The Role of the Nephrologist in Management of Poisoning and Intoxication

Presenter:

DR. Hamedanian

Introduction

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

- the nephrologist is often necessary to manage severe acid-base disorders, electrolyte abnormalities, or kidney dysfunction.

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Toxic Alcohols

Case 1:

- Family members discover a 35-year-old man in his garage confused and poorly responsive. Paramedics find a suicide note and an open jug nearby.
- In the emergency department, he appears inebriated, with tachypnea, tachycardia, and blood pressure of 120/60 mm Hg. His blood chemistry values reveal the following concentrations: serum sodium ([Na+]), 136 mEq/L; potassium ([K+]), 3.2 mEq/L; [total CO2], 10 mEq/L; and chloride ([Cl-]), 100 mEq/ L.
- The calculated serum osmolarity is 290 mOsm/L, and the measured serum osmolality by freezing point depression is 350 mOsm/kg H2O.

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Question 1:

What would be your next step(s) in managing this patient?

a) Normal saline infusion at 150 mL/h.

b) Infusion of sodium bicarbonate 150 mEq added to 1 L of 5% dextrose in water at 150 mL/h.

c) Fomepizole at 15 mg/kg intravenously.

d) Obtain ethylene glycol and methanol results before selecting treatment.

e) Both (b) and (c).

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Epidemiological Features

Alcohol	Common Sources
Methanol	Windshield washer fluid, carburetor cleaner, octane boosters, racing fuels, adulterated ethanol ("moonshine")
Ethylene glycol	Antifreeze, engine coolants, deicing fluids
Isopropyl alcohol	Rubbing alcohol, hand sanitizers
Propylene glycol	Diluent in parenteral medications, "nontoxic" automotive antifreeze
Diethylene glycol	Automotive brake fluids, hydraulic fluids, adulterated liquid medications

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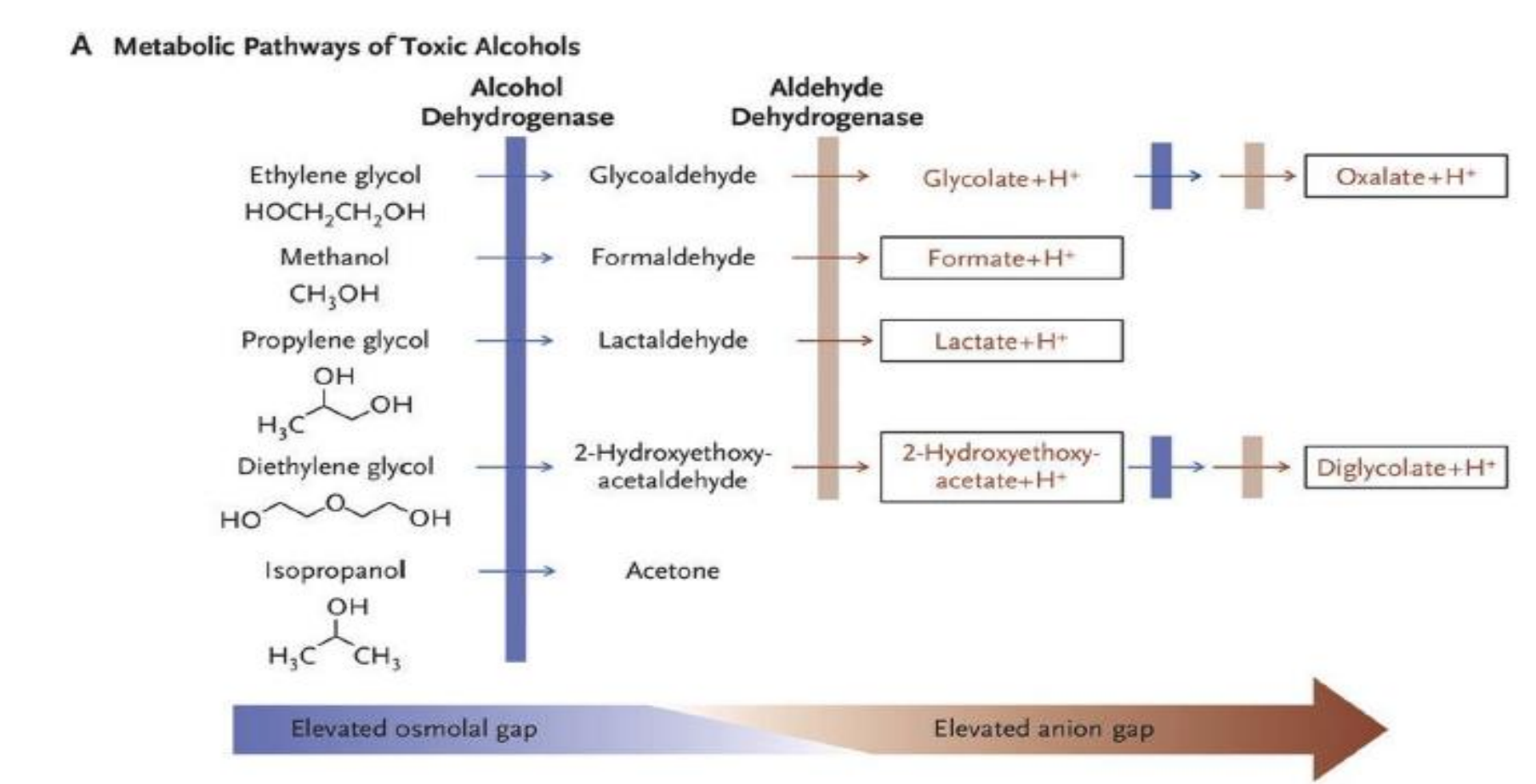
Pathogenesis



