DEFINITION
Poisoning with agents containing ethylene glycol (EG) (antifreeze; aircraft de-icer; solvents; hydraulic brake fluids; windshield washer fluids; agents in condensers, heat exchangers, and home solar units).\(^1,2\) EG is also used in portable basketball goal post bases and toilets of recreational vehicles/homes in colder climes.

Systems. Gastrointestinal tract, CNS, cardiopulmonary, and renal. Vomiting usually within the first few hours; CNS depression, ataxia, weakness, tachypnea, polyuria/polydipsia occur within 1 to 6 hours. By 18 to 36 hours, acute renal failure develops.\(^3,5\)

RELATIVE SPECIES SENSITIVITY
Most Sensitive: cat, rabbit, human
Moderately Sensitive: dog, cattle, pig, rodent
Least Sensitive: fish, poultry

Toxic Doses. Toxic dose has not been established. Lethal dose of undiluted antifreeze (95–97%) by volume is 4.4 to 6.6 ml/kg (dogs) and 1.4 ml/kg (cats).\(^2,3\) Most acute toxicity data based on doses causing early death (acidosis/intoxication) do not account for animals surviving initial stages that later succumb to kidney failure. Thus, any suspected exposure should be considered potential toxicosis, with steps to determine extent. When in doubt, treat as toxic.

STAGE 1—NEUROLOGIC. Typically begins ≤ 30 minutes, lasting to 12 hours.\(^1,4,6\) Vomiting common, most likely because EG irritates gastric mucosa.\(^2,3\) Initial ataxia, disorientation, stupor, polyuria/polydipsia.\(^3,4,6\) These are early indicators of possible poisoning, important because early intervention is more likely to save an animal. Coma and death possible, or animal may appear to partially/fully recover. By 6 to 12 hours, neurologic status may worsen due to severe metabolic acidosis.\(^3,4,6\) Isosthenuria in dogs by 3 hours from osmotic diuresis/serum hyperosmolality-induced polydipsia.\(^2,3\)

STAGE 2—CARDIOPULMONARY. Generally from 12 to 24 hours. Tachypnea, tachycardia, CNS depression, seizures, pulmonary edema may occur.\(^1,4,6\) High anion gap and severe metabolic acidosis typical.\(^3,4,6\) Most deaths in humans reported at this stage.\(^1\)

STAGE 3—OLIGURIC RENAL FAILURE. As early as 12 hours, especially in cats, but generally within 24 to 72 hours.\(^2,3,5,6\) Azotemia, depression, anorexia, vomiting, abdominal pain, and oliguria progressing to anuria.\(^1,3\) Low urine specific gravity and glucosuria with calcium oxalate crystals possible.\(^3,4\) Clinical pathologic abnormalities include increased osmolar gap/anion gap, hyperglycemia, hyperkalemia, decreased blood pH, hypocalcemia.\(^1,3\) BUN and creatinine generally do not increase until ≥ 12 hours after exposure; thus, testing has little benefit.

KINETICS AND METABOLISM
EG is rapidly absorbed, although food in stomach may slow absorption.\(^1,3\) Clinical signs may occur as early as 30 minutes; peak blood concentrations in dogs 1 to 4 hours after ingestion.\(^6\) Plasma half-life is 3 to 5 hours; therapeutic ethanol or fomepizole may increase half-time to 12 to 72 hours.\(^1,3\) Primarily eliminated through kidneys; about 50% excreted unchanged.\(^3,4\)

Metabolism occurs primarily in liver, forming toxic acidic metabolites (see EG Metabolism).\(^1,2,5,6\) Oxalic acid is directly cytotoxic to the renal tubular epithelium and induces...
hypocalcemia by binding to serum calcium to form calcium oxalate crystals.\textsuperscript{1–3} Crystals precipitate in renal tubules, causing mechanical injury and possibly obstructive uropathy.\textsuperscript{2}

**Diagnosis**

**Differentials.** See algorithm on page 18 for ataxia, an early, sentinel sign of EG toxicity. Diagnostic differentials for EG toxicity can be found in standard reference texts.

