



Chapter 141 – Toxic alcohols

Key concepts

- **Serum osmolarity = 2 salt and a sticky BUN.** is calculated by the following equation: $\text{Calculated osmolality} = (2 \times \text{Na}) + \text{Glucose} + \text{BUN} + (1.25 \times \text{ETOH})$
 - The measured osmolar gap is the difference between the measured serum osmolality and calculated serum osmolarity, with a normal range of -15 to $+10$ mOsm.
- The classic finding of an elevated osmolar and anion gap should raise suspicion of methanol or ethylene glycol toxicity **but may not be present, depending on the timing of ingestion.** Early ingestion has a high osmolar gap without acidosis, and late ingestion has acidosis without an osmolar gap.
- A normal osmolar gap does not exclude toxic alcohol ingestion.
- Initiate therapy based on **clinical suspicion** of exposure to methanol or ethylene glycol. Block alcohol dehydrogenase preferably with fomepizole, but ethanol can be used if fomepizole is unavailable.
- The presence of acidosis indicates accumulation of the toxic metabolites of methanol (formic acid) and ethylene glycol (glycolic and oxalic acid). Consult nephrology for emergent hemodialysis to correct acid-base disturbances and remove the parent compound and its toxic metabolites.
- Severe acidosis is a poor prognostic factor, with high mortality rates in methanol and ethylene glycol ingestions. A comatose state at time of presentation also is associated with a higher mortality outcome.
- The main priorities in toxic alcohol exposure are correction of acidosis using bicarbonate solution and hemodialysis, inhibition of the production of toxic metabolites, and elimination of the parent alcohol and its toxic metabolites.
- The findings of an elevated osmolar gap with ketonemia or ketonuria and no development of acidosis indicates isopropanol ingestion. Patients can have a prolonged period of inebriation and can be comatose. Alcohol dehydrogenase inhibition is not indicated in these cases.
- Hypotension and GI bleeding are poor prognostic factors in isopropanol ingestion.
- Diethylene glycol can result in acidosis and renal failure and should be managed similarly to ethylene glycol poisoning with fomepizole and early hemodialysis.

Episode overview

1. What is the normal anion gap? What are causes of an increased anion gap?
2. What is the normal osmolar gap? What are causes of an increased osmolar gap?
3. How do you correct the osmolar gap when there is EtOH present?
4. Describe the metabolism of Methanol, and what is the primary toxin?
5. What are the two main complication of severe methanol poisoning?
6. Describe the metabolism of Ethylene Glycol.
7. What are the primary 3 toxic effects of Ethylene Glycol?
8. What are the 4 stages of Ethylene Glycol toxicity?



9. List 3 ways other than Hx and PEX to diagnose Ethylene Glycol Toxicity
10. Describe the 3 goals of therapy in toxic alcohol poisoning
11. Compare Fomepizole and Ethanol therapy for toxic alcohol poisoning
12. List indications for enzymatic blockade in toxic alcohol poisoning (box 141.1)
13. List indications for dialysis in toxic alcohol poisoning.
14. What cofactors are used in the metabolism of toxic alcohols? (the adjunctive treatments for ethylene glycol and methanol toxicity?)
15. What is the clinical presentation of isopropyl alcohol toxicity?
16. What is the metabolism and cause of morbidity in isopropyl alcohol toxicity?

Wisecracks:

1. What things can cause a “double gap”
2. What are the toxic metabolites & effect of ethylene glycol methanol & isopropyl? (review)
3. What is gasping baby syndrome?
4. How does propylene glycol toxicity present?
5. List 4 substances containing methanol / Ethylene Glycol
6. What is the pathognomonic ocular symptom of methanol ingestion?

Rosen’s In Perspective:

Today we’ll discuss the two and one so-so toxic alcohol: focusing on methanol, ethylene glycol (EG), and isopropyl alcohol (isopropanol). For an awesome primer, check out [FOAMCAST](#) & [CORE-EM](#). Please see Rosen’s Fig. 141.1 for the metabolism of alcohols in the body.

