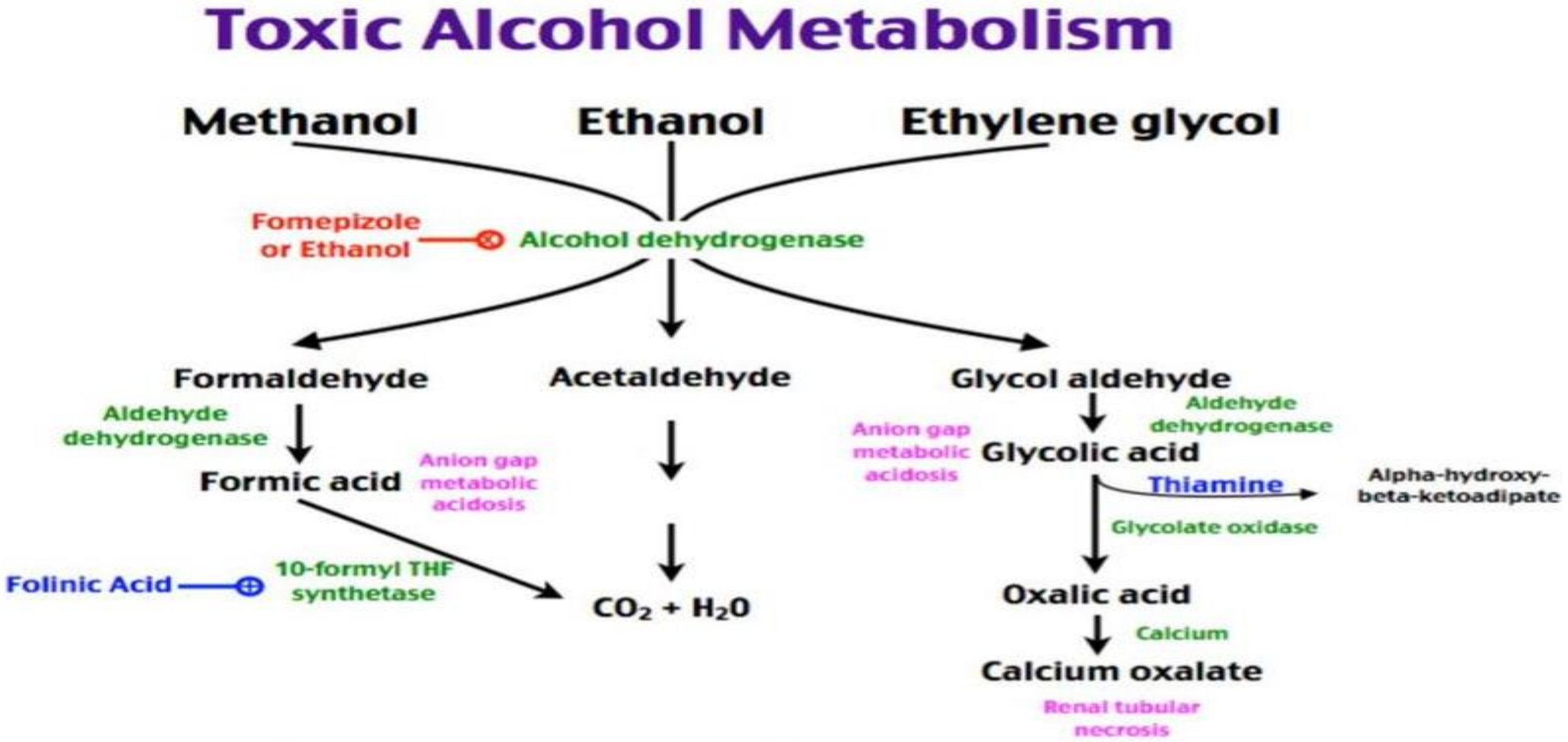
Alcohols and kidney

Hamid Tayyebi Khosroshahi, MD

Professor of Nephrology, Tabriz University of Medical Sciences

File:Toxic alcohol ingestion.JPG

File | File history | File usage | Metadata



Size of this preview: 800 × 561 pixels. Other resolution: 1,003 × 703 pixels

Methanol toxicity

background

- Methanol are frequently found in high concentration in automotive coolant/antifreeze and de-icing solutions, windshield wiper fluid, solvents, cleaners, fuels, and other industrial products.
- **Most serious poisonings occur following ingestion**; inhalation and dermal exposures rarely cause toxicity

Methanol toxicity

- **Colorless, volatile liquid with distinctive “alcohol ”odor**
- Methanol slowly metabolized to formaldehyde by alcohol dehydrogenase
- Formaldehyde then quickly metabolized to formic acid by aldehyde dehydrogenase
- Very toxic formic acid slowly metabolized, which translates to two clinical features:[1]
  - **Latency and delay in onset of symptoms**
  - **Prolonged symptoms due to accumulation of formic acid**