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Clinical Features

Alcohol	Common Clinical Features
Methanol	Abdominal pain; decreased vision, blindness; rarely, Parkinson-like features
Ethylene glycol	Inebriation, AKI
Isopropyl alcohol	Inebriation, depressed sensorium, abdominal pain
Propylene glycol	Liver or kidney disease may increase likelihood of more severe toxicity
Diethylene glycol	Abdominal pain, nausea/ vomiting, acute pancreatitis, AKI

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Diagnosis

- ✓ Because a history of the alcohol ingestion is often lacking, the presumptive diagnosis of toxic alcohol poisoning usually rests on a report of possible exposure in association with the symptoms and physical findings and characteristic blood chemistry abnormalities.
- ✓ Chief among them are high serum osmolality and high anion gap metabolic acidosis.

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- ✓ The 2 methods of measuring serum osmolality are freezing point depression and vapor pressure osmometry. Freezing point depression is more reliable.

- ✓ An osmolal gap of greater than 10-15 mOsm/kg H2O suggests foreign osmotically active substances in the blood.

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- ✓ The normal osmolal gap reported by various clinical laboratories can vary substantially from 2 to 11 mOsm/kg H2O.

- ✓ These differences have important clinical implications because the baseline osmolal gap is an important influence on the actual osmolal gap found when alcohols accumulate in blood.

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Alcohol	MW (Da)	Change in Serum Osmolality
Methanol	32.04	3.09 mOsm/L per 10 mg/dL of alcohol
Ethylene glycol	62.07	1.60 mOsm/L per 10 mg/dL of alcohol
Isopropyl alcohol	60.10	1.66 mOsm/L per 10 mg/dL of alcohol
Propylene glycol	76.09	1.31 mOsm/L per 10 mg/dL of alcohol
Diethylene glycol	106.12	0.9 mOsm/L per 10 mg/dL of alcohol

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- ✓ 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.

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- ✓ Although an elevated serum anion gap is frequently important in indicating that there has been a toxic alcohol exposure, 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

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- ✓ Many hospital laboratories can perform a “volatile screen” using gas chromatography to detect methanol, ethanol, isopropanol, and acetone but not ethylene glycol.

- ✓ point-of-care lactate measurement and a lactate measurement by LDH strongly suggests ethylene glycol poisoning.