In the end, this chapter is all about the following table:

Causes of elevated osmolar and anion gaps			
<i>Osmolar gap</i>	<i>Anion gap (A CAT PILES MUD)</i>	<i>Double gap</i>	<i>Distinguishing features</i>
Methanol	A lcoholic ketoacidosis	Methanol	<ul style="list-style-type: none"> • Vision loss-methanol • Hypocalcaemia and calcium oxalate crystalluria – ethylene glycol • Hyperglycaemia, ketonuria – diabetic ketoacidosis • Normal or low glucose level, ketonuria – alcoholic ketoacidosis • Positive blood cultures – septic shock
Ethylene glycol	C yanide, carbon	Ethylene glycol	
Isopropanol	M onoxide, colchicine	Diabetic ketoacidosis	
Ethanol	A cetaminophen (large ingestion)	Alcoholic ketoacidosis	
Mannitol	T oluene	Uraemia	
Acetone	P araldehyde	Septic shock	
Glycerol	P ropylene glycol	Multiorgan failure	
Propylene glycol	P henformin		
Sorbitol	I soniazid, iron,		
Fructose	i buprofen		
Datrizoate (IV dye)	L actic acidosis		
Acetonitrile	E thylene glycol		
Ethyl ether	S alicylates		
Hyperlipidaemia	M ethanol, metformin		
Diabetic ketoacidosis	U raemia		
Alcoholic ketoacidosis	D iabetic ketoacidosis		
Uraemia			
Multiorgan failure			
Septic shock			



We will be going over it specifically. The “KULT” mnemonic is a good one to think back on, especially when you’re drafting a list of DO-NOT-MISS causes of a **double gap!**

This double gap picture is also dependent on the timing of presentation because early presenters will have only an osmotically active parent compound and late presenters will have acidosis without an elevated osmolar gap (Fig. 141.2).



Plug for Episode 106: <https://emergencymedicinecases.com/toxic-alcohols/>

Questions

1. **What is the normal anion gap? What are causes of an increased anion gap?**
 Approx 8-12, depending on your lab.

$AG = [Na^+] - ([HCO_3^-] + [Cl^-])$.

Ranges from 8-12 depending on lab.

Low albumin can falsely elevate, correct with: $AG\ corrected = AG + (2.5 \times [4.4 - \text{measured serum albumin}])$

NOTE*: A normal AG does not r/o toxic alcohol ingestion as the AG may be falsely elevated secondary to ethanol/lithium/bromide congestions**

2. **What is the normal osmolar gap? What are causes of an increased osmolar gap?**

2 salts & a sticky Bun, arbitrarily set at 10. But can range from -15 to 10 in population

$= 2x [\text{Serum Na}] + \text{BUN}$

$\text{Gap} = \text{Calc Serum Osm} - \text{Measured Serum Osm}$

Osmolar gap	Anion gap (A CAT PILES MUD)
Methanol	Alcoholic ketoacidosis
Ethylene glycol	Cyanide, carbon
Isopropanol	monoxide, colchicine
Ethanol	Acetaminophen (large
Mannitol	ingestion)
Acetone	Toluene
Glycerol	Paraldehyde
Propylene glycol	Propylene glycol



Sorbitol	Phenformin
Fructose	Isoniazid, iron, ibuprofen
Datrizoate (IV dye)	Lactic acidosis
Acetonitrile	Ethylene glycol
Ethyl ether	Salicylates
Hyperlipidaemia	Methanol, metformin
Diabetic ketoacidosis	Uraemia
Alcoholic ketoacidosis	Diabetic ketoacidosis
Uraemia	
Multiorgan failure	
Septic shock	

3. How do you correct the osmolar gap when there is EtOH present?

$(2 \times \text{Na}) + \text{Glucose} + \text{BUN} + (1.25 \times \text{EtOH})$

Using SI units!

4. Describe the metabolism of Methanol, and what is the primary toxin?

- **Methanol** to (via EtOH dehydrogenase) **formaldehyde**
- **Formaldehyde** to (via aldehyde dehydrogenase) **Formic Acid** *** Major Toxin***
- **Formic acid** to (via folate) $\text{CO}_2 + \text{H}_2\text{O}$
 - Formic acid is badness
 - Bind iron efficiently, and will inhibit oxidative metabolism much like cyanide, CO or H_2S poisoning.
 - Begin negative cycle of cellular hypoxia, acidosis, more diffusion of formic acid across cells in lower pH and on and on...
 - In particular, formic acid is quite toxic to retinal cells
 - *Formic acid uniquely targets the optic disk of the retina and retrolaminar optic nerve, potentially due to the high amount of blood and cerebrospinal fluid (CSF) flow through the choriocapillaris. These cells are more susceptible to cellular hypoxia due to low levels of mitochondria and cytochrome oxidase.*
- Please see Rosen's Fig. 141.1 for the metabolism of alcohols in the body.
- **Elimination** = mainly characterized via zero- order kinetics in poisoned patient
- first-order metabolism seen at very low concentrations
- Elimination **half life approx 2-3hours**
- Small amounts eliminated by kidney & lungs
- Formic acid half life approx 20hrs
- Concurrent etoh on board moves the half life to 50 hours by blocking ADH
- Dialysis = 200min half life

5. What are the two main complication of severe methanol poisoning?

Putamen Crisis = Leads to parkinsonism

Optic Neuropathy = Blindness (snowstorm vision)

Note*** After latency period of 1-72hrs, can see massive UGIB from hemorrhagic gastritis***



6. Describe the metabolism of Ethylene Glycol.

- Please see Rosen's Fig. 141.1 for the metabolism of alcohols (including ethylene glycol) in the body.