Methanol toxicity

- **Parent compound causes only mild inebriation**
- **Metabolite (formic acid) causes toxicity both directly and indirectly**
  - Binds to cytochrome oxidase > blockade of oxidative phosphorylation > lactic acidosis
  - In itself causes anion gap metabolic acidosis

Pharmacology

- Peak serum concentration 30- 60 minutes, elimination half-life 12-20 hours
- Permanent blindness reported at as little as 0.1 mL/kg (6-10 mL in adults)
- Lethal dose = 1-2 mL/kg
- Metabolite (eg. formic acid) causes toxicity, but does NOT cause osmolal gap

Clinical Features

Symptoms begin 12-24hr after ingestion (may occur even **later if ETOH is co-ingested** as EtOH competes with alcohol dehydrogenase and has greater affinity for the enzyme than methanol)

Formate causes retinal injury with optic disc hyperemia, edema, and eventually permanent blindness, as well as ischemic or hemorrhagic injury to the basal ganglia [11].

These changes are postulated to result from disruption of mitochondrial function.

Methanol toxicity

CNS depression

- Confusion, ataxia, depressed mental status, seizure
  - Less inebriating than ethanol or ethylene glycol
- Visual disturbances (50% of patients)
  - Development may precede or parallel that of other clinical symptoms
  - Cloudy or blurry vision ("stepping out into a snowstorm")

Anion-gap acidosis

- May be severe (bicarb < 5, pH < 7)
- Compensatory tachypnea

Cardiovascular

- Tachycardia
- Hypotension → can progress to shock

Respiratory

- Tachypnea
- shortness of breath (compensating for metabolic acidosis) → may progress to respiratory depression and/or failure

GI

- Abdominal pain
- nausea and vomiting
- Anorexia
- Pancreatitis and gastritis
- Transaminitis (mild and transient)

Methanol toxicity

- **Coma, seizures, hyperpnea (Kussmaul-Kien respirations), and hypotension all suggest a substantial portion of the parent alcohol has been metabolized to its toxic byproducts.**

Differential Diagnosis

Sedative/hypnotic toxicity

- Barbiturates
- Benzodiazepines
  - Flunitrazepam (Rohypnol)
- Chloral hydrate
- Gamma hydroxybutyrate (GHB)
- Baclofen toxicity
- Opioids
  - Lomotil toxicity
  - Loperamide toxicity
- Toxic alcohols
  - Ethanol
  - Isopropyl alcohol
  - Methanol

Methanol toxicity

Few conditions other than methanol and ethylene glycol intoxication cause a profound high anion gap metabolic acidosis (serum bicarbonate less than 8 meq/L (or 8 mmol/L)), and most of these conditions present in a characteristic fashion with a high serum lactate (eg, status epilepticus, profound shock, ischemic bowel) or diabetic ketoacidosis (table 2).

A lesser degree of metabolic acidosis in an alcoholic patient may also be caused by alcoholic ketoacidosis, sepsis, alcohol withdrawal seizures, diabetic ketoacidosis, or salicylate intoxication

Methanol toxicity

An elevated plasma osmolal gap can be seen in patients with methanol or ethylene glycol intoxication, but also in alcoholic or diabetic ketoacidosis, isopropyl alcohol ingestion, large ethanol ingestions, and other serious illnesses (eg, sepsis, ischemic bowel, shock)

Differential diagnosis of an elevated plasma/serum osmolal gap

With anion gap metabolic acidosis

Major causes of a large osmolal gap

- Ethylene glycol ingestion
- Methanol ingestion
- Propylene glycol infusion

Causes of a smaller osmolal gap

- Severe chronic kidney disease without regular dialysis
- Ketoacidosis (diabetic or alcoholic)
- Lactic acidosis
- Paraldehyde ingestion or injection

Without anion gap metabolic acidosis

- Ethanol
- Isopropanol
- Diethyl ether
- Infusion of mannitol, sorbitol, or glycine
- Pseudohyponatremia (severe hyperlipidemia or hyperproteinemia)

Evaluation, Chemistry

- **Anion gap acidosis**

Serum Osm

- Osm gap (measured - calculated)
  - Calculated serum osm = 2Na + BUN/2.8 + glucose/18 + ethanol/4.6
  - Normal is < 10
  - Note: Cannot rule out toxic ingestion with a "normal" osmol gap
  - **Only parent alcohol is osmotically active**
  - Delayed presentation may mean that much of it is already metabolized

