Hemodialysis in the Poisoned Patient

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ABSTRACT:

Audience: This classic team based learning (cTBL) didactic is aimed for emergency medicine residents and fourth year medical students entering emergency medicine.

Introduction: Over one million visits per year to United States (US) emergency departments (ED) are related to poisonings.[1] Extracorporeal treatment (ECTR), specifically hemodialysis (HD), is one potential method to enhance elimination of certain drugs and their toxic metabolites.[2-12] While HD may be life-saving in certain poisonings, it may have no effect on others and it carries associated risks and costs. It is essential that emergency physicians know the indications for HD in the poisoned patient. This cTBL reviews many poisonings which may be managed by HD.

Objectives: By the end of this cTBL, the learner will: 1) Recognize laboratory abnormalities related to toxic alcohol ingestion; 2) calculate an anion gap and osmolal gap; 3) know the characteristics of drugs that are good candidates for HD; 4) discuss the management of patients with toxic alcohol ingestions; 5) discuss the management of patients with salicylate overdose; 6) know the indications for HD in patients with overdoses of antiepileptic drugs; 7) discuss the management of patients with lithium toxicity.

Method: This didactic session is a cTBL (classic team based learning).

Topics: Toxic alcohols, methanol, ethylene glycol, osmolal gap, anion gap acidosis, osmolality, lithium, dialysis, poisonings, toxicology, extracorporeal treatment, carbamazepine, valproic acid, phenytoin, overdose, salicylates, aspirin, fomepizole.

USER GUIDE

List of Resources:

Learner Audience:
Medical students, interns, junior residents, senior residents, internal medicine residents, critical care fellow

Time Required for Implementation:
Instructor Preparation: 30 minutes
Learner Responsible Content: 0-60minutes
In Class Time: 60-120 minutes, depending on how you manage the group application exercise

Recommended Number of Learners per Instructor:
As with any TBL, only one instructor is required. An ideal size for this didactic is 30 learners, but TBL can be effective in groups larger than 100 learners.

Topics:
Toxic alcohols, methanol, ethylene glycol, osmolal gap, anion gap acidosis, osmolality, lithium, dialysis, poisonings, toxicology, extracorporeal treatment, carbamazepine, valproic acid, phenytoin, overdose, salicylates, aspirin, fomepizole.

Objectives:
By the end of this cTBL, the learner will:

1. Recognize laboratory abnormalities related to toxic alcohol ingestion
2. Calculate an anion gap and osmolal gap
3. Know the characteristics of drugs that are good candidates for HD
4. Discuss the management of patients with toxic alcohol ingestions
5. Discuss the management of patients with salicylate overdose
6. Know the indications for HD in patients with overdoses of antiepileptic drugs
7. Discuss the management of patients with lithium toxicity.

Linked objectives and methods:
The learner demonstrates knowledge of laboratory abnormalities and the anion gap and osmolal gap formulas (objectives 1 and 2) during the readiness assessment tests. The learner then shows how to use these formulas (objective 2) during case #1 in the group application exercise (GAE). The learner manages a theoretical patient with a toxic alcohol ingestion (objective 4), salicylate ingestion (objective 5), lithium (objective 7), and anti-epileptics (objective 6) during the group application exercise. The learner confirms knowledge of the characteristics of dialyzable drugs during the readiness assessment test and again in the post-test. The learner demonstrates knowledge of the indications for HD in overdose patients during the group application exercise and post-test.

Recommended pre-reading for instructor:
The instructor should be familiar with all answers and explanations for this exercise. The instructor may also benefit from reading the following paper:

- Garlich FM, Goldfarb DS. Have advances in extracorporeal removal techniques changed the indications for their use in poisonings? *Adv in Chron Kid Dis*. 2011;18(3):172-179. doi: 10.1053/j.ackd.2011.01.009

The following are the various consensus statements and extracorporeal treatments in poisonings (EXTRIP) guidelines referenced in each of the exercises. The instructor should be aware of these and might review them:

- Anseeuw K, Mowry JB, Burdmann EA, Ghannoum M, Hoffman RS, Gosselin S, et al. Extracorporeal treatment in phenytoin poisoning: systematic review and recommendations from the EXTRIP workgroup. *Am J Kidney Dis.* 2016;67(2):187-197. doi: 10.1053/j.ajkd.2015.08.031
- Ghannoum M, Laliberté M, Nolin TD, et al. Extracorporeal treatment for valproic acid poisoning: systematic review and recommendations from the EXTRIP workgroup, *Clinical Toxicology*. 2015;53(5):454-465. doi: 10.3109/15563650.2015.1035441
- Roberts DM, Yates C, Megarbane B, Winchester JF, Maclaren R, Gosselin S, 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
- Juurlink DN, Gosselin S, Kielstein JT, Ghannoum M, Lavergne V, Nolin TD, et al. Extracorporeal treatment for salicylate poisoning: systematic review and recommendations from the EXTRIP

workgroup. *Ann Emerg Med*. 2015;66(2)165-181. doi: 10.1016/j.annemergmed.2015.03.031
- Decker BS, Goldfarb DS, Dargan PI, Friesen M, Gosselin S, Hoffman RS, et al. Extracorporeal treatment for lithium poisoning: systematic review and recommendations from the EXTRIP Workgroup. *Clin J Am Soc Nephrol.* 2015;10(5):875-887. doi: 10.2215/CJN.10021014
- Ghannoum M, Yates C, Galvao TF, Sowinski KM, Vo TH, Coogan A, et al. Extracorporeal treatment for carbamazepine poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol.* 2014;52(10):993-1004. doi: 10.3109/15563650.2014.973572

