In The Name of God

The Role of the Nephrologist in Management of Poisoning and Intoxication

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Introduction

- In 2019, the American Association of Poison Control Centers recorded over 2.1 million cases of human exposure to poisons.

- Although emergency physicians, hospitalists, and toxicologists manage many of these poisonings, the nephrologist is often necessary to manage severe acid-base disorders, electrolyte abnormalities, or kidney dysfunction.

Case1
Salicylate

A 48-year-old man arrives by ambulance after a large dose of unknown medication. In the emergency department, he has altered mental status ;BP: 110/70; RR :30; HR: 130, Tem:39C.

He complains of hearing a loud "buzzing" sound. His blood chemistry : Na^+: 135 mEq/L; K^+: 3.1 mEq/L; Cl^-: 102 HC03:12 mEq/L; pH :7.40; and PCO_2: 18 mm Hg.

Question1

Which of the items, is most suggestive of salicylate intoxication rather than some other intoxication?

a. Altered mental status
b. Buzzing sound in his ears
c. Hypokalemia
d. Tachycardia
e. Tachypnea

Epidemiology

- Salicylate intoxication can be either **acute or chronic**.

- **Acute salicylate intoxication** occurs after ingestion of **≥100 to 150 mg/kg salicylate** or ingestion of small amounts of **methyl salicylate** (**as low as 5 mL of oil of wintergreen**).

- **Rarely, repeated topical use** of topical analgesic cream (up to **30% methyl salicylate**) may cause serious poisoning.

- **Acute** salicylate intoxication **most commonly** occurs in **adults** taking salicylates in a suicide attempt .

- **Chronic poisoning** is more common in **elderly** individuals or Preexisting kidney disease.

Clinical Features

- **Acute salicylate intoxication :**confusion, agitation, disorientation that can progress to coma, shortness of breath, and tinnitus.

- ✓ **Tachypnea, altered mental status, and hyperthermia indicate severe toxicity .**
- ✓ **Physical findings** :hyperventilation, evidence of volume depletion, noncardiogenic pulmonary edema, hematemesis, and petechiae result from platelet dysfunction.
- ✓ **Chest radiograph** can reveal **pulmonary opacities**.

- **Chronic salicylate poisoning :**Agitation, confusion, hallucinations, slurred speech, seizures, and coma.
- ✓ A delay in diagnosis and initiation of therapy may explain, in part, the higher morbidity reported for chronic intoxication than with acute intoxication.

Diagnosis

- **Prominent laboratory abnormalities :**acid-base disturbances.
  - ✓ ~20% : respiratory alkalosis alone.
  - ✓ 56% :combined respiratory alkalosis and **high anion gap** metabolic acidosis.

- **Less commonly**: a **normal anion gap metabolic acidosis** can develop due to :
  - ✓ excretion of sodium and potassium salts in the urine with subsequent retention of chloride.
  - ✓ false hyperchloremia due to **salicylate interference with the measurement of chloride**.

- **Hypokalemia:** increased losses of potassium in the urine due to: increased excretion of the organic acid anions, augmented aldosterone concentrations, and increased distal sodium delivery.

Measurement of salicylate concentration best confirms the diagnosis.

Review of Case1

- The best answer is **:b** the buzzing sound in his ears.

- The **other findings** are typical of salicylate poisoning but **overlap** with other conditions such as :

diabetic ketoacidosis, sepsis, methylxanthine poisoning, and alcoholic ketoacidosis.

Question2

Which of the following is true?

a. Hemodialysis is usually necessary only if the salicylate concentration is greater than 100 mg/dL.

b. Hemodialysis should commence as soon as possible.

c. Hemodialysis is only necessary if a trial of sodium bicarbonate fails to lower the salicylate concentration.

d. Hemodialysis is only necessary if the serum potassium concentration is high in a salicylate-poisoned patient.

Treatment

- **Aggressive volume resuscitation** with normal saline or lactated Ringer solution is important as fluid losses are common.