Toxic alcohol levels

Methanol

- **<20mg/dL - asymptomatic**
- **>20mg/dL - CNS symptoms may appear**
- **>50mg/dL - ocular problems**
- **>150-200mg/dL - risk of fatality**

Other labs

- Ethanol level
- VBG

Toxic Alcohols Anion/Osmolar Gaps

	Osmolar gap	Anion gap	Management
Ethanol	+	+ if ketoacidosis	Mainly supportive
Ethylene glycol	+	+	Fomepizole, Thiamine, Pyridoxine, +/- Dialysis
Methanol	+	+	Fomepizole, Folinic acid, +/- Dialysis
Isopropyl alcohol	+	-	Mainly supportive

Laboratory evaluation

Basic testing — Routine laboratory evaluation of any poisoned patient should include the following:

- **Fingerstick glucose**, to rule out hypoglycemia as the cause of any alteration in mental status
- **Electrocardiogram (ECG)**, to rule out conduction system poisoning by drugs that effect the QRS or QTc intervals; it is important to note that ethylene glycol can prolong the QTc interval via its effects on serum calcium
- **Pregnancy test** in women of childbearing age

Additional tests with toxic alcohol exposure —

- Basic electrolytes with anion gap determination
- Serum calcium
- BUN and creatinine
- Arterial or venous blood gas analysis
- Serum ethanol concentration
- Serum osmolality
- Serum methanol, ethylene glycol, and isopropyl alcohol concentrations
- **Acetaminophen and salicylate levels**, to rule out these common coingestions

Methanol toxicity

Automotive coolant/antifreeze may also contain anticorrosive agents (e.g. sodium nitrite or nitrate) which are not listed on the product label or safety data sheet. Methemoglobinemia has been reported following large intentional ingestions of such products. Thus, patients with cyanosis and findings related to tissue hypoxia (eg, tachycardia, headache, lethargy) also warrant evaluation for methemoglobinemia

Management

ABC

ADH enzyme blockade

Both fomepizole and ethanol have greater affinity for ADH than methanol.

Fomepizole

- Dosing: 15mg/kg IV over 30min; follow by 10mg/kg q12hr until level <20 or acidosis resolves
- Indications:
  - Methanol level >20mg/dL (=6.24 mmmol/L)
  - Suspected significant methanol ingestion with ETOH level <100mg/dL
  - Coma or altered mental status in patient with unclear history and osm gap >10, unexplained met acidosis and ETOH level <100 mg/dl

Ethanol

- Dosing
  - **IV: load 800mg/kg; then give 100mg/kg/hr**
  - **Oral: 3-4 1-oz "shots" of 80-proof liquor); then give 1-2 "shots" per hour**
- BAL of 100-150 completely saturates alcohol dehydrogenase
- **Disadvantages: makes patients inebriated thus requiring close monitoring for CNS and respiratory depression, individual metabolic variations make dosing complicated, frequent serum level monitoring and dosage adjustments are required, administration of the 10% IV ethanol solution requires central venous access**

Methanol toxicity

Correction of metabolic acidosis

Profound acidemia is corrected with sodium bicarbonate

- Bicarbonate 1-2mEq/kg IV bolus Follow by infusion of 150mEq/L in D5 at 1.5-2x maintenance fluid rate
- Monitor for worsening hypocalcemia

Dialysis:

Methanol toxicity

Indications for dialysis:

1. Refractory metabolic acidosis (pH <7.25) with AG >30
2. Renal insufficiency
3. Visual symptoms
4. Deteriorating vital signs despite aggressive supportive care
5. Electrolyte abnormalities refractory to conventional therapy
6. Methanol level >50mg/dL (controversial)

Enhanced formic acid metabolism

1. Folinic acid 50mg IV q4hr
    1. May facilitate breakdown of formic acid into carbon dioxide and water

Ethylene glycol toxicity

Ethylene glycol toxicity

Background

- Component of antifreeze, automobile coolants, de-icing agents, industrial solvents and hydraulic brake fluid.
- Sweet taste
- Parent compound causes inebriation; metabolite (glycolic acid) causes toxicity

Ethylene glycol toxicity

Pharmacology

Peak serum concentration 1-4 hours, elimination half-life ~9 hours

- Ethanol coingestion roughly doubles ethylene glycol half-life
- Minimum lethal dose 1-1.5 mL/kg
  - Volume depends on percentage of ethylene glycol in solution, typically 0.6 g/mL
  - 60 kg patient lethal dose ~ 100 mL
- Metabolites (eg. oxalate acid, glycolic acid) cause toxicity, but do NOT cause osmolal gap

Clinical Features

Stage 1 - CNS

•30min-12hr after ingestion

•Appears intoxicated (nausea/vomiting, slurred speech, nystagmus, ataxia, stupor, seizure, coma)