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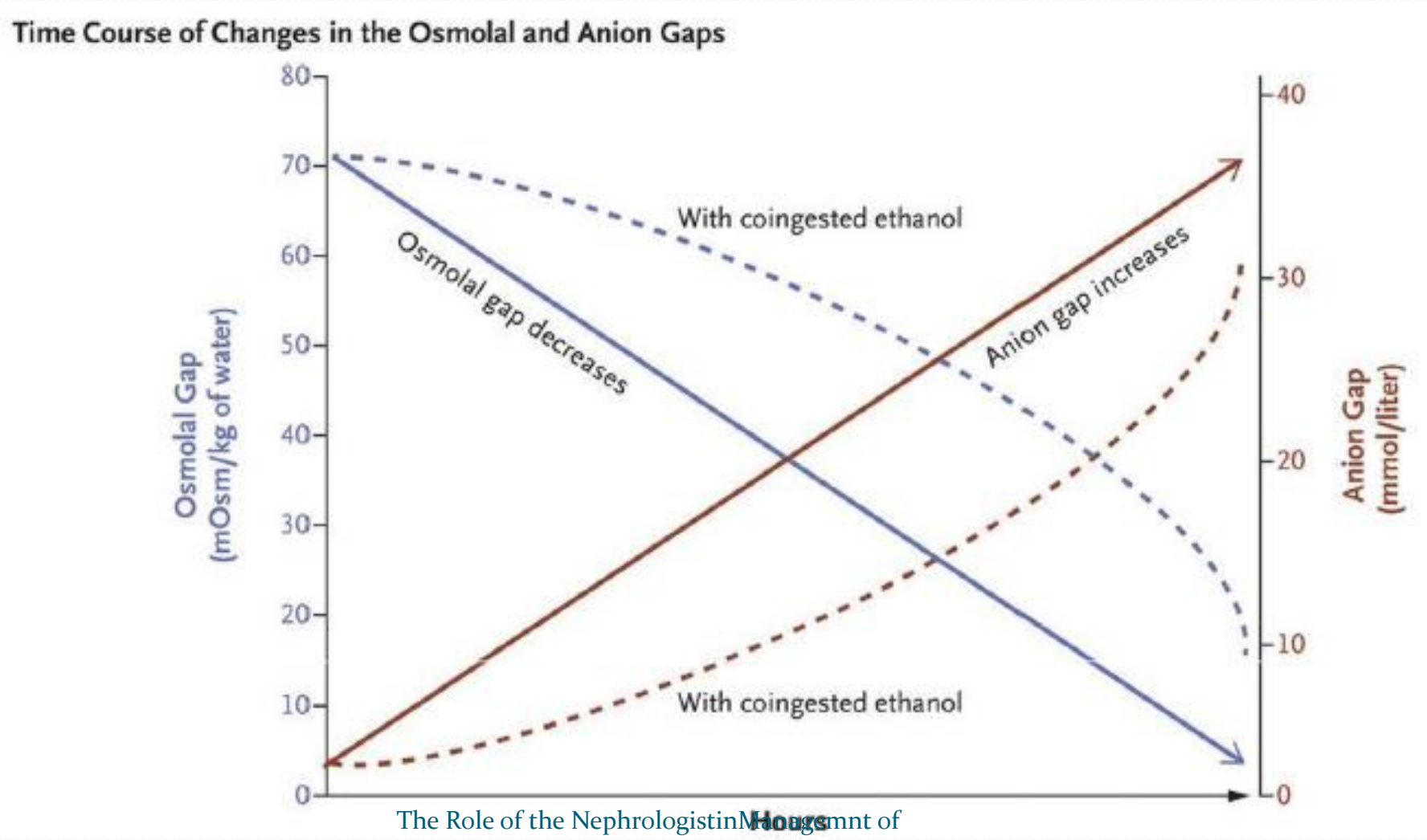
- ✓ Oxalate crystals in the urine also suggest ethylene glycol Poisoning.

- ✓ Definitive diagnosis of methanol and ethylene glycol uses high performance gas or liquid chromatography.



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Treatment

- ✓ Treatment of toxic alcohol poisonings primarily includes antidotal use of fomepizole or ethanol (inhibitors of ADH) to delay or prevent metabolism to their toxic metabolites

- ✓ hemodialysis to remove the parent alcohol and its toxic byproducts.