If the instructor is unfamiliar with toxic alcohols and salicylates, they could consider reading any textbook chapter on toxic alcohols and salicylates, such as:

- Long, H. Acetaminophen, aspirin, and NSAIDs. In: Adams JG, Barton ED, Collings JL, DeBlieux PMC, Gisondi MA, Nadel ES, eds. *Emergency Medicine: Clinical Essentials.* 2nd ed. Philadelphia, PA: Elsevier; 2014:1231-1238.
- Mycyk MB. Toxic alcohols. In: Adams JG, Barton ED, Collings JL, DeBlieux PMC, Gisondi MA, Nadel ES, eds. *Emergency Medicine: Clinical Essentials.* 2nd ed. Philadelphia, PA: Elsevier; 2014:1292-1298.

Other useful papers:

- O'Malley GF. Emergency department management of the salicylate-poisoned patient. *Emerg Med Clin N Am*. 2007;25(2):333-46. doi: 10.1016/j.emc.2007.02.012

Learner Responsible Content (LRC):

The learner may read any textbook chapters on toxic alcohols and salicylate overdose, such as:

- Long, H. Acetaminophen, aspirin, and NSAIDs. In: Adams JG, Barton ED, Collings JL, DeBlieux PMC, Gisondi MA, Nadel ES, eds. *Emergency Medicine: Clinical Essentials.* 2nd ed. Philadelphia, PA: Elsevier; 2014:1231-1238.
- Mycyk MB. Toxic alcohols. In: Adams JG, Barton ED, Collings JL, DeBlieux PMC, Gisondi MA, Nadel ES, eds. *Emergency Medicine: Clinical Essentials.* 2nd ed. Philadelphia, PA: Elsevier; 2014:1292-1298.
- Cohen JP, Quan D. Alcohols. In: Tintinalli JE, Stapczynski J, Ma O, Yealy DM, Meckler GD, Clind DM, eds. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide.* 8th ed. New York, NY: McGraw-Hill; 2016:1243-1250.
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- Segeer DL, Murray L. Aspirin and nonsteroidal agents. In: Marx JA, Hockberger RS, Walls RM, et al. eds. *Rosen's Emergency Medicine: Concepts and Clinical Practice*. 8th ed. Philadelphia, PA: Elsevier; 2014:1965-1969.
- Garlich FM, Goldfarb DS. Have advances in extracorporeal removal techniques changed the indications for their use in poisonings? *Adv in Chron Kid Dis*. 2011;18(3):172-9. doi: 10.1053/j.ackd.2011.01.009

Results and tips for successful implementation:

This didactic was originally piloted on a group of first- through third-year emergency medicine residents (approximately 20 learners). The session was rated as "highly relevant" by 100% of learners who completed the course evaluation (n=8). Evaluators recommended that we develop a PowerPoint with answers for the readiness assessment test and group application exercise; they also recommended a Kahoot post-test.

This session is ideally run in groups of four learners. We recommend groups with mixed levels of learners. The instructor should assign the groups at the beginning of the session.

Prior to the session, the instructor should prepare materials:

- One individual readiness assessment test (iRAT) per learner
- One group readiness assessment test (gRAT) per four learners (one per group)
- One group application exercise (GAE) per four learners (one per group)
- Send out the assigned reading one week prior to the session

The instructor may choose to give the optional Powerpoint and post-test (Kahoot), so the session should have a computer with internet connection and projector.

You will need between one and two hours to conduct the session, depending on whether you have all groups do all four cases in the group application exercise (between 1.5 and 2 hours for this version) or whether you have each group do a different case (between 1 and 1.5 hours). We suggest the following timeline:

USER GUIDE

1. Introduce session (1 minute).
2. Learners complete the iRAT (5-10 minutes).
3. Place learners in groups of four learners.
4. Groups complete the gRAT (5-10 minutes).
5. Review answers for the gRAT (15 minutes); call on groups one at a time to answer each question; then show slide with answer.
6. Groups complete the GAE (15 – 50 minutes, depending on whether every group will complete all four cases or whether each group does a different case).
7. Review answers from the GAE (20 minutes). If each group will do all four cases (longer version), go through the explanations in between each case. If each group does a different case, go through all explanations at the end. Call on groups one at a time to answer each question; then show slide with answer.
8. Post-test (Kahoot) (5 minutes)

References/suggestions for further reading:

1. Albert M, McCraig LF, Uddin S. Emergency department visits for drug poisonings: United States, 2008-2011. NCHS data brief, no 196. Hyattsville, MD: National Center for Health Statistics, 2015.
2. Anseeuw K, Mowry JB, Burdmann EA, Ghannoum M, Hoffman RS, Gosselin S, et al. Extracorporeal treatment in phenytoin poisoning: systematic review and recommendations from the EXTRIP workgroup. *Am J Kidney Dis.* 2016;67(2):187-197. doi: 10.1053/j.ajkd.2015.08.031
3. Baird-Gunning J, Lea-Henry T, Hoegberg LCG, Gosselin S, Roberts DM. Lithium poisoning. *J Intensive Care Med.* 2017;32(4):249-263. doi: 10.1177/0885066616651582
4. Juurlink DN, Gosselin S, Kielstein JT, Ghannoum M, Lavergne V, Nolin TD, et al. Extracorporeal treatment for salicylate poisoning: systematic review and recommendations from the EXTRIP workgroup. *Ann Emerg Med*. 2015;66(2)165-181. doi: 10.1016/j.annemergmed.2015.03.031
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6. Decker BS, Goldfarb DS, Dargan PI, Friesen M, Gosselin S, Hoffman RS, et al. Extracorporeal treatment for lithium poisoning: systematic review and recommendations from the EXTRIP Workgroup. *Clin J Am Soc Nephrol.* 2015;10(5):875-887. doi: 10.2215/CJN.10021014
7. Garlich FM, Goldfarb DS. Have advances in extracorporeal removal techniques changed the indications for their use in poisonings? *Adv in Chron Kid Dis*. 2011;18(3):172-179. doi: 10.1053/j.ackd.2011.01.009
8. Ghannoum M, Laliberté M, Nolin TD, et al. Extracorporeal treatment for valproic acid poisoning: systematic review and recommendations from the EXTRIP workgroup, *Clinical Toxicology*. 2015;53(5):454-465. doi: 10.3109/15563650.2015.1035441
9. Ghannoum M, Yates C, Galvao TF, Sowinski KM, Vo TH, Coogan A, et al. Extracorporeal treatment for carbamazepine poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol.* 2014;52(10):993-1004. doi: 10.3109/15563650.2014.973572
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12. Roberts DM, Yates C, Megarbane B, Winchester JF, Maclaren R, Gosselin S, 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
13. Liamis G, Filippatos TD, Liontos A, Elisaf MS. Serum osmolal gap in clinical practice: usefulness and limitations. *Postgrad Med*. 2017;129(4);456-459. doi: 10.1080/00325481.2017.1308210
14. Kraut JA, Madias NE. Serum anion gap: its uses and limitations in clinical medicine. *Clin J Am Soc Nephrol.* 2007;2(1):162-174. doi: 10.2215/CJN.03020906
15. Brent J. Fomepizole for ethylene glycol and methanol poisoning. *N Engl J Med*. 2009;360(21):2216-2223. doi: 10.1056/NEJMct0806112
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17. Mycyk MB. Toxic alcohols. In: Adams JG, Barton ED, Collings JL, DeBlieux PMC, Gisondi MA, Nadel ES, eds. *Emergency Medicine: Clinical Essentials.* 2nd ed. Philadelphia, PA: Elsevier; 2014:1292-1298.
18. Long, H. Acetaminophen, aspirin, and NSAIDs. In: Adams JG, Barton ED, Collings JL, DeBlieux PMC, Gisondi MA, Nadel ES, eds. *Emergency Medicine: Clinical Essentials.* 2nd ed. Philadelphia, PA: Elsevier; 2014:1231-1238.
19. Minns AB, Cantrell FL, Clark RF. Death due to acute salicylate intoxication despite dialysis. *J Emerg Med.* 2011;40(5):515-517. doi: 10.1016/j.jemermed.2010.02.015
20. O'Malley GF. Emergency department management of the salicylate-poisoned patient. *Emerg Med Clin N Am*. 2007;25:333-346. doi: 10.1016/j.emc.2007.02.012

Hemodialysis in the Poisoned Patient: individual Readiness Assessment Test (iRAT)

1. What chemical properties favor a substance being dialyzable?

Property	Circle one	
Molecular Weight	Small	Large
Volume of Distribution	Small	Large
Tissue Binding	Good	Poor

2. Name at least two complications of dialysis:

3. In an overdose setting, name at least four drugs that are good candidates for dialysis:

4. Please complete the following table: Key: AG = Anion Gap, OG = Osmolal Gap

Toxic Alcohol	AG? (Y/N)	OG? (Y/N)	Ketones? (Y/N)	Household agent; where it is found?	Name of toxic metabolite(s)
Methanol					
Ethylene Glycol					
Isopropanol					

5. What lab tests do you need to order to calculate an osmolal gap?

6. Besides the toxic alcohols above, name at least four other causes for an elevated osmolal gap.

7. What is the formula for calculating an anion gap?

8. Name at least six causes for an elevated anion gap:

Hemodialysis in the Poisoned Patient: group Readiness Assessment Test (gRAT)

1. What chemical properties favor a substance being dialyzable?

Property	Circle one	
Molecular Weight	Small	Large
Volume of Distribution	Small	Large
Tissue Binding	Good	Poor