**Causes of Increased Anion Gap.**
- Decreasing unmeasured cations (hypocalcemia, hypomagnesemia, hypokalemia)\textsuperscript{7}
- Increasing unmeasured anions (ketoacids, lactate, phosphates, sulfates, salicylates, methanol, albumin)\textsuperscript{7}
- Most common cause (dogs and cats) is metabolic acidosis due to lactic acidosis, renal failure, or ketoacidosis\textsuperscript{7}

**Ruleouts for acute renal failure.**
- Acute decompensation of chronic renal failure
- Cholecalciferol/vitamin D\textsubscript{3} derivatives, hypervitaminosis D, hypercalcemia
- Glomerulonephritis
- Grapes or raisins
- Heavy metal intoxication (lead, mercury, cadmium, arsenic, zinc)
- Heatstroke
- Hemoglobinuria, myoglobinuria
- Hypoadrenocorticism
- Hypovolemia
- Leptospirosis
- Nephrototoxic antibiotics
- NSAID overdose
- Oxalic acid ingestion
- Plant ingestion (\textit{Lilium} species, \textit{Hemerocallis} species [in cats only], rhubarb leaves, and \textit{Oxalis} species)
- Septic shock
- Crota
id snake bite
- Urinary obstruction

**Ruleouts for metabolic acidosis.**
- Acute renal failure
- Aspirin or NSAID overdose
- Diabetes mellitus
- Ethanol, methanol, other short-chain alcohols
- Metaldehyde toxicity

**BLOOD AND URINE ANALYSIS**

**Early diagnosis/treatment essential.** Diagnosis based on history, clinical signs, laboratory testing. Peak EG levels reached \( \leq 1 \) to 4 hours, but tests can be done from 0.5 to 12 hours.\textsuperscript{3} One kit is available for veterinary use (EGT Kit—PRN Pharmacal). Labeled for dogs with levels > 50 mg/dl, this kit can be invaluable in determining if treatment is warranted.\textsuperscript{3,4} False-positive results can occur (presence of propylene glycol in some activated charcoal solutions and injection solutions such as pentobarbital and diazepam, other glycols, or formaldehyde in the circulation).\textsuperscript{3,4,6} Blood should be taken before administering any such solutions/agents. Products causing false positives are metaldehyde, glycerin/glycerol, or diethylene glycol. Other alcohols (e.g., ethanol, methanol, or isopropanol) do not interfere.\textsuperscript{3}

Cats are more sensitive to EG than dogs, and kit may not diagnose toxicity. Positive results are significant, but negative results do not rule out toxicity. Some human laboratories run quantitative EG analysis. Any detectable EG warrants treatment.

**Other Diagnostic Procedures.**
- Measure anion gap (>25 mEq/L) or serum osmolality (> 20 mOsm/kg).\textsuperscript{2–4,6}
- Crystalluria (not conclusive)\textsuperscript{2}
- Calcium oxalate crystals in urine can be seen 6 hours after ingestion; may be octahedral (envelope-like), prismatic (spindle, hippocurate-like), or dumbbell shaped.\textsuperscript{1}
- Examine urine under Wood’s lamp; will show fluorescein dye up to 6 hours.\textsuperscript{3}

**EG METABOLISM**

1. EG oxidation to glycoaldehyde via alcohol dehydrogenase.
2. Glycoaldehyde oxidation to glycolic acid via mitochondrial aldehyde dehydrogenase.
3. Glycolic acid oxidation to glyoxylic acid, the most toxic metabolite. Short half-life of glyoxylic acid prevents accumulation of toxic concentrations.\textsuperscript{1}
4. Glyoxylic acid oxidation through several pathways to produce oxalic acid, glycine, formic acid, hippurate, benzoic acid, and other compounds.
5. Oxalic acid binds to serum calcium and forms calcium oxalate crystals.

**Diagnosing Toxicosis.**
- Increased osmolar gap (>20 mOsm/kg)
- Decreased blood pH
- Increased anionic gap (>25mEq/L)
- Toxin in serum or urine
- Hypocalcemia
- Early-phase ataxia (1–3 hours)
- Calcium oxalate crystalluria
- Fluorescence of urine or vomitus on Wood’s lamp

**Postmortem Findings.**

**Renal:** Proximal tubular degeneration/necrosis, calcium oxalate deposition; calcium oxalate crystals in intestinal mucosa, liver, heart, brain.\textsuperscript{3,4}

**CNS:** Cerebral edema, multifocal hemorrhage, inflammatory cell infiltration.\textsuperscript{3,4}
Treatment

Must be timely and aggressive. Failure to initiate in first several hours may result in irreversible renal damage/death. Goals are to stabilize, prevent absorption, interfere with toxin metabolism, provide supportive care.