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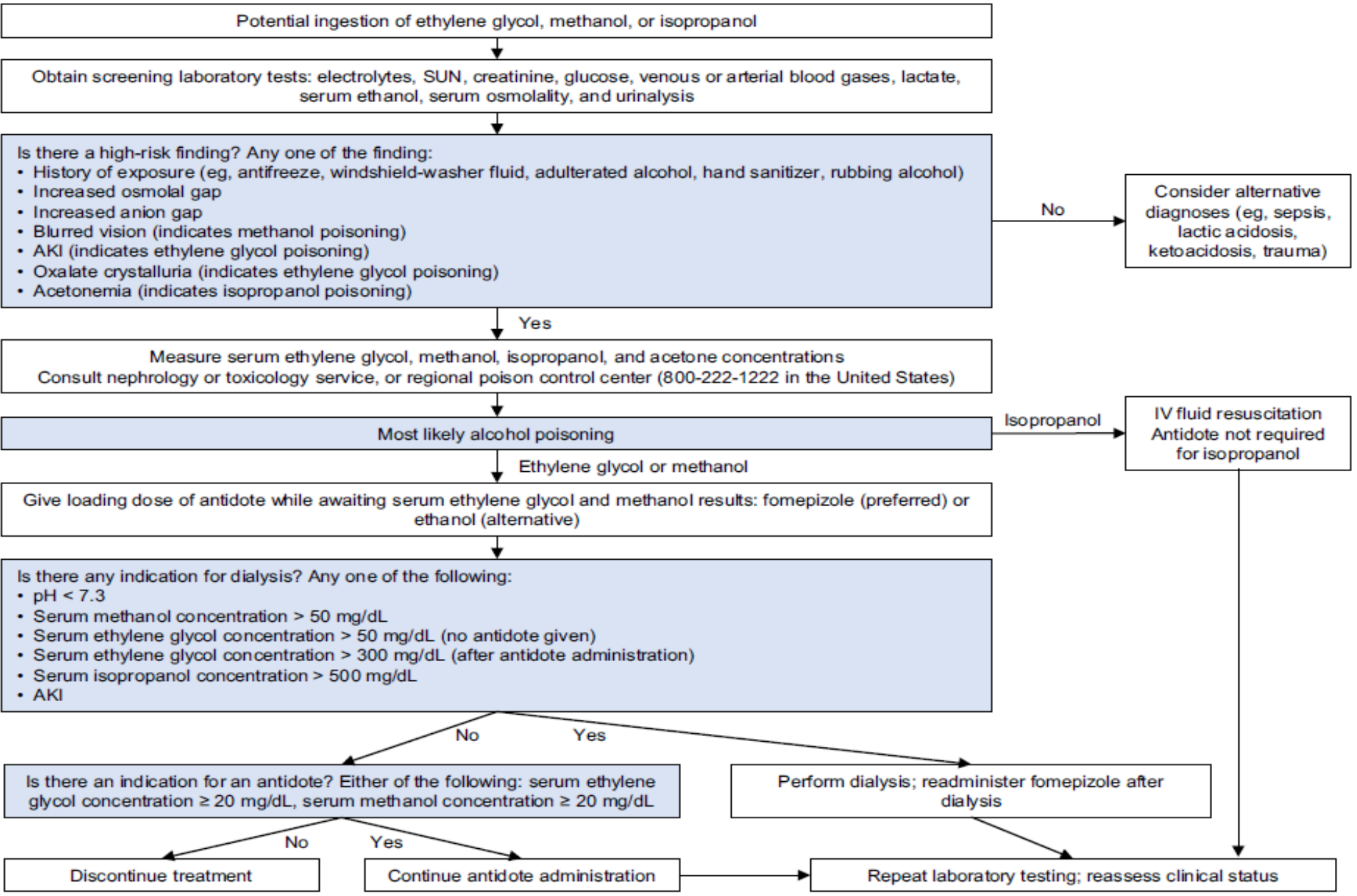

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Methanol and Ethylene Glycol

- ✓ Gastric decontamination is usually not helpful.
- ✓ sodium bicarbonate corrects metabolic acidosis and increases methanol's ionization to formic acid.