2. Name at least two complications of dialysis:

3. In an overdose setting, name at least four drugs that are good candidates for dialysis:

4. Please complete the following table: Key: AG = Anion Gap, OG = Osmolal Gap

Toxic Alcohol	AG? (Y/N)	OG? (Y/N)	Ketones? (Y/N)	Household agent; where it is found?	Name of toxic metabolite(s)
Methanol					
Ethylene Glycol					
Isopropanol					

5. What lab tests do you need to order to calculate an osmolal gap?

6. Besides the toxic alcohols above, name at least four other causes for an elevated osmolal gap.

7. What is the formula for calculating an anion gap?

8. Name at least six causes for an elevated anion gap:

Hemodialysis in the Poisoned Patient: Group Application Exercise (GAE)

Case #1: She's glowing!

A 26-year-old woman presents to the emergency department with altered mental status. Her (ex-?) boyfriend states that he broke up with her last night and she texted him stating that she was going to drink antifreeze. He went to check on her today and found her unconscious, so he called 911. The patient is obtunded. Her vital signs are: heart rate (HR) 148, blood pressure (BP) 140/70, respiratory rate (RR) 24, temperature (T) 35.1°C. She is intubated.

Her labs are as follows:
Na^+=147 mEq/L
K^+= 7.7 mEq/L
Cl^- = 105 mEq/L
HCO_3^- = <5 mEq/L
Blood Urea Nitrogen (BUN) = 18 mg/dL
Creatinine (Cr) = 2.4 mg/dL
Glucose = 137 mg/dL
Ca^{2+} = 8.3 mg/dL
Lactate = 3.6 mmol/L
Ethanol = Not detected
Acetaminophen < 5.0 mcg/ml
Salicylate <4 mg/dL
Osmolality = 338 mOsm/kg
ABG (arterial blood gas): pH 6.75 / pCO_2 23.7/ HCO_3 3.3/ pO_2 582.9

1. What is her anion gap?

2. What is the formula for calculating an osmolal gap?

3. What is her osmolal gap?

4. Is she a candidate for gastric decontamination? Why/why not?

5. What antidote should be given? Dose?

6. How does the antidote work?

7. Should you start dialysis on this patient? Do you need other tests back to decide?

8. What are the complications of ethylene glycol ingestion?

9. What other poisoning with potential retinal toxicity can be treated with the antidote in 5? What is the dose?

10. What are the indications for dialysis for the toxin in 9 (Hint, there is a paper by Roberts DM, et al. as part of the EXTRIP group)?

LEARNER MATERIALS

Case #2: Anyone else hear that ringing??!

A 45-year-old male presents to the emergency department complaining of nausea, vomiting, tinnitus, and generalized weakness. Of note, the patient was seen one week ago in the ED for rib fracture he sustained while falling off of his motorcycle.
His vital signs are as follows: HR 120 beats/min, RR 30 breaths/min, BP 110/70 mmHg, T=38.5°C, O_2 saturation 95% RA.

His labs are as follows:
Na^+: 140 mEq/L
K^+: 3.3 mEq/L
Cl^-: 105 mEq/L
HCO_3^-: 16 mEq/L
BUN: 20 mg/dL
Cr: 1.1 mg/dL
Glucose: 75 mg/dL

1. In addition to an ABG, what additional laboratory studies would you like to order?

2. Your ABG returns with a pH value of 7.46, pCO_2 = 25 mmHg, HCO_3 = 16 mEq/L. Additionally, your serum salicylate level is 75 mg/dL. Your patient states that he has been taking aspirin to control the pain from his rib fracture. What are some of the signs and symptoms associated with salicylate toxicity:

3. What is the treatment?

4. What are the indications for dialysis? (Hint: EXTRIP)

LEARNER MATERIALS

Case #3: Oh Limey!

A 45-year-old female with bipolar disorder presents to the emergency department. She states that her mania has been getting worse and her psychiatrist adjusted her medications two weeks ago. She started developing nausea, vomiting, and diarrhea 5 days ago. Now, she is starting to feel worsening agitation, dizziness, and tremors.

1. What medication was probably adjusted?

2. What is the normal serum concentration of this drug?

3. What signs and symptoms can occur with toxicity from this drug?

4. What is the treatment, and what are the indications for dialysis in overdose?

LEARNER MATERIALS

Case #4: Can't fight the seizure...but we can try

A 30-year-old male with epilepsy went on vacation and forgot to bring his medications. After returning home, he took all of his medications in order to "catch up." He is feeling confused and lethargic. He can't remember the name of the antiepileptic drug that he is taking. You mention valproic acid, phenytoin, and carbamazepine. He says, "It's definitely one of those!"

What symptoms would you expect for each and what are the indications for dialysis for each?