Induction of emesis helpful only < 1 hour. Feeding dry bread before emesis may increase success. Emesis contraindicated with hyperactivity, tremor, seizures: consider gastric lavage. Effective emetic is 1 teaspoon 3% hydrogen peroxide per 5 lb, not to exceed 3 tablespoons. Usually occurs in minutes; dose can be repeated once if initially unsuccessful. Another option is apomorphine hydrochloride, administered topically to eye or parenterally at 0.03 mg/kg IV or 0.04 mg/kg IM in dogs; 0.04 mg/kg IV or 0.08 mg IM or SC in cats. CNS/respiratory depression, excitation, protracted vomiting can occur, especially after IV administration.

Activated charcoal can be given (1–3 g/kg, 1–3 hours after ingestion). Effectiveness is controversial—aliphatic alcohols may not be well adsorbed by charcoal. Take samples for EG analysis before activated charcoal to prevent false positives resulting from detection of glycols in these compounds.

Altering Kinetics. IV fomepizole and ethanol have been successful. Compounds aim to delay/prevent breakdown of toxin to more toxic metabolites, allowing excretion of unchanged parent compound in urine.

Fomepizole inhibits alcohol dehydrogenase; considered preferred treatment for dogs but may not be effective in cats. Unlike ethanol, does not cause hyperosmolarity, metabolic acidosis, CNS depression

Administer every 12 hours for 36 hours. Dosing is 20 mg/kg slow IV over 15 to 30 minutes, then 15 mg/kg slow IV at 12 and 24 hours, then 5 mg/kg at 36 hours. Ethanol competes with EG as substrate for alcohol dehydrogenase; can be used in dogs and cats. Inexpensive and readily available; has serious drawbacks (worsening of metabolic acidosis and CNS depression), making evaluation of degree of toxicosis difficult. Ethanol treatments are time-intensive and require constant monitoring. Ideally, administer 8.6 ml/kg 7% ethanol solution bolus, maintain at 100 mg/kg/hr up to 200 mg/kg/hr constant-rate infusion. Or, make a 20% ethanol solution (dogs: 5.5 ml/kg IV every 4 hours for 5 treatments, then every 6 hours for 4 treatments; cats: 5.0 ml/kg IV every 6 hours for 5 treatments, then every 8 hours for 4 treatments.)

For dogs, a negative EG test means treatment with fomepizole or ethanol may be discontinued; however, fluid therapy and supportive care should continue until animal fully recovers.

Supportive Care. Preventing further kidney damage/maintaining fluid, electrolyte, acid–base balance are crucial. Fluid therapy is foundation of acute renal failure treatment, comprising fluid diuresis with isotonic alkalinizing crystalloid solution (e.g., lactated Ringer’s) twice maintenance rate. Goals are to correct fluid and electrolyte imbalances, improve renal blood flow, initiate diuresis. Monitor patient to avoid volume overload and possible pulmonary edema. Oliguria necessitates attempts to increase urine output (furosemide, 1 mg/kg/hr for 4 hours then 3 to 8 µg/kg/min to maintain urine flow). Dopamine may increase urine output (dogs); administer at 2 to 3 µg/kg/min. Consider peritoneal dialysis in oliguric/anuric animals. Sodium bicarbonate can be used for acidosis (i.e., blood pH < 7.10 to 7.15 or total CO2 < 10-12 mEq/L). Continue treatment until animal is clinically normal, with at least 24 hours’ normal renal function, acid-base parameters.

Precautions. Overhydration: Electolyte imbalances, volume overload, possibly pulmonary edema

Overuse of sodium bicarbonate: Ionized calcium deficits, CSF acidosis, cerebral edema

Ethanol: Worsening of metabolic acidosis, CNS depression

ALTERNATIVE THERAPY

High doses of fomepizole may be safe and effective in cats if therapy is initiated < 3 hours after ingestion; > 4 hours, mortality rate is 100%. Initiating alcohol therapy at home in cases of time delay in obtaining veterinary help has been reported. In these cases, 2.25 ml/kg PO 40% alcohol (e.g., vodka, rum) can be administered orally. Hemodialysis considered superior to peritoneal dialysis in eliminating EG/metabolites in humans but limited availability in veterinary medicine. Pyridoxine and thiamine—cofactors for EG metabolism—recommended in human literature adjunctively.
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Dr. Gelatt’s more than 3 decades of academia has included teaching more than 2,500 veterinary students and the training of 36 residents and postdoctoral fellows in comparative ophthalmology. He has presented more than 290 professional talks both nationally and internationally and has published a number of articles, abstracts, chapters, and books. Dr. Gelatt’s research interests have concentrated on canine glaucomas, inherited cataracts in the dog, clinical pharmacology of drugs that change intraocular pressure, and ophthalmic surgery.