- **Oral activated charcoal** reduces further salicylate absorption when given within **1 to 2 hours of ingestion and may be useful beyond 2 hours** if persistently high salicylate concentrations suggest the possibility of a gastric bezoar of acetylsalicylic acid.

- **Alkalinizing the urine** (**target urine pH of 7.5 or greater**) with IV sodium bicarbonate. **Increasing urine pH by 1 unit** from 6.5 to 7.5 can **triple urinary salicylate clearance**. **Oral bicarbonate should be avoided because it might enhance gastrointestinal absorption.**

J Med Toxicol. 2015;11:140-152.

Treatment…

- **Potassium replacement :**(both IV and orally) should accompany sodiumbicarbonate administration.This prevents worsening hypokalemia and facilitates urinary alkalinization.

- **Hemodialysis:**

✓ fastest and most effective method of eliminating salicylate from the body.

✓ **Intermittent hemodialysis** is the preferred method, but hemoperfusion and CRRT are acceptable should intermittent hemodialysis not be available or if the patient is hemodynamically unstable.

Am J Emerg Med. 2017;35(6):899-903.

Indications for Hemodialysis in salicylate intoxication

- Concentration > 7.2 mmol/L (100 mg/dL)
- Concentration > 6.5 mmol/L (90 mg/dL) with AKI or CKD
- Concentration > 6.5 mmol/L (90 mg/dL) after IV fluids, sodium bicarbonate, and potassium
- Concentration > 5.8 mmol/L (80 mg/dL) after IV fluids, sodium bicarbonate, and potassium and with AKI or CKD
- Altered mental status
- Respiratory distress or new hypoxemia requiring supplemental oxygen
- pH ≤ 7.2

Review of Case1 (Question2)

The best answer to question 2 is :b

- hemodialysis should commence as soon as possible because delays in hemodialysis can result in a fatal outcome.

- Tachypnea, altered mental status, and hyperthermia indicate severe toxicity in this patient.

Case 2
Acetaminophen

A 29-year-old woman comes to the emergency department after texting a friend that she had ingested “handfuls” of acetaminophen .

She arrives approximately 6 hours after ingestion. Her blood chemistry values :

Na^+: 140 mEq/L; K^+: 3.5 mEq/L; Cl^- :100 mEq/ L; HCO3: 10 mEq/L; BUN: 25 mg/dL; Scr:1.5mg/dL; Ph:7.21; PCO_2: 26 mmHg. AST: 122 IU/L ALT : 115 IU/L

serum acetaminophen concentration is 980 mg/L.

Question3

Which one of the following regarding hemodialysis in acetaminophen overdose is true?

a) Acetaminophen has a high protein binding in the plasma and is not easily dialyzable.

b) Hemodialysis is only indicated if antidotal treatment with acetylcysteine fails to reduce the acetaminophen concentration.

c) Indications for hemodialysis include serum acetaminophen concentration > 900 mg/L or the presence of severe metabolic acidosis.

d) AST activity greater than 1,000 IU/L is an indication for hemodialysis.

Clinical Findings

- On the first day after an acetaminophen ingestion, the patient may have nausea and abdominal pain or may be asymptomatic.
- On day 2 Rising AST and ALT activities will become apparent, with peak values around day 3.
- INR may rise about 1 day after the rise in AST and ALT. Peak toxicity occurs around day 3 or 4.
- Severe cases may have hepatic encephalopathy and cerebral edema.
- AKI with ATN may appear.

Clin Toxicol (Phila.). 2020;58:1284-1296.

Clinical Findings…

Criteria for liver transplantation :

- blood pH < 7.30 at any time
- composite of Scr > 3.3 mg/dL
- PT>100 seconds
- severe (grade III or IV) hepatic encephalopathy.