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Treatment guidelines recommend an ADH inhibitor

When:

1. the serum methanol or ethylene glycol concentration exceeds 20 mg/dL
2. osmolal gap greater than 10 mOsm/kg H_2O
3. metabolic acidosis

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TABLE 20.4 Indications for Treatment of Ethylene Glycol or Methanol Poisoning with Ethanol or Fomepizole

1. Documented plasma ethylene glycol or methanol concentrations >20 mg/dL
   or
2. Documented recent (hours) history of ingestion of toxic amounts of ethylene glycol or methanol and osmolal gap >10 mmol/kg
   or
3. History or strong clinical suspicion of ethylene glycol or methanol poisoning and at least two of the following criteria:
   - Arterial pH <7.3
   - Serum bicarbonate <20 mmol/L
   - Osmolal gap >10 mmol/kg[a]
   - Urinary oxalate crystals (in the case of ethylene glycol) or visual signs or symptoms (in the case of methanol) present

Daugirdas JT, Blake PG, IngTS.Handbook of dialysis. FIFTH EDATION

- ✓ Intravenous ethanol was the major therapy before FDA approval of fomepizole.
- ✓ Fomepizole is a strong inhibitor of ADH with very high enzyme affinity.
- ✓ The loading dose is 15 mg per kilogram of body weight and the subsequent maintenance dose is 10 mg/kg every 12 hours.
- ✓ hemodialysis removes fomepizole,

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Table 67.6 Antidote Dosage During Toxic Alcohol Poisoning

Dose	Absolute Ethanol	10% IV Ethanol[b]	Fomepizole
Loading dose[a]	600 mg/kg	7.6 mL/kg	15 mg/kg IV
Maintenance dose	66 mg/kg per hour (nondrinker) 154 mg/kg per hour (chronic drinker)	0.8 mL/kg per hour (nondrinker) 2.0 mL/kg per hour (chronic drinker)	10 mg/kg q12h × 4 doses, then 15 mg/kg q12h
Maintenance dose during IHD	169 mg/kg per hour (nondrinker) 257 mg/kg per hour (chronic drinker)	2.1 mL/kg per hour (nondrinker) 3.3 mL/kg per hour (chronic drinker)	Same dose but q4h or a constant infusion of 1.0–1.5 mg/kg per hour

[a]Assumes initial ethanol concentration is zero; dose is independent of chronic drinking status.
[b]Equivalent to 7.9 g ethanol/dL.
IHD, Intermittent hemodialysis.

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TABLE 20.7 Guidelines for Use of Fomepizole in the Treatment of Ethylene Glycol and Methanol Poisoning

1. Loading dose: 15 mg/kg IV in 100 mL 0.9% saline over 30 minutes to 1 hour
2. Maintenance dose: 10 mg/kg every 12 hours for four doses, then 15 mg/kg every 12 hours
3. Dose adjustments during hemodialysis: 15 mg/kg every 4 hours or 1–1.5 mg/kg per hour infusion during dialysis
4. Continue until methanol or ethylene glycol concentrations are <20 mg/dL and patient is asymptomatic with normal arterial pH

Daugridas JT, Blake PG,IngTS. Handbook of dialysis. FIFTH EDATION

The Extracorporeal Treatments in Poisoning Workgroup has guidelines for the use of hemodialysis in the treatment of methanol Poisoning :

1) severe metabolic acidosis
2) serum methanol concentrations higher than 50 mg/dL (16 mmol/L)
3) deteriorating vital signs despite supportive care
4) AKI
5) problems with vision.

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TABLE 20.5 Indications for Hemodialysis in Patients with Severe Ethylene Glycol or Methanol Poisoning

1. Severe metabolic acidosis (pH <7.25–7.30)
2. Renal failure
3. Visual symptoms/signs
4. Deteriorating vital signs despite intensive supportive care
5. Ethylene glycol or methanol levels >50 mg/dL unless fomepizole is being administered and patient is asymptomatic with a normal pH[a]

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- ✓ Experts suggest that fomepizole allows a hemodialysis threshold as high as 300 mg/dL for ethylene glycol when acidosis is mild or not present.

- ✓ EXTRIP guidelines indicate a hemodialysis threshold of 70 mg/dL for methanol poisoning treated with fomepizole.

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- ✓ Adjunctive treatments may promote conversion of toxic metabolites to less toxic metabolites.

For ethylene glycol Poisoning:

1) thiamine
2) magnesium
3) Pyridoxine (vitamin B6)

- ✓ For methanol poisoning, high-dose folic acid or folinic acid (1mg/kg of either).

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Propylene Glycol

discontinuation of the medication containing propylene glycol and administration of IV fluids are generally sufficient treatment

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Diethylene Glycol

intermittent hemodialysis along with administration of fomepizole is often necessary.