Anti-epileptic drug	Symptoms in overdose	Treatment	Indications for dialysis
Phenytoin			
Carbamazepine			
Valproic Acid			

Hemodialysis in the Poisoned Patient: Brief Wrap Up

Please find the associated Powerpoint to use for going over the answers.
Also, there is a Kahoot post-test: https://play.kahoot.it/#/k/ba8deea7-4ca1-486f-b6a8-32ed4b62b623 or you may use the following paper post-test:

1. Which of the following properties of a drug makes it more dialyzable?
    a. High tissue binding
    b. Large volume of distribution
    c. Small molecular weight
    d. Poor water solubility

2. Which of the following drugs is a good candidate for hemodialysis in overdose?
    a. Digoxin
    b. Lidocaine
    c. Theophylline
    d. Warfarin

3. Which of the following does isopropanol ingestion cause?
    a. Elevated anion gap
    b. Elevated osmolal gap
    c. Both

4. Which of the following is a feared complication of ethylene glycol overdose?
    a. Blindness
    b. Tinnitus
    c. Hepatotoxicity
    d. Renal failure

5. What is the most appropriate antidote for early ethylene glycol or methanol ingestion?
    a. Fomepizole
    b. Hemodialysis
    c. L-carnitine
    d. N-acetylcysteine

6. Which of the following is an indication for hemodialysis in salicylate poisoning?
    a. Hypoxemia
    b. Respiratory alkalosis
    c. Salicylate level > 40 mg/dL
    d. Tinnitus

7. Which drug in overdose can cause hyperammonemia and cerebral edema?
    a. Carbamazepine
    b. Lithium
    c. Phenytoin
    d. Valproic Acid

INSTRUCTOR MATERIALS

Answer keys to all exercises with explanations, are on the following pages.

Learners: please do not proceed.

INSTRUCTOR MATERIALS

Hemodialysis in the Poisoned Patient: Readiness Assessment Test Key (RAT Key)

1. **Traditionally, what properties of toxins make them appropriate for hemodialysis?**

   Molecular Weight
   Small

   Volume of Distribution
   Small

   Tissue/protein binding
   Poor

   Explanations:[7,10]
   Low molecular weight: Traditionally, molecules amenable to dialysis are small in molecular weight (due to pore size), but recent advances with larger pore size of dialysis membranes are allowing for larger (but still <500 Daltons).
   Low volume of distribution: Relatively more drug found in the vascular space (average volume of distribution of a person is 0.6L/kg).
   Water soluble: Lower volume of distribution.
   Low tissue and protein binding: However, some highly protein bound drugs have lower protein binding at toxic levels (higher saturation of protein bound molecules; therefore, a higher percentage of free drug in the serum).
   Other features of effectively dialyzed toxins:
   - Compelling indication for dialysis should be present (secondary to low but real frequency of complications)
   - High water solubility
   - Poor or impaired endogenous clearance
   - Clinical benefit of hemodialysis has been demonstrated

2. **What are some complications of dialysis?**[7]
   Complications of dialysis include:
   - Complications related to catheter placement
   - Bleeding, infection, thrombosis

- Complications related to sites specific catheters: retroperitoneal hemorrhage (femoral), pneumothorax (subclavian), carotid arterial cannulation (internal jugular)
- Difficulty maintaining hemodynamic stability (blood pressure fluctuations)
- Use of heparin
- Cost: Dialysis nurse, nephrologist, setting up machine
- Air embolism

3. **In an overdose setting, which toxins are good candidates for dialysis:**[5,10,11]
   (The **bolded** drugs are more commonly dialyzed.)
   Aminoglycosides, aminophylline, atenolol, carbamazepine, carisoprodol, chloral hydrate, disopyramide, ethchlovynol, **ethylene glycol,** isopropanol, **lithium,** meprobamate, **methanol,** methotrexate, mushroom, paraquat, phenobarbital, phenothiazine, phenytoin, **salicylates, theophylline,** trichloroethanol, **valproic acid**

4. **Please complete the following table:**
   Anion Gap (AG)
   Osmolal Gap (OG)

Toxic Alcohol	AG? (Y/N)	OG? (Y/N)	Ketones? (Y/N)	Household agent; where it is found?	Name of toxic metabolites
Methanol	Yes	Yes	No	Windshield washer fluid	Formaldehyde Formic Acid
Ethylene Glycol	Yes	Yes	No	Antifreeze	Glycolic Acid Oxalic Acid
Isopropanol	No	Yes	Yes	Rubbing Alcohol	Acetone

5. **What labs do you need to order to calculate an osmolal gap?**[13]
   Sodium, BUN, glucose, ethanol (EtOH), serum osmolality

6. **Besides the toxic alcohols above, what are other causes for an elevated osmolal gap?**[13]
   Alcoholic ketoacidosis (AKA), renal failure, diabetic ketoacidosis (DKA), shock, mannitol, toxic alcohols, severe lactic acidosis, pseudohyponatremia, levothyroxine/lithium (high doses), activated charcoal

7. **Anion Gap formula:**[14]
   Anion Gap = Sodium - (Chloride + Bicarbonate)

8. **Name at least six causes for an elevated anion gap.**
   Methanol, Uremia, Diabetic Ketoacidosis, Paraldehyde, Iron, Isoniazid, Inborn Errors of Metabolism, Lactic Acidosis, Ethylene Glycol, Salicylates (mnemonic: MUDPILES).