- **Lactic acidosis and hypoglycemia are sensitive indicators of severe hepatotoxicity.**
- Blood lactate concentrations **above 3.0 mmol/L** on initial assessment or **above 2.5 mmol/L after fluid resuscitation** are highly sensitive for **acute liver failure**.

Diagnosis

Depends upon the serum acetaminophen concentration.

Treatment

- Supportive care and the administration of **NAC** If the acetaminophen concentration exceeds at **150mg/L at4 hours.**
- Severe cases with **profound metabolic acidosis and very high acetaminophen** concentrations (**exceeding 700 mg/L**) warrant **hemodialysis**.
- Intermittent hemodialysis is the preferred modality, but CRRT is acceptable if the patient is hemodynamically unstable or if hemodialysis is unavailable.
- **Fomepizole**, the ADH antagonist used in toxic alcohol poisoning, Case reports and case series suggest that fomepizole **may be useful** in patients with extremely **high acetaminophen concentrations >700 mg/L with metabolic acidosis.**

Ann Intensive Care. 2020;10(1):157.

Review of Case2

- **The best answer for question 3 is: c**, the indications for hemodialysis include serum acetaminophen concentration > 900 mg/L or the presence of severe metabolic acidosis.

Acetaminophen

- Concentration > 1,000 mg/L (6,620 μmol/L)
- Concentration > 700 mg/L (4,630 μmol/L) with altered mental status, metabolic acidosis, or elevated lactate

Case3
Metformin

A 63-year-old man comes to the emergency department reporting a headache. The patient has a history of type 2 diabetes mellitus for which he takes metformin and small doses of insulin.

He is awake and responsive. BP:110/70 mm Hg without orthostatic changes. Na^+: 138 mEq/L; K+: 3.0 mEq/L; HCO3: 8 mEq/L; Cl^-: 100 mEq/L; BUN: 25 mg/ dL; Scr: 2.5 mg/dL; pH, 7.15; and PCO_2, 24 mm Hg. His initial lactate concentration is 15 mmol/L.

Question 4

Which of the following statements is true?

a. This patient has diabetic ketoacidosis and requires insulin in addition to IV fluid resuscitation.
b. Lactic acidosis only occurs in patients with metformin overdose.
c. Lactic acidosis can develop in patients taking therapeutic doses of metformin.
d. Hemodialysis does not remove metformin.

Epidemiology

- Complications appearing in as many as 20% to 30% of patients are not life threatening and usually include nausea, vomiting, and decreased appetite.

- **Mortality** can be as high as **61%** in some cases.

Clinical Findings

- Gastrointestinal symptoms are common . Abdominal tenderness may mimic an acute abdomen.

- In severe cases, patients may have serious hemodynamic instability and depressed consciousness.

- **Laboratory findings include elevated lactate concentrations (>5 mmol/L) and acidemia.**

Treatment

- **Sodium bicarbonate** to treat the acidemia and supportive therapy to stabilize the blood pressure.
- **Early hemodialysis** is the most effective therapy to remove metformin and to correct the acidosis
- Intermittent hemodialysis is effective in hemodynamically stable patients with a drug clearance of 200 mL/min.
- CRRT is acceptable in hemodynamically challenged patients.
- Mortality **approaches 40%** with high blood concentrations (**above 50 mg/L**), but most clinical laboratories cannot measure metformin concentrations.

Indications for Hemodialysis

Metformin

- Lactate > 10 mmol/L
- pH < 7.2
- Shock
- Failure of standard supportive measures (IV fluids, sodium bicarbonate)
- Decreased level of consciousness

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Review of Case 3

- ✓ **The best answer to question 4 is: c** , lactic acidosis occurs most often among patients **taking therapeutic doses** of metformin.
- ✓ Lactic acidosis does not require acute overdose of metformin.
- ✓ Hemodialysis removes metformin and corrects acidosis.

Case4
Lithium

A 55-year-old woman arrives to the emergency department via the emergency medical service after neighbors found her with confusion. She had been well until she developed an acute diarrheal illness for the past 2 days.

