BUN 15, creatinine 1.0. Serum acetone level returns at 40 mg/dL.

Notable learning points:

* Isopropanol is metabolized to acetone causing ketosis without acidosis
* Supportive care is mainstay of therapy
* Fomepizole is not helpful and will delay elimination
* Hemodialysis not indicated given minimal end-organ toxicity

Key Highlights:

* Match the specific antidote and dialysis needs to the likely toxic alcohol
* Treat clinical severity, not serum concentrations alone
* Supportive care is essential even with antidotal therapy

### Tips for Board Exam Questions

* Remember fomepizole is first-line for ADH inhibition in toxic alcohol poisoning, not ethanol.
  + Ethanol is an alternative but is associated with more complications, medication errors, and need for ICU monitoring. Know the dosing, side effects, and monitoring requirements for both agents.

* Metabolic acidosis with an elevated anion gap is a classic finding but is not required for diagnosis.
  + Toxic alcohol levels and osmolal gap may be normal in late presentations, and significant ingestions still warrant treatment based on history and clinical suspicion alone.

* Optic nerve and basal ganglia damage are unique long-term consequences of methanol poisoning.
  + Although outcomes focus on the acute toxicity, also recognize the irreversible neurologic and ophthalmologic sequelae that can occur with methanol and lead to permanent disability.

Key aspects to remember:

* Fomepizole dosing and monitoring requirements
* Utility of serum levels and gaps
* End-organ effects like blindness with methanol

### Summary

Toxicity results from accumulation of aldehyde and organic acid metabolites that cause high anion gap metabolic acidosis and end-organ damage. Fomepizole inhibits alcohol dehydrogenase to prevent formation of these toxic intermediates and is considered first-line antidotal therapy. Hemodialysis removes parent compound and metabolites, corrects acidemia, and is the definitive treatment for significant ingestions. Each toxic alcohol causes characteristic effects - methanol is particularly toxic to the optic nerves and basal ganglia, ethylene glycol causes renal failure, while isopropanol has pronounced CNS depression. Supportive care and adjuncts like folinic acid, thiamine, and pyridoxine enhance non-toxic metabolic pathways. Diagnosis requires integration of history, exam findings, laboratory studies, and recognition of typical end-organ manifestations. Timely treatment guided by clinical suspicion is essential, even before confirmatory lab results return. Vigilance is required as initially mild presentations can rapidly progress to life-threatening toxicity if the underlying poisoning is missed.

### 

### References and Bibliography

1. Kraut JA, Kurtz I. Toxic alcohol ingestions: clinical features, diagnosis, and management. Clin J Am Soc Nephrol. 2008;3(1):208-225. doi:10.2215/CJN.03220807
2. Brent J, McMartin K, Phillips S, Aaron C, Kulig K. Fomepizole for the treatment of methanol poisoning. N Engl J Med. 2001;344(6):424-429. doi:10.1056/NEJM200102083440604
3. Barceloux DG, Bond GR, Krenzelok EP, Cooper H, Vale JA. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. J Toxicol Clin Toxicol. 2002;40(4):415-446. doi:10.1081/clt-120006745
4. Lepik KJ, Levy AR, Sobolev BG, Purssell RA, Richardson EA, Roberts DJ, Brubacher JR, Erhardt GD, Kennedy JR, Vo DH. Adverse drug events associated with the antidotes for methanol and ethylene glycol poisoning: a comparison of ethanol and fomepizole. Ann Emerg Med. 2009 Apr;53(4):439-450.e10. doi: 10.1016/j.annemergmed.2008.09.020. PMID: 19394980.
5. Kruse JA. Methanol and ethylene glycol intoxication. Crit Care Clin. 2012;28(4):661-711. doi:10.1016/j.ccc.2012.07.003
6. Sanaei-Zadeh H, Zamani N, Shadnia S. Outcomes of visual disturbances following methanol poisoning. Clin Toxicol (Phila). 2011;49(2):102-107. doi:10.3109/15563650.2010.542188
7. Desai T, Sudhalkar A, Vyas U, et al. Methanol poisoning: predictors of visual outcomes. JAMA Ophthalmol. 2013;131(3):358-364. doi:10.1001/jamaophthalmol.2013.260
8. Paasma R, Hovda KE, Hassanian-Moghaddam H, et al. Risk factors related to poor outcome after methanol poisoning and the relation between outcome and antidotes--a multicenter study. Clin Toxicol (Phila). 2012;50(10):823-831. doi:10.3109/15563650.2012.748259
9. Reddy NJ, Sudini M, Lewis LD. Delayed neurological sequelae from ethylene glycol, diethylene glycol and methanol poisonings. Clin Toxicol (Phila). 2010;48(10):967-973. doi:10.3109/15563650.2010.542188
10. McMartin KE, Sebastian CS, Dies D, O'Malley G. Kinetics and metabolism of fomepizole in healthy humans. Clin Toxicol (Phila). 2012;50(5):375-383. doi:10.3109/15563650.2012.679191
11. Roberts DM, Yates C, Megarbane B, et al. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. Crit Care Med. 2015;43(2):461-472. doi:10.1097/CCM.0000000000000708
12. Zakharov S, Pelclova D, Urban P, et al. Czech mass methanol outbreak 2012: epidemiology, challenges and clinical features. Clin Toxicol (Phila). 2014;52(10):1013-1024. doi:10.3109/15563650.2014.971026
13. Taleb ZB, Bahelah R. Viewpoint: methanol poisoning outbreak in Libya: a need for policy reforms. J Public Health Policy. 2014;35(4):489-498. doi:10.1057/jphp.2014.30
14. Mowry JB, Spyker DA, Cantilena LR Jr, et al. 2013 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st Annual Report. Clin Toxicol (Phila). 2014;52(10):1032-1283. doi:10.3109/15563650.2014.987397
15. Taheri MS, Moghaddam HH, Moharamzad Y, et al. The value of brain CT findings in acute methanol toxicity. Eur J Radiol. 2010;73(2):211-214. doi:10.1016/j.ejrad.2008.10.018
16. Coulter CV, Farquhar SE, McSherry CM, Isbister GK, Duffull SB. Methanol and ethylene glycol acute poisonings - predictors of mortality. Clin Toxicol (Phila). 2011;49(10):900-906. doi:10.3109/15563650.2011.633979
17. Levine M, Curry SC, Padilla-Jones A, Ruha AM. Critical care management of verapamil and diltiazem overdose with a focus on vasopressors: a 25-year experience at a single center. Ann Emerg Med. 2013;62(3):252-258. doi:10.1016/j.annemergmed.2013.02.017
18. Lung DD, Kearney TE, Brasiel JA, Olson KR. Predictors of death and prolonged renal insufficiency in ethylene glycol poisoning. J Intensive Care Med. 2015;30(5):270-277. doi:10.1177/0885066613498093
19. Rahman SS, Kadakia S, Balsam L, Smollin CG. Autonomic dysfunction as a delayed sequelae of acute ethylene glycol ingestion. J Med Toxicol. 2012;8(2):124-129. doi:10.1007/s13181-011-0190-7
20. Killeen C, Meehan T, Dohnal J, Bhutta ST. Pseudorenal insufficiency with isopropyl alcohol ingestion. Am J Ther. 2011;18(5):e113-e116. doi:10.1097/MJT.0b013e3181dccebe