Stage 2 - Cardiopulmonary

•12-24hr after ingestion

•Most deaths occur during this stage

- Hypertension, tachycardia, CHF
- ARDS, pulmonary infiltrates, hypoxia
- Hyperventilation (compensation for severe metabolic acidosis)
- Hypocalcemia (chelation by oxalate)
- Myositis & CK elevation
- Arrhythmias, prolonged QT
- Multi-organ system failure

Stage 3 - Renal

- 24-72hr after ingestion
  - Flank pain, CVA tenderness
  - Hematuria, proteinuria, calcium oxalate crystals (50%)
  - Oliguria or anuria

Differential Diagnosis

Sedative/hypnotic toxicity

- Barbiturates
- Benzodiazepines
  - Flunitrazepam (Rohypnol)
- Chloral hydrate
- Gamma hydroxybutyrate (GHB)
- Baclofen toxicity
- Opioids
  - Lomotil toxicity
  - Loperamide toxicity
- Toxic alcohols
  - Ethanol
  - Isopropyl alcohol
  - Methanol

Evaluation,Chemistry

- Anion gap acidosis
  - Will not be present immediately after exposure (only metabolite causes acidosis)
- Hypocalcemia secondary to formation of calcium oxalate crystals
- Renal failure
- Glucose - may be low in setting of decreased caloric intake

Ethylene glycol toxicity

Serum osmolality

Osm gap:

- Calculated serum osm - measured serum osm
- Calculated serum osm = 2Na + BUN/2.8 + glucose/18 + ethanol/4.2)
- Normal < 10
- >50 highly suggestive of toxic alcohol poisoning

Note: Cannot rule out toxic ingestion with a "normal" osmol gap

- Only parent alcohol is osmotically active

Alcohol levels

May be useful however even if elevated, patients can still have ingested a toxic alcohol

Ethylene glycol toxicity

Although some patients with ethylene glycol poisoning present with elevated lactate levels, the rise in lactate is insufficient to account for the degree of acidosis.