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Isopropanol

- ✓ Generally, supportive measures are sufficient.

- ✓ Intermittent hemodialysis has been recommended:
  1) the serum isopropanol concentration is .500 mg/dL
  2) hypotension
  3) severe lactic acidosis develops.

- ✓ In contrast to the other toxic alcohols, alcohol dehydrogenase inhibitors are unnecessary.

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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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Salicylate Intoxication

Case 2: A 48-year-old man arrives by ambulance after a large dose of unknown medication. In the emergency department, he has altered mental status; blood pressure, 110/70 mm Hg; respiratory rate of 30; heart rate of 130, and temperature of 39C.

He complains of hearing a loud “buzzing” sound.

His blood chemistry values reveal the following: [Na+], 135 mEq/L; [K+], 3.1 mEq/L; [total CO2], 12 mEq/L; [Cl-], 102 mEq/L; pH 7.40; and PCO2, 18 mm Hg.

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Question 2: Which of the items presented above 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

- ✓ Acute salicylate intoxication occurs after ingestion of >100 to 150 mg/kg salicylate or ingestion of small amounts of methyl salicylate .

- ✓ The most common source of salicylate poisoning is acetylsalicylic acid or aspirin.

- ✓ Chronic poisoning is more common in elderly individuals.

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Clinical Features

- ✓ Patients with acute salicylate intoxication can present with confusion, agitation, disorientation,coma.

- ✓ Physical findings can include hyperventilation, noncardiogenic pulmonary edema, hematemesis, and petechiae.

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Diagnosis

- ✓ Prominent laboratory abnormalities include acid-base disturbances.
- ✓ In adults, approximately 20% will have respiratory alkalosis alone, and 56% will have combined respiratory alkalosis and high anion gap metabolic acidosis.

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- ✓ Hypokalemia results from increased losses of potassium in the urine due to:
  - increased excretion of the organic acidm anions
  - augmented aldosterone concentrations
  - increased distal sodium delivery.

- ✓ Measurement of salicylate concentration best confirms the diagnosis.

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Treatment

Question 3: Which of the following is true?

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

b) Tachypnea is a sign of respiratory distress, and the patient requires intubation before considering hemodialysis.

c) Hemodialysis should commence as quickly as possible.

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

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

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- ✓ Aggressive volume resuscitation with normal saline or lactated Ringer solution is important .

- ✓ Oral activated charcoal reduces further salicylate absorption when given within 1 to 2 hours of ingestion .

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- ✓ alkalinization of the blood and urine with IV sodium bicarbonate is important.
- ✓ Oral bicarbonate should be avoided because it might enhance gastrointestinal absorption.
- ✓ blood gases should be monitored carefully during Therapy.

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- ✓ alkalemia can worsen any hypocalcemia, making monitoring of ionized calcium important.
- ✓ Potassium replacement (both IV and orally) should accompany sodium bicarbonate administration.

Salicylate

- 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

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Indications for ECTR include any of the following attributable to salicylate poisoning[16]:

- Neurologic symptoms (e.g., confusion, seizures, coma)
- Pulmonary edema
- pH < 7.25
- Serum salicylate concentration > 90 mg/dL (6.5 mmol/L)
- Acute kidney injury

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Acetaminophen (Paracetamol)

Case 3: A 29-year-old woman comes to the emergency department after texting a friend that she had ingested "handfuls" of acetaminophen from a container bought earlier in the day at a "big box" retailer. She arrives approximately 6 hours after ingestion. Her blood chemistry values reveal the following: [Na+], 140 mEq/L; [K+] 3.5 mEq/L; [Cl.], 100 mEq/L; [total CO2], 10 mEq/L; [SUN], 25 mg/dL; serum creatinine concentration ([Scr]), 1.5 mg/dL (134 ìmol/L); pH 7.21; and PCO2, 26 mm Hg. Her serum acetaminophen concentration is 980 mg/L (6,500 ìmol/L). Her serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are 122 and 115 IU/L, respectively.

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Question 4: 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 (6,000 ìmol/L) or the presence of severe metabolic acidosis.

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

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Epidemiology

- ✓ Acetaminophen (paracetamol) is the most frequent pharmaceutical agent involved in human poisonings.