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Dr. Gregory earned her DVM and MS in veterinary pathology from Oklahoma State. She completed a residency in veterinary oncology and was in small animal practice for 8 years following graduation. Dr. Gregory has served in her current position for 6 years and before that as research assistant for the biochemistry department.

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Dr. Gwaltney-Brant is an on-line consultant for the Veterinary Information Network and has authored or co-authored several peer-review articles and book chapters on toxicology and pathology. She also enjoys participating in draft work and water work with her Newfoundlands, and is a member of the Research Advisory Committee of the Newfoundland Club of America.

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Dr. Hoefler is a graduate of Ross University School of Veterinary Medicine. She completed an internship in small animal medicine and surgery at The Animal Medical Center in New York and continued there, first as a resident in avian and exotic medicine then in a staff appointment for 9 years. She has written widely and lectured nationally and internationally. Her clinical practice is limited to birds, reptiles, and small mammals.

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In addition to serving as an officer and member of many professional associations, Dr. Kunkle is known for her education of students and residents, as well as continuing education for practitioners in her specialty of dermatology. Dr. Kunkle’s research interests include feline and canine allergy, infectious diseases, and ectoparasites. She is the recipient of a number of awards, including the Woman Veterinarian of the Year and the ACVD Award for Excellence.

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Dr. Leib received his DVM from the University of Georgia and his MS at Colorado State University. He has been at Virginia Maryland Regional College since 1983, where he was chief of small animal medicine from 1985-1990. Dr. Leib has received several teaching awards; been investigator on more than 25 funded research projects; authored numerous publications, including a textbook; and served in various editorial and continuing education capacities.

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Dr. Lobprise graduated from Texas A&M University. She then completed a residency in veterinary dentistry. Dr. Lobprise has published many articles and co-authored two books, including The Veterinarian’s Companion to Common Dental Procedures. She has lectured internationally and is past president of the Texas Academy of Veterinary Practitioners and American Veterinary Dental Society.

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Dr. Meyer has contributed extensively to clinical, research, and veterinary teaching programs at the University of California-Davis, University of Florida-Gainesville, and Colorado State University. He has spent 12 years in the development of novel drugs for human indications and is recognized nationally and internationally for his expertise in clinical pathology, diagnostic cytology, and hepatic histopathology. He has co-authored 3 texts and numerous articles and book chapters regarding those areas.

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Independent Contractor  
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Dr. Moon-Massat’s current responsibilities at New England Veterinary Anesthesia Services include technical and medical writing as well as providing clinical anesthesia for clients such as the University of California-Davis. Additionally, she contributes to continuing education seminars and wet laboratories, as well as editing and reviewing for NAVC and the Journal of Veterinary Anesthesia and Analgesia. Her current research interests include improving the anesthetic management of critically ill patients.

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Dr. Moore has been affiliated with Tufts University since 1988. Dr. Moore received his veterinary degree from the University of Sydney and completed his residency in veterinary oncology at the University of California-Davis. He was recipient of the MSD AgVet Award for Creativity in Teaching in 1996 and the Tufts University Outstanding Faculty Award in 1997. He is co-author of two books, Managing the Veterinary Cancer Patient and Feline Oncology.

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Dr. Neilson graduated from the University of Florida and after 2 years in private practice was selected as first Friskies PetCare Companion Animal Behavior Resident at UC Davis, where she completed her residency program and board certification. Dr. Neilson then returned to Portland and opened a behavior referral practice. She also acts as an industry consultant, a visiting instructor at the University of Florida, and lectures across the country about animal behavior.

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Dr. Overall has been a regular columnist for both Canine Feline Practice and Feline Practice journals and currently writes a bimonthly column for DVM Newsmagazine. Dr. Overall’s research interests focus on development of genetic and behavioral animal models for human psychiatric illness.

Our review board is growing. Look for additional introductions in the future.
...at a glance

TIME OF EXPOSURE
• < 1 hour: Induce emesis
• 1–3 hours: 1-3 g/kg activated charcoal

THEN
• Dogs: fomepizole—20 mg/kg slow IV over 15-30 mins every 12 hrs for 36 hrs; then 15 mg/kg slow IV at 12 and 24 hrs; then 5 mg/kg at 36 hrs. Tx of choice
OR
• Cats or dogs: ethanol—8.6 ml/kg 7% ethanol solution bolus, maintain at 100 mg/kg/hr up to 200 mg/kg/hr constant-rate infusion
OR
• 20% ethanol solution (homemade)
  □ Dogs: 5.5 ml/kg IV every 4 hrs, 5X; then every 6 hrs, 4X
  □ Cats: 5.0 ml/kg IV every 6 hrs, 5X; then every 8 hrs, 4X

PLUS
• Fluid therapy (diuresis with isotonic alkalinizing crystalloid, e.g., lactated Ringer’s), twice maintenance rate

Advice for Owners. The veterinary community can help spread the word about antifreeze safety. Motorists can help prevent accidental EG ingestion. Among considerations are using antifreeze that contains propylene glycol, which is less toxic than EG.

