



# Clinical Chemistry Trainee Council

## Pearls of Laboratory Medicine

[www.traineecouncil.org](http://www.traineecouncil.org)

**TITLE: Ethylene Glycol Poisoning**

**PRESENTER: Amanda Martin**

---

**Slide 1:**

Hello, my name is Dr. Amanda Martin. I am the Pathology Chief Resident in the Department of Pathology and Laboratory Medicine at the University of Rochester Medical Center. Welcome to this Pearl of Laboratory Medicine on “Ethylene Glycol Poisoning.”

**Slide 2:**

Ethylene glycol is a sweet-tasting, synthetic solvent found in numerous household and cleaning products, such as antifreeze, de-icing solutions, and hydraulic brake fluid.

**Slide 3:**

Ingestion of ethylene glycol is a relatively infrequent cause of acute poisoning in the United States, comprising only a small fraction of the nearly 1.3 million patient visits to American emergency departments for treatment of acute poisoning in 2010. In 2010, 5,725 cases of single exposure to ethylene glycol were reported to the American Association of Poison Control Centers (AAPCC). According to the annual report released by the AAPCC’s National Poison Data System, 528 occurred in children less than 5 years, 145 occurred in children ages 6-12 years, 479 occurred in teenagers ages 13-19 years, and the majority of cases occurred in adults greater than 20 years. Of all reported ingestions, 800 ingestions were determined to be intentional. 2,165 ingestions were treated in a health facility. In terms of patient outcome, 926 minor outcomes, 452 moderate outcomes, 151 major outcomes, and 7 deaths were reported.

**Slide 4:**

Because ethylene glycol poisoning is infrequently encountered in the emergency room setting, detecting it often poses significant challenges to both clinicians and hospital laboratories. Among other things, offering definitive in-house testing for ethylene glycol is a substantial undertaking that requires highly trained technical staff and the acquisition of highly specialized instrumentation. Moreover, since most hospitals infrequently encounter these types of cases, hospital laboratories often find it difficult to maintain competency. Nevertheless, given that ethylene glycol poisoning is an important cause of metabolic acidosis of unknown source and is associated with a rapid onset of renal failure if left untreated, it is imperative that patients receive prompt diagnosis and treatment.

**Slide 5:**

The clinical presentation of ethylene glycol poisoning is described as three sequential phases, which are neurological, cardiopulmonary, and renal phases. Neurological symptoms, which can occur in as little as thirty minutes after ingestion, are similar to those seen in early ethanol intoxication. The duration of these neurological symptoms is usually due to the short half-life of ethylene glycol ( $t_{1/2} = 6$  hours) and occurs before the onset of metabolic acidosis, which is due to the metabolism of ethylene glycol into its more toxic acid metabolites. Approximately twelve to twenty-four hours after ingestion, cardiopulmonary symptoms typically appear and can include hypertension, tachycardia, tachypnea, congestive heart failure, pulmonary edema, and shock. The final phase, or the renal phase, is heralded by flank pain, oliguria, and renal failure. The renal phase can occur anywhere from twenty-four to seventy-two hours after ingestion. If left untreated, severe cases of ethylene glycol poisoning can be fatal in twenty-four to thirty-six hours.

**Slide 6:**

Interestingly enough, ethylene glycol by itself is not a toxic substance. Rather, it is ethylene glycol's various acid metabolites that cause all of the toxic effects that are attributed to ethylene glycol poisoning. One important acid metabolite is glycolic acid which can cause metabolic acidosis. Studies have shown that the serum concentration of glycolic acid directly correlates to the severity of the clinical presentation. Another important acid metabolite is oxalic acid, which contributes to the formation of oxalate crystals that can accumulate in the kidneys and result in renal failure.

**Slide 7:**

How is ethylene glycol metabolized in the human body? Ethylene glycol is rapidly absorbed from the gastrointestinal tract, reaching peak plasma concentration in as little as one to three hours after ingestion. Ethylene glycol is primarily metabolized in the liver, where it is first broken down by the hepatic enzyme alcohol dehydrogenase into glycoaldehyde. It is then further metabolized by aldehyde dehydrogenase into glycolic acid and oxalic acid. Oxalate, when combined with calcium, forms calcium oxalate crystals. Once in circulation, the crystals begin to accumulate in the blood and other tissues, including the brain, heart, and lungs. As stated previously, they can also reach the kidneys, resulting in decreased glomerular filtration and renal failure.

**Slide 8:**

There are essentially two approaches that clinicians and hospital laboratories use to diagnose ethylene glycol poisoning: indirect and direct. Most hospitals in the United States employ the indirect method, which relies upon observing an increased serum osmolal gap  $>10$  mOsm/kg H<sub>2</sub>O in addition to an increased anion gap. The serum osmolality should be measured by the freezing-point depression method. Volatile alcohols can evaporate quickly if measured by the boiling-point elevation method, yielding erroneous results. An increased serum osmolal gap indicates the presence of an osmotically active substance that is not normally present in blood, whereas an increased anion gap indicates metabolic acidosis, which is a key laboratory finding in cases of ethylene glycol poisoning.