Ethylene glycol toxicity

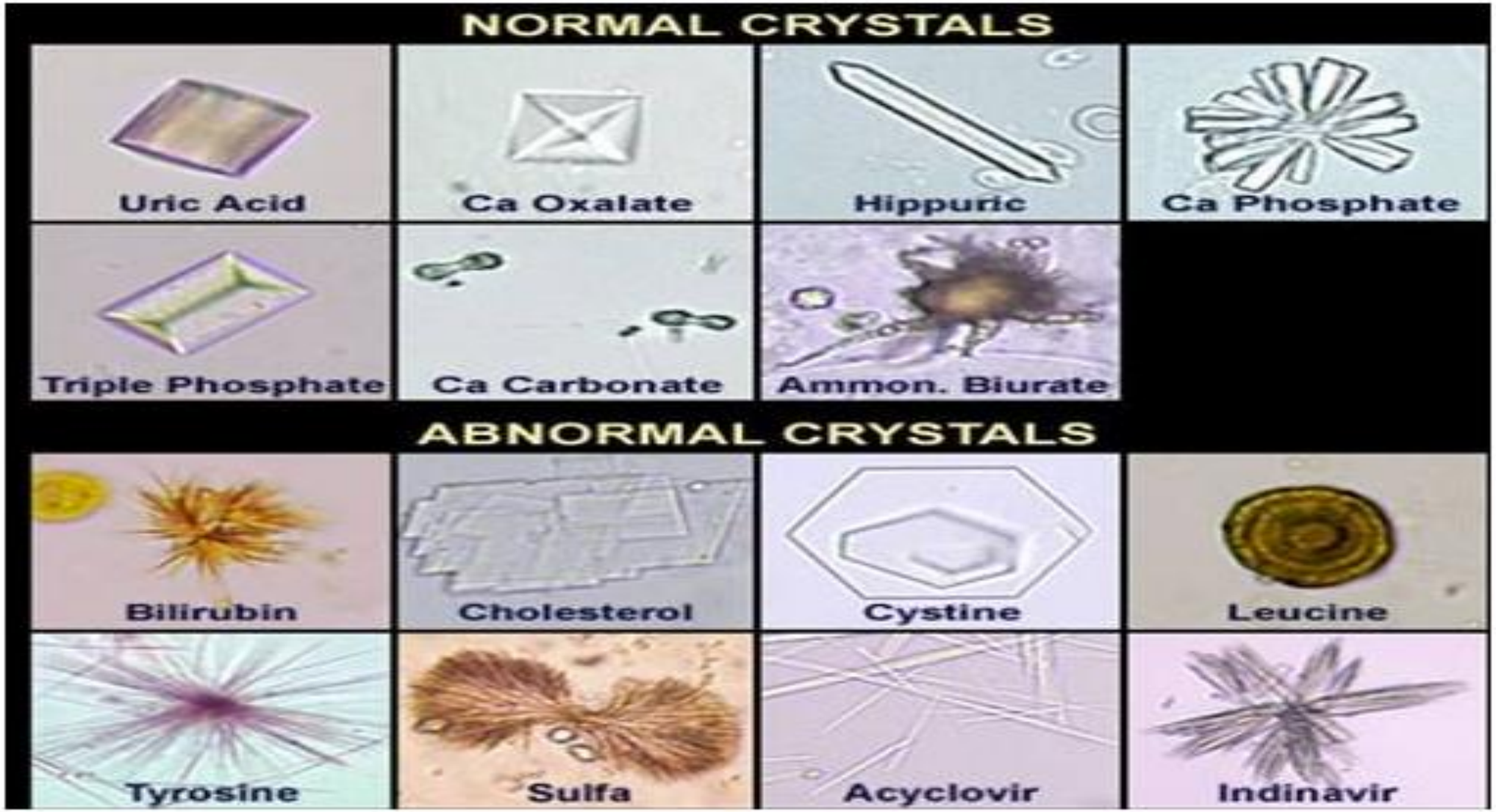
Urinalysis

- **Hematuria, proteinuria, pyuria**
- **Calcium oxalate crystals (late finding; only seen in 50%)**
- **Urinary fluorescence (may be seen 6 hours after ingestion), but lacks sensitivity and specificity**

Ethylene glycol toxicity

Urine testing — Examination of the urine for oxalate crystals and fluorescence is frequently performed in patients with possible ethylene glycol poisoning, but care should be taken not to over-interpret positive or negative results.

The formation of oxalate crystals in the urine is a late and nonspecific finding following ethylene glycol ingest. Two types of calcium oxalate crystals may be seen: needle-shaped monohydrate crystals, which may be misread as hippurate crystals, and envelope-shaped dihydrate crystals.


NORMAL CRYSTALS
Uric Acid
Ca Oxalate
Hippuric
Ca Phosphate
Triple Phosphate
Ca Carbonate
Ammon. Biurate
ABNORMAL CRYSTALS
Bilirubin
Cholesterol
Cystine
Leucine
Tyrosine
Sulfa
Acyclovir
Indinavir

Ethylene glycol toxicity

Laboratory evaluation

Basic testing — Routine laboratory evaluation of any poisoned patient should include the following:

- Fingerstick glucose, to rule out hypoglycemia as the cause of any alteration in mental status
- Electrocardiogram (ECG), to rule out conduction system poisoning by drugs that effect the QRS or QTc intervals; it is important to note that ethylene glycol can prolong the QTc interval via its effects on serum calcium
- Pregnancy test in women of childbearing age

Additional tests with toxic alcohol exposure

- Basic electrolytes with anion gap determination
- Serum calcium
- BUN and creatinine
- Arterial or venous blood gas analysis
- Serum ethanol concentration
- Serum osmolality
- Serum methanol, ethylene glycol, and isopropyl alcohol concentrations
- Acetaminophen and salicylate levels, to rule out these common coingestions

Automotive coolant/antifreeze may also contain anticorrosive agents (e.g. sodium nitrite or nitrate) which are not listed on the product label or safety data sheet.

Methemoglobinemia has been reported following large intentional ingestions of such products.

Thus, patients with cyanosis and findings related to tissue hypoxia (eg, tachycardia, headache, lethargy) also warrant evaluation for methemoglobinemia

Total CK

Useful to assess for signs of rhabdomyolysis especially if the patient was found laying down

Venous blood gas

Needed to assess degree of acidosis. An ABG is not necessary since pH can be approximated with a clinical degree via a VBG

ECG

- QT prolongation ~ hypocalcemia

Acetaminophen or Aspirin levels

- Useful to discern the cause of the anion gap as well as assess for other toxic ingestion

Management

ADH enzyme blockade

Fomepizole:

- **Indications**:
  - Ethylene glycol level >20mg/dL
  - Suspected significant ethylene glycol ingestion with ETOH level <100mg/dL
  - Coma or altered mental status in patient with unclear history and osm gap >10
  - Coma or altered mental status in patient with unclear history and unexplained met acidosis and ETOH level <100
- **Dosing**
  - 15mg/kg IV over 30min; follow by 10mg/kg q12hr until level <20 or acidosis resolves

Ethanol:

- Ethanol drips are rarely used
- BAL of 100-150 completely saturates alcohol dehydrogenase
- Dosing:
  - IV: load 800mg/kg; then give 100mg/kg/hr
  - Oral: 3-4 1-oz "shots" of 80-proof liquor); then give 1-2 "shots" per hour