INSTRUCTOR MATERIALS

Hemodialysis in the Poisoned Patient: Group Application Exercise (GAE) Key

Case #1: She's glowing!

A 26-year-old woman presents to the emergency department with altered mental status. Her (ex-?) boyfriend states that he broke up with her last night and she texted him stating that she was going to drink antifreeze. He went to check on her today and found her unconscious, so he called 911. The patient is obtunded. Her vital signs are: HR 148/min, BP 140/70, RR 24, T 35.1. She is intubated.

Her labs are as follows:
Na^+=147 mEq/L
K^+= 7.7 mEq/L
Cl^- = 105 mEq/L
HCO_3^- = <5 mEq/L
Blood Urea Nitrogen (BUN) = 18 mg/dL
Cr = 2.4 mg/dL
Glucose = 137 mg/dL
Ca^{2+} = 8.3 mg/dL
Lactate = 3.6 mmol/L
Ethanol = Not detected
Acetaminophen < 5.0 mcg/ml
Salicylate <4 mg/dL
Osmolality = 338 mOsm/kg
ABG: pH 6.75 / pCO_2 23.7/ HCO_3 3.3/ pO_2 582.9

1. **What is her anion gap**?
   Anion Gap (AG): Na – (Cl + HCO_3)
   147 – (105 + <5)
   AG = > 37

2. **What is the formula for calculating an osmolal gap?**[13]
   $Osm_{(Meas)}$ – $Osm_{(Calc)}$
   $Osm_{(Calc)}$ = [2(Na) + (BUN)/2.8 + Gluc/18 + EtOH/4.6]

3. **What is her osmolal gap?**
   Osm(Meas) – Osm(Calc)
   338 – [2(Na) + (BUN)/2.8 + Gluc/18 + EtOH/4.6]
   338 – [294 + 6.4 + 7.6 + 0]
   338 – 308
   OG = 30 mOsm/kg
   The proper conversion factor for Ethanol is an area of continued debate. The conversion factor here is 4.6 (one-tenth of ethanol's molecular weight), but there is good evidence that in reality a better conversion factor might be as low as 3.7, while 4.2 is also fairly commonly used. We use 4.6 in this equation.

4. **Is she a candidate for gastric decontamination? Why/why not?**
   No: Ethylene glycol is rapidly absorbed and does not bind well to activated charcoal. It has been several hours since her ingestion.

5. **What antidote should be given?**[15]
   Fomepizole 15mg/kg IV
   Also consider ethanol 0.8 g/kg (less desirable)

6. **How does the antidote work?**
   Fomepizole is a competitive Alcohol Dehydrogenase (ADH) Inhibitor, which is the first step in the metabolism of ethylene glycol. Therefore, it may not be as effective in this case, since it has been several hours since the ingestion and all ethylene glycol may be metabolized.