**Slide 9:**

The main advantages of using the indirect method are cost-effectiveness, a reduction in the level of technical skill required, and quicker turn-around times.

However, there are two major pitfalls with using this method. Although a serum osmolal gap  $>10$  mOsm/kg H<sub>2</sub>O coupled with an increased anion gap is highly suggestive of ethylene glycol poisoning, it is not specific for this condition. In fact, a diagnosis of ethylene glycol poisoning can only be confirmed after eliminating other causes of increased anion gap (or metabolic acidosis) as represented by the acronym MUDPILES (methanol, uremia, diabetic ketoacidosis, propylene glycol, isoniazid, lactic acidosis, ethylene glycol, and salicylates). Moreover, a normal anion gap does not necessarily rule out ethylene glycol poisoning. This is especially true if a patient presents very soon after ingestion (i.e. the ethylene glycol has not had the chance to convert to its acid metabolites or the patient has co-ingested ethanol, with anion gap being normal) or very late after ingestion (i.e. all of the ingested ethylene glycol has already been converted to non-acidic calcium oxalate).

Some hospital laboratories may also rely upon being able to detect calcium oxalate crystals in urine. The crystals can present in two different forms, namely calcium oxalate di-hydrate (envelope-shaped crystals) and the more thermodynamically stable calcium oxalate monohydrate (needle-shaped crystals). Unfortunately, only 50% or less of all patients present with urine crystals upon admission. In addition, calcium oxalate crystals are typically found late in the course of illness; thus, relying upon the presence of calcium oxalate crystals can result in significant delays in treatment. Furthermore, finding calcium oxalate crystals is not specific to ethylene glycol poisoning and can also be found in hypercalcemic states and in patients with inborn errors of metabolism.

**Slide 10:**

The most definitive and direct method to detect ethylene glycol poisoning is gas chromatography-mass spectrometry, or GC-MS. Many laboratories have also achieved similar results using gas chromatography-flame ion detector, or GC-FID. The main advantage of GC-MS is that it can give accurate measurements of ethylene glycol and its metabolite glycolic acid, the levels of which are very useful in predicting a patient's clinical course. However, GC-MS requires complex sample processing and derivatization in addition to a high level of technical expertise and high levels of maintenance. All of these factors have restricted widespread application of this technology.

Other direct methods of detecting ethylene glycol poisoning include enzymatic assays, colorimetric assays, and liquid chromatography.

**Slide 11:**

Because ethylene glycol poisoning can result in significant morbidity and mortality, it is imperative that patients be treated as quickly as possible. Fortunately, treatment for patients with ethylene glycol poisoning is relatively straightforward. In the past, patients were treated with ethanol due to its ability to effectively compete with ethylene glycol for binding to hepatic aldehyde dehydrogenase, thus preventing metabolism of ethylene glycol into its more toxic derivatives and allowing for its eventual elimination via the kidneys. Unfortunately, the use of ethanol is not without its drawbacks. These include central nervous system (CNS) depression and unpredictable pharmacokinetics, which require frequent dosing and monitoring of patients in an intensive care setting. For these reasons, fomepizole (Antizol) is routinely used for ethylene glycol poisoning. Though more expensive than ethanol, its advantages over ethanol are that it does not cause CNS depression and possesses more predictable pharmacokinetics. Depending on the clinical situation, metabolic acidosis can be corrected by the administration of intravenous sodium bicarbonate. However, if severe acidosis and/or renal failure is present, hemodialysis is required.

**Slide 12:**

In summary, ingestion of ethylene glycol, a sweet-tasting solvent, is a relatively infrequent cause of acute poisoning in the United States. Although it is rarely encountered in the emergency room setting, ethylene glycol poisoning is a medical emergency that requires prompt diagnosis and treatment. The clinical manifestations of ethylene glycol poisoning are described as three sequential phases, namely neurological, cardiopulmonary, and renal phases. Clinicians and hospitals use two main approaches to diagnose ethylene glycol poisoning: indirect and direct. Indirect methods rely upon finding an increased osmolal gap, which detects substances not normally present in blood, and an increased anion gap, which indicates metabolic acidosis, a key laboratory finding in ethylene glycol poisoning. Although direct methods, such as GC-MS and GC-FID, are more definitive in diagnosing ethylene glycol poisoning, most hospitals still resort to using the indirect method due to cost-effectiveness, reduced level of technical skill required, and quicker turnaround times. Effective treatment of ethylene glycol poisoning with resolution of metabolic acidosis typically involve the use of sodium bicarbonate, fomepizole, and, in instances of severe metabolic acidosis, hemodialysis.

**Slide 13: References****Slide 14: Disclosures****Slide 15: Thank You from [www.TraineeCouncil.org](http://www.TraineeCouncil.org)**

Thank you for joining me on this Pearl of Laboratory Medicine on “Ethylene Glycol Poisoning.” My name is Amanda Martin.