FUTURE CONSIDERATIONS
Researchers at Colorado State University are investigating use of fomepizole in EG-exposed cats.

See Aids & Resources, back page, for references, further reading, and contacts.
EVALUATING ATAXIA IN SUSPECTED ETHYLENE GLYCOL TOXICITY

**Dx** History and Physical Examination
- Presence of additional clinical signs of vomiting and lethargy
- Evidence of potential exposure to an ethylene glycol product
- Roaming animal or animal without direct supervision
- Wood’s lamp fluorescence of urine, stomach contents, or fur

**Dx** Ethylene Glycol Test Kit

- **Negative Dog**
  - Could see a negative EG test in a dog if test not performed 30 minutes to 12 hrs of exposure

- **Positive Dog or Cat**
  - Increased anion gap (> 25 mEq/L)
  - Increased osmolality (>20 mOsm/kg)
  - Metabolic Acidosis
  - +/- Azotemia (may not see in first 6-12 hrs)

- **Negative Cat**
  - Any detectable level

**Dx** Ethylene Glycol Analysis

- **Dog**
  - Levels > 50 mg/dl
  - Fomepizole is treatment of choice

- **Cat**
  - Levels < 50 mg/dl
  - Ethanol is treatment of choice

**Dx** Check Osmolality, Anion Gap, Renal Values, Acid/base

- **Normal Dog/Cat**

**Tx** Initiate EG Treatment
- **Dog**
  - Levels > 50 mg/dl
  - Fomepizole is treatment of choice

- **Cat**
  - Any detectable level
  - Ethanol is treatment of choice

**Tx** Dog
- Levels < 50 mg/dl
- No detectable level

**Tx** Cat
- Levels > 50 mg/dl
- Fomepizole is treatment of choice

**Tx** Dog or Cat
- Levels < 50 mg/dl
- No detectable level
EVALUATING ATAXIA IN SUSPECTED ETHYLENE GLYCOL TOXICITY

Lesion in cerebral cortex or diencephalon

Brain stem
Cerebellum
Peripheral vestibular dysfunction
Central vestibular dysfunction

Etiologies:
Degenerative
Metabolic
Neoplastic
Inflammatory

Pelvic limb paresis
Tetraparesis

Normal gait or slightly abnormal postural reaction

Abnormal gait

Dx

Consider Other Rule Outs

RULE OUTS FOR ATAXIA WITH NEGATIVE ETHYLENE GLYCOL TEST RESULTS

False-negative EG test could occur if sample is drawn >12 hours after ingestion

Consider ethylene glycol toxicosis
• Metabolic acidosis
• Increased anion gap (> 25 mEq/L)
• Increased osmality (> 20 mOsm/kg)
• Azotemia

Lead toxicosis
• Lead levels > 0.1 ppm when clinical signs present
• Radiographic presence of metallic objects

Marijuana toxicosis
• Can be confirmed via urine test at human hospital lab
• Increased water intake may result in false-positive test

Other CNS depressants
Most human hospital labs provide a STAT screen for a variety of CNS depressants
• Quantitative ethanol and methanol levels can be checked at most human labs
• Qualitative levels of barbiturates can be evaluated; radiographs may reveal radiopaque objects in stomach with intact phenobarbital tablets
• Qualitative testing for presence of benzodiazepine is helpful to confirm presence
• Urine analysis of phenothiazines can be checked through a human lab; unabsorbed phenothiazines are radiopaque in the gastrointestinal tract

Cholinesterase inhibitors
• Test dose atropine (0.01-0.02 mg/kg IV); if atropinization is seen, consider other rule outs
• Whole blood cholinesterase level can be evaluated through diagnostic lab

A thorough neurological examination may help diagnose CNS lesion

A thorough neurological examination may help diagnose CNS lesion

Normal gait or slightly abnormal postural reaction

Abnormal gait

Lesion in cerebral cortex or diencephalon

Head involvement
No head involvement

Brain stem
Cerebellum
Peripheral vestibular dysfunction
Central vestibular dysfunction

Etiologies:
Degenerative
Metabolic
Neoplastic
Inflammatory