Correction of metabolic acidosis

- Acidemia leads to protonation of oxalate which increases penetration to end organ tissues and causes more damage
- Bicarbonate 1-2mEq/kg IV bolus to attain pH = 7.45-7.50
  - Follow by infusion of 150mEq/L in D5 @ 1.5-2 times maintenance fluid rate
- Monitor for worsening hypocalcemia
  - Must correct hypocalcemia, but be cautious of increased calcium oxalate crystal production

Dialysis

- **Indications:**
  - **Metabolic acidosis** (pH <7.25) with AG >30 and base deficit < -15
  - **Renal insufficiency** (serum Cr >3.0 mg/dL or increase in Cr by 1.0 mg/dL)
  - **Deteriorating vital signs** despite aggressive supportive care
  - **Electrolyte abnormalities** refractory to conventional therapy
  - **Ethylene glycol level >50mg/dL** (controversial)
  - **Glycolic acid level > 8 mmol/L** (glycolic acid is metabolite that causes anion gap acidosis)

Decrease oxalate production

- Thiamine 100mg IV q6hr x2d
  - May promote glyoxalate conversion to alpha-hydroxy-beta-ketoadipate
- Pyridoxine 50mg q6hr x2d
  - May inhibit metabolism of glyoxalate to oxalate
- Magnesium 2gm IV x1

Ethanol toxicity

Ethanol toxicity

Background

Alcohol (ethanol) is a CNS depressant that can cause respiratory depression, coma, or death when consumed rapidly or in large quantities.

Rate of ETOH elimination is 15-30mg/dL/hr (depending on degree of chronic alcohol intake)

Ethanol is involved in 30-50% of all traumatic injuries in the US[1

Ethanol toxicity

Clinical feature, Classic Features

- Diminished fine motor control
- Impaired judgment and coordination
- Slurred speech
- Nystagmus
- Ataxia
- Nausea and vomiting
- Alcohol odor on breath
- Respiratory depression
- Lethargy
- Coma

Other Features (if malnourished)

- Hypoglycemia
- Ketoacidosis
- Lactic acidosis
- Epigastric pain (pancreatitis)

Ethanol toxicity

Ethanol related disease processes

- Ethanol toxicity
- Alcohol use disorder
- Alcohol withdrawal
  - Alcohol withdrawal seizures
  - Delerium tremens
- Electrolyte/acid-base disorder
  - Alcoholic ketoacidosis
  - Beer potomania syndrome
  - Beriberi
  - Thiamine deficiency
  - Wernicke-Korsakoff syndrome

Differential Diagnosis

Sedative/hypnotic toxicity

- Barbiturates
- Benzodiazepines
  - Flunitrazepam (Rohypnol)
- Chloral hydrate
- Gamma hydroxybutyrate (GHB)
- Baclofen toxicity
- Opioids
  - Lomotil toxicity
  - Loperamide toxicity
- Toxic alcohols

Altered mental status

Diffuse brain dysfunction

- Hypoxic encephalopathy
- Acute toxic-metabolic encephalopathy (Delirium)
  - Hypoglycemia
  - Hyperosmolar state (e.g., hyperglycemia)
  - ElectrolyteAbnormalities (hyperor hyponatremia, hypercalcemia)
  - Organ system failure
  - Hepatic Encephalopathy
  - Uremia/Renal Failure
  - Endocrine (Addison's disease, Cushing syndrome, hypothyroidism, myxedema coma, thyroid storm)
  - CO2 narcosis
- Limbic encephalitis

- Hypertensive Encephalopathy
- Toxins
- TTP / Thrombotic thrombocytopenic purpura
- Alcohol withdrawal
- Drug reactions (NMS, Serotonin Syndrome)
- Environmental causes
  - Hypothermia
  - Hyperthermia
- Deficiency state
  - Wernicke encephalopathy
  - Subacute Combined Degeneration of Spinal Cord (B12 deficiency)
  - Vitamin D Deficiency
  - Zinc Deficiency
- Sepsis
- Osmotic demyelination syndrome (central pontine myelinolysis)

Primary CNS disease or trauma

- Direct CNS trauma
- Vascular disease
- SAH
- Stroke
- CNS infections
- Neoplasms
- Seizures
- Dementia

Psychiatric

- Malingering

Ethanol toxicity

Evaluation

Clinical diagnosis. *No specific workup required when there is clear evidence of alcohol intake, but the following may be considered based on clinical picture/gestalt:*

- Fingerstick glucose (recommended as minimum workup in all patients with AMS)
- **Consider blood alcohol level (BAL) when a good history cannot be obtained or patient fails to improve as expected**
  - Correlates poorly with degree of intoxication[3]
- **Maintain low threshold for imaging** in intoxicated patient with signs of trauma