Her basic metabolic panel reveals AKI with a Scr: of 2.4 mg/dL (compared with 1.2 mg/dL 1 month earlier). Her anion gap is 6 mmol/L (compared with 10 mmol/L 1 month earlier). Further history reveals that she takes lithium carbonate for bipolar disorder and that her psychiatrist increased her dose 1 month earlier.

Question 5

Which of the following statements are true?

a. Forced diuresis with normal saline and IV furosemide is the appropriate treatment.
b. Kayexalate is effective in removing lithium.
c. The indication for hemodialysis depends solely on the serum concentration of lithium.
d. Central nervous system dysfunction is an indication for hemodialysis regardless of the lithium concentration.

Lithium…

- Lithium (usually as lithium carbonate) has a very **narrow therapeutic range** (serum Li^+ usually between 0.6 and 1.3 mmol/L) and is sensitive to modest changes in kidney function.

- **Acute-on chronic lithium toxicity** most often results from AKI from other causes (such as dehydration from diarrhea) or from rapid escalation of the dose.

- Acute overdose can rapidly produce high lithium concentrations.

Treatment

- Indications for **hemodialysis** depend upon the **Li^+**, **kidney function, and neurological symptoms.**

- Recommended hemodialysis **when Li^+ > 4.0 mEq/L or** if the patient has a **decreased level of consciousness, seizures, or life-threatening dysrhythmias, regardless of the Li^+.**

- CRRT is an acceptable alternative if hemodialysis is unavailable or inadvisable.

Br J Clin Pharmacol. 2020

Review of Case4

Returning to case 4, d is the best answer.

Central nervous system dysfunction is an indication for hemodialysis regardless of Li^+.

Lithium

- Concentration > 5.0 mEq/L
- Concentration > 4.0 mEq/L with AKI or CKD
- Decreased level of consciousness, seizures, or lifethreatening dysrhythmias at any lithium concentration
- Estimated time to reach lithium concentration < 1 mEq/L exceeds 36 hours

Toxic Alcohols
Epidemiological Features

In the 2019 AAPCC report, **isopropanol was the most frequent** cause of toxic alcohol poisoning **followed by ethylene glycol and methanol**.

Toxic Alcohols…

- In adults, **methanol and ethylene glycol intoxication** may develop after ingestion of **adulterated liquids** with a toxic alcohol substituted for ethanol.

- Adults typically ingest **ethylene glycol** in a suicide attempt.

- **Isopropanol** intoxication is generally the consequence of ingesting rubbing alcohol, hand sanitizer, or various industrial products.

Or by inhalation or absorption through dermal or rectal routes.

- **Diethylene glycol** intoxication can occur sporadically after ingestion of **automotive brake fluids** or **industrial products**.

Toxic Alcohols…

- **Propylene glycol** intoxication may occur in the **hospital setting** with **high-dose** infusions of relaxants such as **lorazepam or diazepam**, both of which contain **40% propylene glycol.**

- **Propylene glycol** is also the principal ingredient of automotive antifreeze products marketed as being "**nontoxic" or "environmentally friendly**."