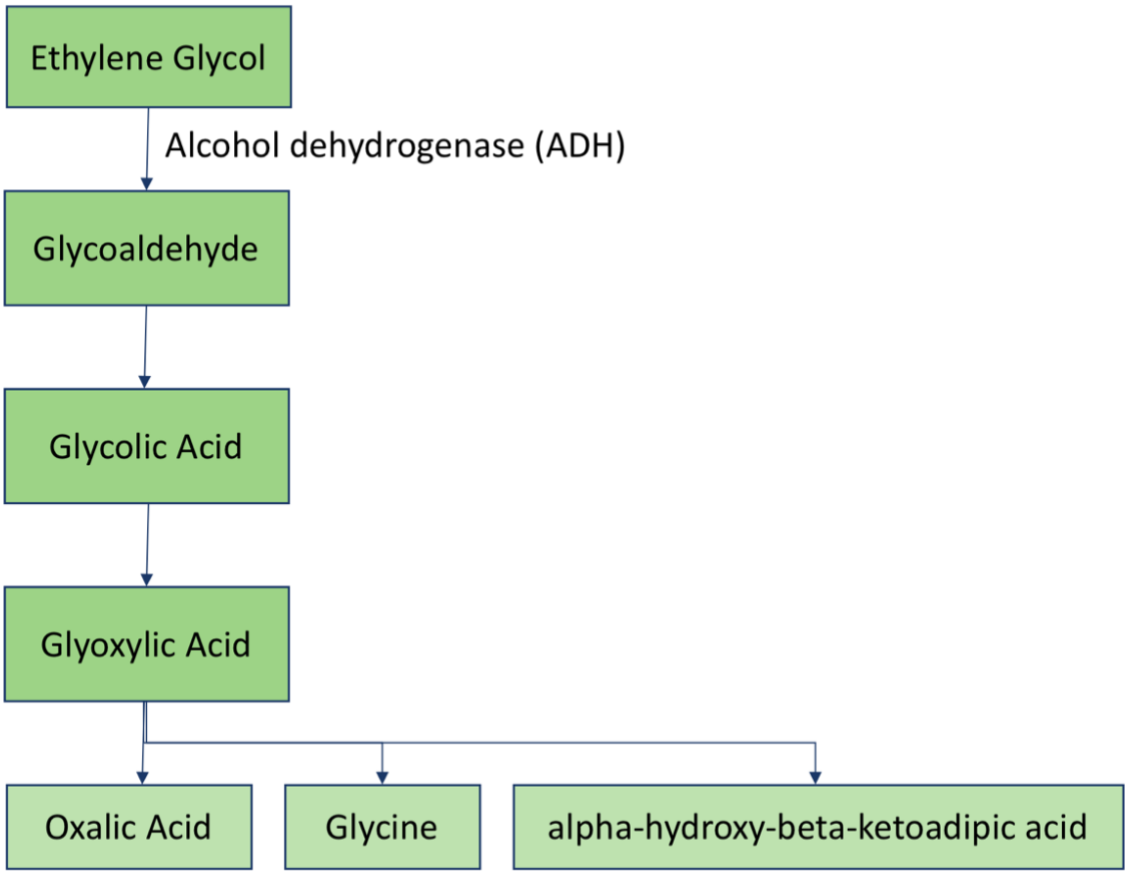

Figure 1: Ethylene glycol metabolism

7. **Should you start dialysis on this patient? Do you need other tests back to decide?**
   Yes, you have sufficient cause to start dialysis and you do not need to wait for an ethylene glycol level; it won't come back in time.
   The patient is significantly acidemic and needs dialysis to clear the active metabolites (fomepizole will not clear the metabolites that have already formed).
   The patient has a suspected ethylene glycol ingestion, plus a pH<7.3 and should therefore be dialyzed.

8. **What are the complications of ethylene glycol ingestion?**[16,17]
   -Renal insufficiency/failure
   -Hypocalcemia secondary to crystal formation (depletes calcium levels)
   -Cranial neuropathies
   -Severe acidemia: cardiopulmonary complications/ARDS (acute respiratory distress syndrome)

9. **What other poisoning with potential retinal toxicity can be treated with the antidote in 5? What is the dose?[15]**
   Methanol, same dose (fomepizole 15mg/kg)

10. **What are the indications for dialysis for the toxin in 9 (Hint, there is a paper by Roberts DM, et al. as part of the EXTRIP group)?[12]**
    Coma, seizures, new vision defects, metabolic acidosis (blood pH<7.15), persistent metabolic acidosis despite supportive measures and antidote, serum anion gap >24 mmol/L, serum methanol concentrations >500mg/L if fomepizole not available; >700mg/L if fomepizole therapy available.

INSTRUCTOR MATERIALS

Case #2: Anyone else hear that ringing??!

A 45-year-old male presents to the emergency department complaining of nausea, vomiting, tinnitus, and generalized weakness. Of note, the patient was seen one week ago in the ED for rib fracture he sustained while falling off of his motorcycle.
His vital signs are as follows: HR 120 beats/min, RR 30 breaths/min, BP 110/70, T=38.5°C, O_2 saturation 95% RA.

His labs are as follows:
Na^+: 140 mEq/L
K^+: 3.3 mEq/L
Cl^-: 105 mEq/L
HCO_3^-: 16 mEq/L
BUN: 20 mg/dL
Cr: 1.1 mg/dL
Glucose: 75 mg/dL

1. **What additional laboratory studies would you like to order?**
   -Blood cultures (this may look like sepsis from pneumonia)
   -Salicylate level
   -Lactate
   -Urinalysis

2. **Your ABG returns with a pH value of 7.46, pCO_2 = 25 mmHg, HCO_3 = 16 mEq/L. Additionally, your serum salicylate level is 75 mg/dL. Your patient states that he has been taking aspirin to control the pain from his rib fracture. What are some of the symptoms associated with salicylate toxicity?**[18-20]
   CNS: Tinnitus, confusion, agitation, lethargy, coma, seizure, syndrome of inappropriate antidiuretic hormone (SIADH)
   GI: Nausea, vomiting, abdominal pain, gastritis, decreased motility
   CV: Tachycardia (2/2 Hypovolemia and hyperpyrexia)
   Pulm: ARDS, tachypnea
   Heme: Prolonged PT, platelet dysfunction
   Acid/base: Respiratory alkalosis, metabolic acidosis, respiratory acidosis, hypokalemia, hyponatremia or hypernatremia,

Metabolic: Hyperthermia, hyper- or hypoglycemia, hypoglycorrhachia, ketonemia, ketonuria

3. **What is the treatment?** [18]
   -Consider multidose activated charcoal (MDAC)
   -IV fluids
   -Urine alkalinization ("ion trapping") is indicated for ASA level >40 mg/dL (1-2 mEq/kg sodium bicarbonate by IV bolus 3 amps $NaHCO_3$ + 40mEq KCl in 1L D5W for goal urine pH 7.5, serum pH 7.45-7.55).
   -Consider hemodialysis

4. **What are the indications for dialysis?**[4]
   -Salicylate 100 mg/dL (or 90 mg/dL with impaired renal function)
   -Altered mental status
   -Hypoxemia

   If standard therapy fails, consider HD in the following:
   Salicylate >90 mg/dL (or 80mg/dL with impaired renal function)
   -pH 7.20 or lower

INSTRUCTOR MATERIALS

Case #3: Oh Limey!