7. What are the primary 3 toxic effects of Ethylene Glycol?

- Neurologic - intoxication / cranial neuropathies
- Cardiac - Myocardial Dysfunction and pulmonary edema
- Renal Failure

8. What are the 4 stages of Ethylene Glycol toxicity?

- acute neurologic stage (<12 hrs)
 - inebriation and euphoria
 - In severe poisonings, CNS depression can progress to coma, hypotonia, and seizure
 - Look for nystagmus, ataxia, and myoclonic jerks
 - Cerebral edema from calcium oxalate crystal deposition and cytotoxic damage
- cardiopulmonary stage (12-24hrs)
 - Myocardial dysfunction & pulm edema
 - hypocalcemia
- renal stage (1-3 days)
- Delayed Neuro sequelae (1-3 weeks)
 - Cranial neuropathies

9. List 3 ways other than Hx and PEX to diagnose Ethylene Glycol Toxicity

- Hallmark of ethylene glycol toxicity is renal failure!
- **Lab abnormalities:**
 - Osmolar Gap
 - Parent compound ethylene glycol causes Osm Gap
 - *The contribution of EG to the osmolar gap is relatively small compared to other alcohols, and an EG concentration of 50 mg/dL (~8 mmol/L) will only cause an 8- to 10-mOsm rise in the osmolar gap. Thus, an elevated osmolar gap can suggest EG ingestion, but a normal gap does not exclude it.*
 - Anion Gap produced by glycolic acid + oxalic acid (metabolites)
 - Serum Hypocalcemia
 - Oxalic acid precipitates with serum calcium
 - Positive birefringent calcium oxalate crystals in the urine
 - *Calcium oxalate crystalluria is not specific for EG and is only present in up to 50% of cases of EG ingestion.*
- Renal Failure



10. Describe the 3 goals of therapy in toxic alcohol poisoning

- Correct Acidosis
- ADH Blockade
 - Fomepizole or ethanol
- Cofactors
- Hemodialysis

Note*** Activated Charcoal is ineffective. Gastric suctioning can be considered in recent massive ingestion

Ethylene Glycol

- Fomepizole 15mg/kg IV or ethanol
- Thiamine 100mg IV
- Pyroxidine 50mg IV
- Hemodialysis

Methanol

- Fomepizole 15mg/kg IV or ethanol
- Folic acid 50mg IV
- Hemodialysis

Don't forget that good supportive care is essential as well: correct hypoglycemia, hypokalemia, hypomagnesemia (high risk for arrhythmias due to long QT), and anything else that's abnormal!

11. Compare Fomepizole and Ethanol therapy for toxic alcohol poisoning

Please check Rosen's Box 141.2 for fomepizole dosing

ETOH

- Aim for serum concentration of 20-30 mmol/L (100-150mg/dl)
- ***Fomepizole is preferable due to its safety profile and ease of administration, sevenfold reduction in adverse drug event rate versus ethanol.
 - Less risk for:
 - Hypoglycemia
 - Electrolyte derangements
 - Subtherapeutic levels
 - CNS suppression
 - Withdrawal state
- If ethanol is used to inhibit ADH, maintain serum ethanol concentrations between 100 and 150 mg/dL. The affinity of ADH for ethanol is 10 times greater than for methanol.
- Ethanol no longer recommended



12. List indications for enzymatic blockade in toxic alcohol poisoning (box 141.1)

Please check Rosen's Box 141.2 for criteria for initiation of ADH blockade for methanol or ethylene glycol poisoning

13. List indications for dialysis in toxic alcohol poisoning.

- acidosis (pH < 7.3)
- renal failure
- vision abnormalities with methanol exposure
- electrolyte imbalances unresponsive to conventional therapy (ie, hyperkalemia)
- hemodynamic instability
- methanol or EG concentration more than 50 md/dL.

Mnemonic: **RAVED 3**

Renal acidosis

Acidosis

Visual changes

Electrolyte disturbance

Deterioration

Why is dialysis preferred for methanol poisoning?