Table 1. Clinical and Laboratory Features of the Toxic Alcohols

Alcohol	MW (Da)	Change in Serum Osmolality	Common Sources	Common Clinical Features	Notable Laboratory Features	Half-life, h	
						−EtOH	+EtOH
Methanol	32.04	3.09 mOsm/L per 10 mg/dL of alcohol	Windshield washer fluid, carburetor cleaner, octane boosters, racing fuels, adulterated ethanol ("moonshine")	Abdominal pain; decreased vision, blindness; rarely, Parkinson-like features	Osmolal gap; HAGMA	14-30	43-96
Ethylene glycol	62.07	1.60 mOsm/L per 10 mg/dL of alcohol	Antifreeze, engine coolants, deicing fluids	Inebriation, AKI	Osmolal gap, HAGMA, calcium oxalate crystalluria, elevated lactate with point-of-care analyzer	2-6	17-18
Isopropyl alcohol	60.10	1.66 mOsm/L per 10 mg/dL of alcohol	Rubbing alcohol, hand sanitizers	Inebriation, depressed sensorium, abdominal pain	Osmolal gap, acetonemia, spurious increase in creatinine (Jaffe reaction)	NA	NA
Propylene glycol	76.09	1.31 mOsm/L per 10 mg/dL of alcohol	Diluent in parenteral medications, "nontoxic" automotive antifreeze	Liver or kidney disease may increase likelihood of more severe toxicity	Increased osmolal gap; lactic acidosis; rarely, AKI	1.4-3.3	17
Diethylene glycol	106.12	0.9 mOsm/L per 10 mg/dL of alcohol	Automotive brake fluids, hydraulic fluids, adulterated liquid medications	Abdominal pain, nausea/vomiting, acute pancreatitis, AKI	Osmolal gap, HAGMA, AKI	4-6	Unknown

Abbreviations: AKI, acute kidney injury; +EtOH, with coingested alcohol; −EtOH, without coingested alcohol; HAGMA, high anion gap metabolic acidosis; MW, molecular weight; NA, not applicable.

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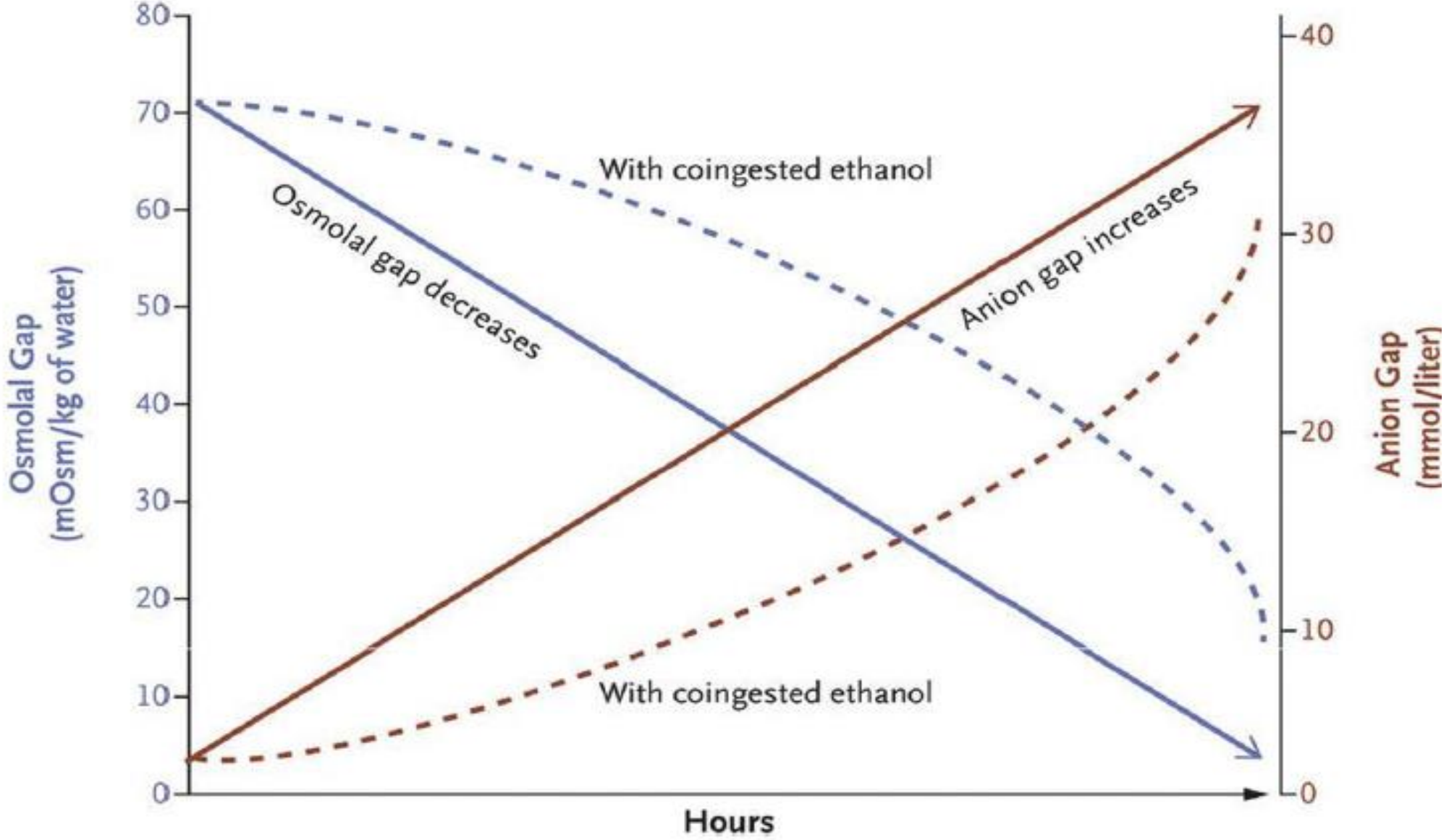
B Time Course of Changes in the Osmolal and Anion Gaps