- ✓ It accounts for approximately 5% of the over 100,000 cases reported annually to US poison centers and remains a leading cause of poisoning death

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Pathogenesis

- ✓ The principal toxic effects occur in the liver.

- ✓ Three aspects of acetaminophen poisoning may come to the attention of a nephrologist:
  - The first is severe metabolicacidosis.
  - The second is AKI after acute acetaminophen overdose.
  - The third and rarest is high anion gap metabolic acidosis

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Clinical Findings

- ✓ On the first day after an acetaminophen ingestion, the patient may have nausea and abdominal pain or may be asymptomatic.

- ✓ Rising AST and ALT activities will become apparent on day 2, with peak values around day 3.

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- ✓ The international normalized ratio (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 encephalopathym and cerebral edema.
- ✓ AKI with acute tubular necrosis may appear.

- Kings College Criteria for liver transplantation include:
  - a blood pH < 7.30 at any time or a composite of Scr > 3.3 mg/dL,
  - prothrombin time >100 seconds
  - severe hepatic encephalopathy

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- ✓ 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.

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Diagnosis

- ✓ the diagnosis depends upon the serum acetaminophen concentration.

- ✓ If the acetaminophen concentration exceeds the treatment line starting at 150mg/L (993 ìmol/L) at 4 hours, the patient should receive antidotal NAC either IV

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Treatment

- ✓ The main therapeutic measures are supportive care and the administration of NAC.
- ✓ Severe cases with profound metabolic acidosis and very high acetaminophen concentrations (exceeding 700 mg/L or 4,630 ìmol/L) warrant hemodialysis.
- ✓ Hemodialysis removes acetaminophen and corrects acidosis

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- ✓ Case reports and case series suggest that fomepizole may be useful in patients with extremely high acetaminophen concentrations

(>700 mg/L or >4,630 ìmol/L) with metabolic acidosis.

Indications for Hemodialysis

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

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Metformin

Case 4: A 63-year-old man comes to the emergency department reporting a headache. The patient has a history of type 2 diabetesmellitus for which he takesmetformin and small doses of insulin.

He is awake and responsive.

His blood pressure is 110/70 mm Hg without orthostatic changes. His blood chemistry values reveal the following: [Na+], 138 mEq/L; [K+], 3.0 mEq/L; [totalCO2], 8 mEq/L; [Cl.], 100mEq/L; [SUN], 25mg/ dL; [Scr], 2.5 mg/dL; pH, 7.15; and PCO2, 24 mm Hg.

His initial lactate concentration is 15 mmol/L. A point-of-care ketone measurement (â -hydroxybutyrate) is 0.5 mmol/L.

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Question 5: 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.

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Epidemiology

- ✓ Metformin-associated lactic acidosis (MALA) occurs in 3 to 10 cases per 100,000 patient-years. Mortality can be as high as 61% in some cases.

- ✓ metformin is contraindicated in patients with an eGFR of <.30 mL/ min/1.73 m2 (CKD 4 or 5).

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Pathogenesis

- ✓ Metformin inhibits glycerol-3-phosphate dehydrogenase and the glycerophosphate shuttle.

- ✓ inhibition of the mitochondrial respiratory chain complex in peripheral tissues augments lactic acid production.

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Clinical Findings

- ✓ Gastrointestinal symptoms are common in patients with metformin-related lactic acidosis.
- ✓ patients may have serious hemodynamic instability and depressed consciousness.
- ✓ Laboratory findings include elevated lactate concentrations (>5 mmol/L) and acidemia.

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Treatment

- ✓ Treatment includes sodium bicarbonate to treat the acidemia and supportive therapy to stabilize the blood pressure.
- ✓ Mortality approaches 40% with high blood concentrations (above 50 mg/L or 388 ìmol/L)
- ✓ Early hemodialysis is the most effective therapy to remove metformin and to correct the acidosis.

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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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Lithium

Case 5: 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.

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Question 6: Which of the following statements are true?

a) Forced diuresis with normal saline and IV furosemide is the appropriate treatment.

b) Sodium polystyrene resin (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.

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

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

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Indications for Hemodialysis

Lithium

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

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با سپاس فراوان از توجه شما

اساتید محترم