At toxic concentrations, the elimination half-life of methanol is nearly 24 hours. The metabolite, formic acid, has a half-life of nearly 20 hours. With ADH inhibition by concurrent consumption of ethanol or administration of fomepizole, the half-life of methanol extends upward to more than 50 hours. With dialysis, the half-life of methanol is approximately 200 minutes.

14. What cofactors are used in the metabolism of toxic alcohols? (the adjunctive treatments for ethylene glycol and methanol toxicity?)

- Fomepizole: Blocks alcohol dehydrogenase
- Ethanol: Blocks alcohol dehydrogenase; preferentially metabolised
- Thiamine (B1): Promotes alternate metabolism of glycolic acid
- Pyridoxine: Promotes alternate metabolism of glycolic acid
- Folic Acid: Promotes metabolism of formic acid to CO₂ + H₂O
- Dialysis: Removes parent ETOH

15. What is the clinical presentation of isopropyl alcohol toxicity?

Much more inebriating than ETOH.

Neuro (intoxication / ALOC / coma)

GI symptoms (N/V abdominal pain / gastritis / GI hemorrhage / pancreatitis)

Other: respiratory depression, hypotension

Classically presents with profound ETOH-like intoxication, and osmolar gap, but NO anion GAP. Also, in isolation isopropyl alcohol ingestions usually have euglycemia.



16. What is the metabolism and cause of morbidity in isopropyl alcohol toxicity?

Please see Rosen's Fig. 141.1 for the metabolism of alcohols in the body, including isopropyl alcohol.

Main morbidity:

- GI irritation complications:
 - N/V, hemorrhagic gastritis or hematemesis
 - Pancreatitis
 - Aspiration into tracheobronchial tree
- CNS:
 - Seizures, coma, hypoxia, respiratory depression, hypothermia, rhabdomyolysis.
- Metabolic effects:
 - *As IPA is converted to acetone, ketosis will occur. Ketosis is present in conditions such as diabetic ketoacidosis, alcoholic ketoacidosis, starvation ketosis, salicylism, and cyanide and acetone ingestion. ARF can develop from rhabdomyolysis*
- Derm:
 - Direct contact leads to defatting dermatitis, chemical burns (in children), dry skin

Management:

- Supportive
 - Due to the profound CNS depressant effects, some people require intubation and vasopressors
- Look carefully for any other co-ingestions
- PPI for hemorrhagic gastritis and get GI follow-up.

If the patient is persistently hypotensive, despite standard resuscitative measures, initiate HD. ADH blockade with fomepizole or ethanol is not indicated because this will only prolong the hypotensive and CNS depressant effects of IPA.

Wisecracks:

1. What things can cause a “double gap”

Note: these are substances that cause both an osmolar gap and an AGMA

Mnemonic:

R: renal failure

A: aka

M: methanol

M: multi-organ failure

E: ethylene glycol

D: DKA

2. What are the toxic metabolites & effect of ethylene glycol methanol & isopropyl? (review)



Methanol (Formic Acid)

- Putamen Crisis
- Optic Neuropathy

Ethylene Glycol (Oxalic Acid)

- Neurological (intoxication, cranial neuropathies)
- Cardiac (myocardial dysfunction and pulmonary edema)
- Renal Failure

Isopropyl (Acetone)

- Neuro (intoxication, ALOC)
- GI (abdo pain / N/V/gastiritis)

3. What is gasping baby syndrome?

“Benzyl alcohol poisoning can cause the gasping syndrome in neonates. The infants had a typical course of gradual neurologic deterioration, severe metabolic acidosis, the striking onset of gasping respirations, thrombocytopenia, hepatic and renal failure, hypotension, cardiovascular collapse and death.”

4. How does propylene glycol toxicity present?

- As always - **coma, seizures and hypoglycemia**
- metabolized into pyruvic acid / acetic acid / lactic acid and propionaldehyde (a potentially hazardous substance)
- NEED large amounts of ingestion, nearly impossible in oral ingestion (unless in kids) but can happen as iatrogenic injury (like in ICU with diazepam or lorazepam infusions)

5. List 4 substances containing methanol / Ethylene Glycol

Methanol

- Antifreeze
- Windshield wiper fluid
- Photocopy fluid
- Paint thinners / removers
- Camp stove fuel
- Embalming fluid

*** **Note:** “Inhalation of methanol from carburetor cleaning fluid results in toxicity necessitating antidotal therapy and hemodialysis.” ***

Ethylene Glycol

- Antifreeze
- Brake Fluid

6. What is the pathognomonic ocular symptom of methanol ingestion?

“Snow Storm Vision”