N Engl J Med2018

Clinical Features

- To varying degrees, alcohols—particularly **ethylene glycol and isopropanol**—produce **some inebriation**.

- Accumulation of their toxic metabolites produces organ dysfunction.

Methanol intoxication

- Frequently impairs vision and can produce permanent blindness in some cases.
- Pulmonary dysfunction, abdominal pain, coma, and, rarely, Parkinson-like symptoms can occur.
- The **clinical abnormalities usually** evolve **over 6 to 24 hours**, but **coingested ethanol can delay the toxic effects.**
- Rarely, neurologic sequelae may occur days or weeks after exposure.

Ethylene glycol intoxication

- **Ethylene glycol** metabolism forms glycolic acid and then oxalate crystals.
- Glycolic acid is the principal cause of acidosis.
- Oxalate crystals produce AKI. **Cranial nerve damage**, sometimes delayed for days, can also occur.
- **Typically**, **neurologic dysfunction** develops within the **first 12 hours**, followed by **cardiac and pulmonary dysfunction in the next 12 hours**, and **AKI** at **48 to 72 hours after exposure.**
- Dysfunction of **all 4 organ systems can occur concomitantly**.
- Coingested ethanol delays the accumulation of toxic metabolites and the appearance of clinical abnormalities.

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Isopropanol intoxication

- **Depresses the sensorium** and can cause **respiratory dysfunction**, **cardiovascular collapse**, **acute pancreatitis**, and **hypotension-induced lactic acidosis.**

- Serum isopropanol concentrations **above 500 mg/dL** are clinically significant; those in **excess of 1,500 mg/dL** result in deep coma.

- The **major metabolite acetone** can produce a **spurious increase in serum creatinine concentration** due to its interference with laboratory measurements using the **Jaffe reaction**.

Diethylene glycol intoxication

- Abdominal pain, nausea, vomiting, diarrhea, acute pancreatitis, altered mental status, hepatic disease, central and peripheral neuropathy (occasionally causing quadriplegia), AKI, and death.

- The **AKI** often appears many hours after exposure (**8 to 24 hours**), may require hemodialysis, and is a major cause of death.

- **Coingestion of ethanol can delay toxicity by as much as 48 to 72 hours**.

- **Cranial nerve palsies and other neurologic complications can appear several days after exposure.**

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Propylene glycol intoxication

- Propylene glycol intoxication often leads only to an **increase in the osmolal gap, but it can cause lactic acidosis and AKI.**

- The predisposing factors are preexisting kidney disease, hepatic disease, or both.