A 45-year-old female with bipolar disorder presents to the emergency department. She states that her mania has been getting worse and her psychiatrist adjusted her medications two weeks ago. She started developing nausea, vomiting, and diarrhea five days ago. Now, she is starting to feel worsening agitation, dizziness, and tremors.

1. **What medication was probably adjusted?**
   Lithium

2. **What is the normal serum concentration of this drug**
   0.8 - 1.2 mEq/L

3. **What symptoms can occur in toxicity?**[3]
   Cardiovascular: Wandering atrial pacemaker, sinus bradycardia, ST-segment elevation, unmasking Brugada syndrome, prolonged QT
   Neurologic: Lethargy, ataxia, confusion, agitation, tremors, fasciculations, myoclonic jerks, hyperreflexia, seizures
   GI: Nausea, vomiting, diarrhea, ileus

4. **Treatment?**
   Supportive
   Consider dialysis if:
   - Li^+ >4.0 mEq/L (with impaired kidney function)
   - Decreased level of consciousness, seizures, or dysrhythmias
   - Li^+>5.0mEq/L
   - Expected time to reduce Li^+<1.0mEq/L with optimal management is >36 hours

INSTRUCTOR MATERIALS

Case #4: Can't fight the seizure...but we can try

A 30-year-old male with epilepsy went on vacation and forgot to bring his medications. After returning home, he took all of his medications in order to "catch up." He is not feeling well. He can't remember the name of the anti-epileptic drug that he is taking. You mention valproic acid, phenytoin, and carbamazepine. He says, "It's definitely one of those!"

What symptoms would you expect for each and what are the indications for dialysis for each?[2,8,9]

Anti-epileptic drug	Symptoms in overdose	Treatment	Indications for dialysis
Phenytoin	Multidirectional nystagmus, Dizziness, Nausea, vomiting, Ataxia, Coma, Respiratory depression, Agitation, Irritability, Slurred speech, Hypotension, Cardiac arrest	Supportive Consider charcoal	-Reasonable in selected cases of severe phenytoin poisoning -Prolonged coma -Incapacitating ataxia -Do not perform based on the dose ingested -Do not perform solely based on serum concentrations
Carbamazepine	Movement disorders, Altered mental status, Seizures, Respiratory depression, Tachycardia, Hypotension, Anticholinergic effects, Myocardial depression, Conduction disturbances, QRS widening, Bundle branch blocks,	Hypertonic sodium bicarbonate (QRS widening) Multiple-dose activated charcoal Consider dialysis	-Intractable seizures -Life threatening dysrhythmias -Prolonged coma or respiratory depression requiring mechanical ventilation -Significant toxicity with rising concentrations

	Brugada type patterns, AV blocks (Atrioventricular blocks), PVCs (Premature ventricular contractions)		
Valproic Acid	Coma, sedation, lethargy, Ataxia, Respiratory depression, Cerebral edema, Shock, Hypernatremia, hypocalcemia, Thrombocytopenia, Impaired mitochondrial function (i.e., metabolic acidosis and hyperlactatemia), Hyperammonemia, Hepatotoxicity	Carnitine supplementation Consider activated charcoal Supportive Consider dialysis	-VPA level = 1300 mg/L -Shock -Cerebral edema Consider for: -VPA = 900- mg/L Respiratory depression requiring mechanical ventilation -Acute hyperammonemia -pH <7.10

Hemodialysis in the Poisoned Patient: Brief Wrap Up Key

1. Which of the following properties of a drug makes it more dialyzable?
    a. High tissue binding
    b. Large volume of distribution
    c. Small molecular weight
    d. Poor water solubility

    See RAT key, explanation to question 1

2. Which of the following drugs is a good candidate for hemodialysis in overdose?
    a. Digoxin
    b. Lidocaine
    c. Theophylline
    d. Warfarin

    See RAT key, explanation to question 3.

3. Which of the following does isopropanol ingestion cause?
    a. Elevated anion gap
    b. Elevated osmolal gap
    c. Both

    See RAT key, explanation to question 4.

4. Which of the following is a feared complication of ethylene glycol overdose?
    a. Blindness
    b. Tinnitus
    c. Hepatotoxicity
    d. Renal failure

    See GAE Case #1, explanation to G

5. What is the most appropriate antidote for early ethylene glycol or methanol ingestion?
    a. Fomepizole
    b. Hemodialysis
    c. L-carnitine
    d. N-acetylcysteine

See GAE Case #1, explanation to E&F

6. Which of the following is an indication for hemodialysis in salicylate poisoning?
   a. Hypoxemia
   b. Respiratory alkalosis
   c. Salicylate level > 40 mg/dL
   d. Tinnitus

See GAE Case #2, explanation to D

7. Which drug in overdose can cause hyperammonemia and cerebral edema?
   a. Carbamazepine
   b. Lithium
   c. Phenytoin
   d. Valproic Acid

See GAE Case #4, explanation