- Patients receiving a **continuous infusion** for more than 48 hours of high-dose lorazepam (>10 mg/h), which contains 40% propylene glycol, are at **higher risk**.

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Diagnosis
osmolal gap…

- Each alcohol has a different metabolic rate **(**the half-life is as short as **8 hours for methanol and 3 hours for ethylene glycol).**

- If the baseline **osmolal gap** is low or even negative, the accumulation alcohol has a high molecular weight, or significant metabolism of the alcohol has occurred, the osmolal gap may be normal. **For these reasons, serum osmolal gap alone may not be a sensitive test for detecting exposure to toxic alcohol.**

- Despite these caveats, **serial changes in the osmolal gap** reflect changes in the **parent alcohol's concentration,** particularly during hemodialysis.

- **An osmolal gap $\leq$ 10 m Osm/kg H_2O may be one indicator to discontinue therapy.**

N Engl J Med. 2018;378(3):270-280.

Diagnosis…

Disorders other than toxic alcohols such as **lactic acidosis, diabetic ketoacidosis, alcoholic ketoacidosis, chronic kidney disease, and sickle cell syndrome may increase in the serum osmolal gap**, but it **rarely exceeds 20 m Osm/kg**.

N Engl J Med. 2018;378(3):270-280.

Diagnosis
Anion gap…

- An increase in the serum anion gap **can be absent** for several reasons.

- For patients with a baseline serum anion gap at the low end of range, the serum anion gap might remain in the normal range even in the presence of substantial accumulation of the organic acid anions.

- If blood is sampled early after the toxic alcohol exposure before extensive metabolism of the toxic alcohol, the serum anion gap might be normal.

N Engl J Med. 2018;378(3):270-280.

Treatment

- Some experts recommend early treatment when toxic alcohol poisoning is **strongly suspected** or there is **unexplained metabolic acidosis.**

- **Antidotal use** of fomepizole or ethanol to delay or prevent metabolism to their toxic metabolites, and **hemodialysis** to remove the **parent alcohol and its toxic byproducts**.

Treatment…

- **Gastric decontamination:** is usually **not helpful** because the **absorption of methanol and ethylene glycol in the gastrointestinal tract is so rapid.**

- **IV sodium bicarbonate :**corrects metabolic acidosis and increases methanol's ionization to formic acid. This promotes its urinary excretion and reduces its penetration into the optic nerve.

- **ADH inhibitor :**

✓ The serum methanol or ethylene glycol concentration exceeds **20 mg/Dl.**
✓ High suspicion of toxic alcohol ingestion with either an osmolal gap greater than 10 mOsm/kg H_2O
✓ Metabolic acidosis of unknown cause.
✓ **Not for Isopropanol**

Treatment…

- **Ethanol remains an alternative**, particularly when fomepizole is not available.
- **The target ethanol concentration is 100 mg/dL.**
- Ethanol is generally available and inexpensive but requires compounding by a pharmacist for **IV** use.
- The serum ethanol concentration requires **careful monitoring**, so patients usually require hospitalization in the ICU.
- It may be difficult to discern the degree of inebriation attributable to the toxic alcohol and to the ethanol used as an antidote.

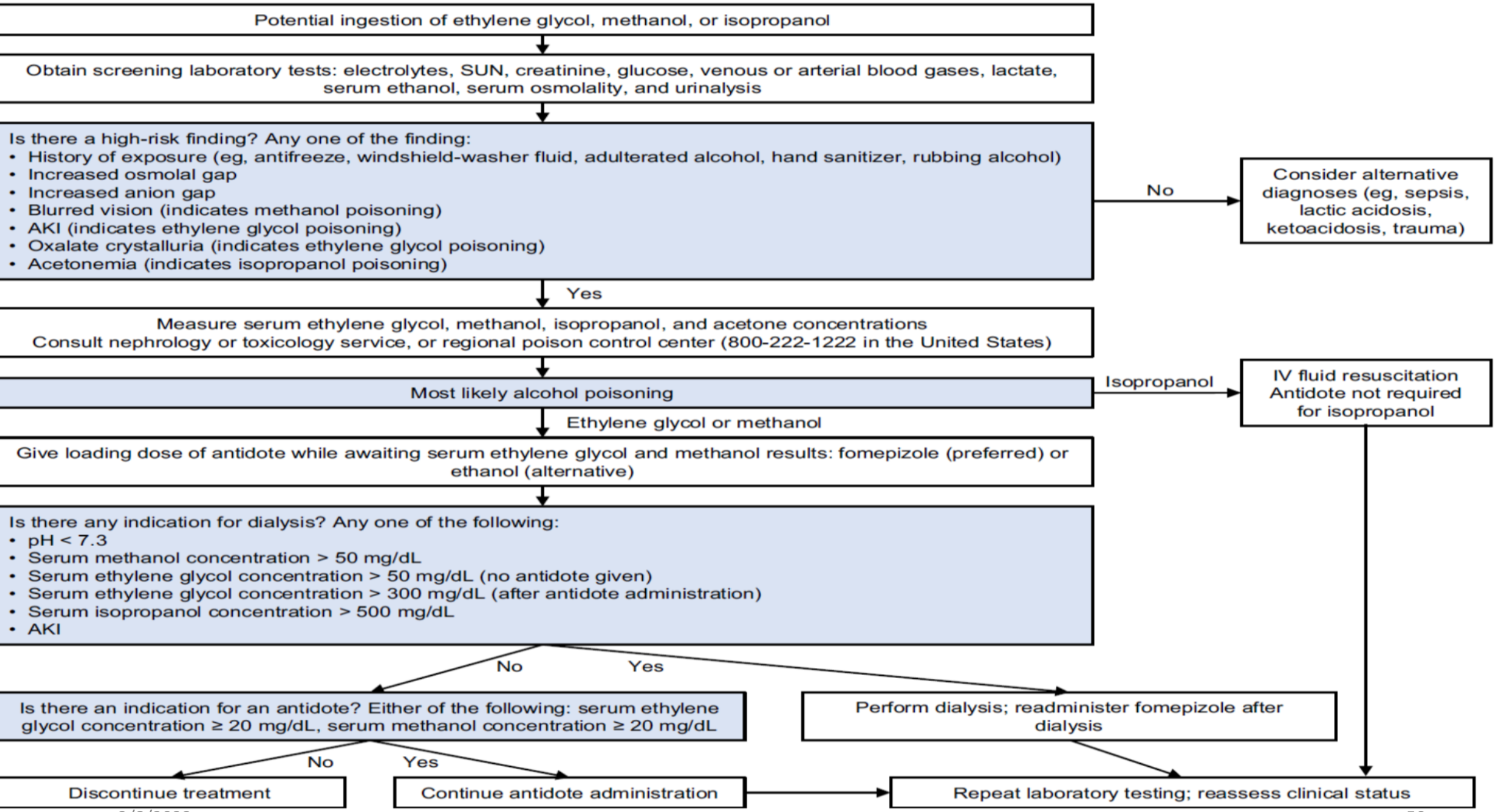

Figure 2. Algorithm for the diagnosis and treatment of methanol, ethylene glycol, and isopropanol intoxications. This algorithm pro-

Box 1. Indications for Hemodialysis

Toxic Alcohols

- Ethylene glycol or methanol concentration > 50 mg/dL without ADH inhibitor (fomepizole or ethanol)
- Ethylene glycol concentration > 200-300 mg/dL *with* ADH inhibitor *and* normal kidney function
- Methanol concentration > 70 mg/dL *with* ADH inhibitor *and* normal kidney function
- Isopropanol concentration > 400-500 mg/dL
- Any toxic alcohol: severe acidemia (pH < 7.2) *or* AKI

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Have a
good time!