Management

- **Supportive care is mainstay of ED treatment and is based on clinical presentation**
  - Manage ABCs
  - Benzodiazepines or haloperidol for agitation

Vitamin Prophylaxis for Chronic alcoholics

- At risk for thiamine deficiency, but no symptoms: thiamine 100mg PO q day
- Give multivitamin PO; patient at risk for other vitamin deficiencies

Banana bag

*The majority of chronic alcoholics do **NOT** require a banana bag*[6][7]

- Thiamine 100mg IV
- Folate 1mg IV (cheaper PO)
- Multivitamin 1 tab IV (cheaper PO)
- Magnesium sulfate 2mg IV
- Normal saline as needed for hydration

Disposition

- Caution should be taken when BAL is measured on arrival as clinical exam cannot be used alone for discharge
- **Can be discharged once patient at baseline mental status, able to tolerate PO and ambulate without assistance**

Isopropyl alcohol toxicity

Background

- Main component of rubbing alcohol
- Hallmark is osmolar gap, that is without acidosis
  - Metabolized to acetone, not to an acid
- Takes 30-60 min for acetone to appear in blood; 3 hr to appear in urine
- Lethal Dose: 4-8 g/kg or 250 mL in average adult (calculated using volume of pure isopropyl alcohol)
  - Typical store bought rubbing alcohol is 70% isopropyl alcohol by volume, so lethal dose is ~ 350 mL

Isopropyl alcohol toxicity

Pharmacology[1]

- Unlike other toxic alcohols (methanol, ethylene glycol), toxic effects caused by parent agent (IA) rather than metabolite (acetone)
- Metabolized to acetone by alcohol dehydrogenase
- Maximal distribution in ≤ 2 hours
- Lethal dose > 200 mg/dL, although variable literature

Isopropyl alcohol toxicity

Clinical Features

- **CNS depression**
  - Similar to ETOH intoxication, but longer-lasting
  - Usually peaks in first hour of ingestion
- **GI**
  - Nausea/vomiting / abdominal pain / hemorrhagic gastritis
- **Respiratory depression**
  - Fruity breath from acetone
- Hypotension, hypothermia from peripheral vasodilation
- Hypoglycemia (in malnourished patients)

Differential Diagnosis

- Starvation ketoacidosis
- Diabetic Ketoacidosis
- Inborn errors of metabolism
- Salicylate Toxicity
- Acetone ingestion

Sedative/hypnotic toxicity

- Barbiturates
- Benzodiazepines
  - Flunitrazepam (Rohypnol)
- Gamma hydroxybutyrate (GHB)
- Baclofen toxicity
- Opioids
  - Lomotil toxicity
  - Loperamide toxicity
- Toxic alcohols

Isopropyl alcohol toxicity

Evaluation,

Fingerstick glucose

- Complete metabolic panel
- Serum ketones
- Serum Osmolality
- Urinalysis
- VBG
- Aspirin/Tylenol levels
- ECG
- Serum isopropyl alcohol level (if available)
- Total CK

Isopropyl alcohol toxicity

Evaluation

- Osmolal gap > 10; see Osmolal or Osmolar Gap
- Absence of anion gap
- Absence of metabolic acidosis
- Absence of serum beta hydroxybutyrate
- Presence of serum and urine ketones
  - Consider other diagnosis if absent 2hr after ingestion
- Creatinine may be falsely elevated due to acetone interference with laboratory measurement of Cr

Isopropyl alcohol toxicity

Management

- **Treatment is supportive.**
- **No role for fomepizole or ethanol**
  - Blockade of alcohol dehydrogenase (ADH) will prolong intoxication
- **Hemodialysis indications:**
  - Hypotension
  - Comatose
  - Consider if IA serum level >200mg/dL

Disposition

- Generally may be discharged once clinically sober.

Alcohol Misuse and Kidney Injury:

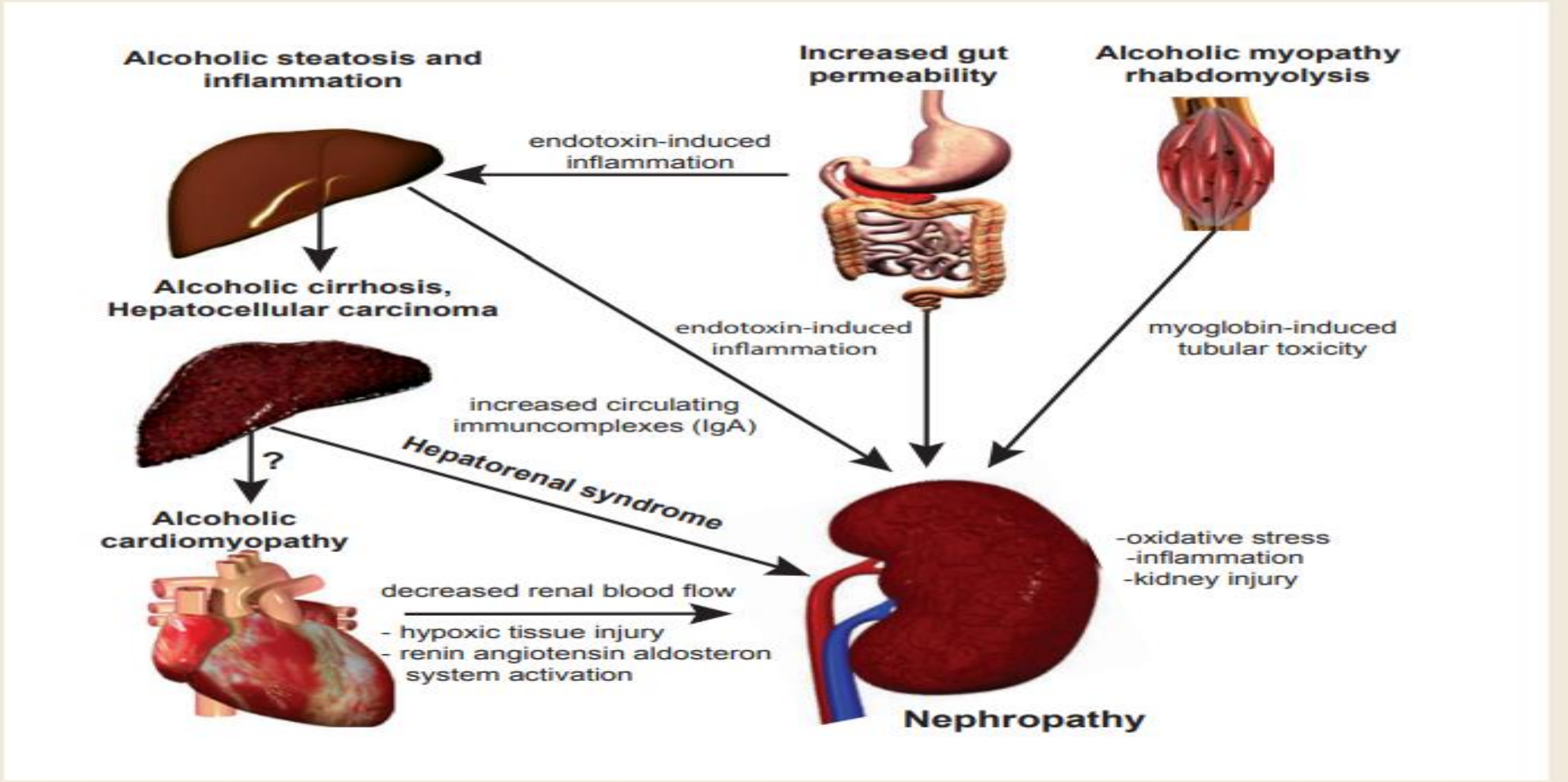


Figure Possible mechanism for alcohol-induced kidney injury. Chronic alcohol consumption induces profound injury in several organs that may affect and aggravate the deleterious

Potential Mechanisms of Alcoholic Kidney Injury: Lessons From Experimental Studies

If alcohol consumption does in fact influence kidney disease, the question remains: How?

There is direct and indirect evidence for several possible mechanisms. These changes are caused either by alcohol itself or by excessive amounts of the products formed when cells break down (or metabolize) alcohol, including acetaldehyde, NADH, and free radicals.

These alcohol-related pathophysiologic changes in cells have been linked to damage in many organs and may play a role in kidney damage.

In addition, complex interactions between organs may further complicate and accentuate the development of kidney pathology in people with AUD (see figure).

Oxidative Stress

Free radicals (also called reactive oxygen species [ROS]) are one of the **by-products of alcohol metabolism** and are known to cause cellular damage, unless the body can use antioxidants to clean them up.

Oxidative stress occurs when the body cannot detoxify free radicals as fast as they are being produced, and it is pivotal in triggering alcohol-related tissue injury.

Studies suggest that several mechanisms produce ROS in alcohol-damaged organs, including the liver (Cederbaum et al. 2009), heart (Tan et al. 2012; Varga et al. 2015), and kidney (Latchoumycandane et al. 2015).

The body mainly metabolizes alcohol using the enzyme alcohol dehydrogenase, which is expressed primarily in the liver. **However, during chronic ethanol consumption, the body also uses CYP2E1 in the liver as well as the kidneys.** Interestingly, studies find that CYP2E1 induction is much more robust in the kidneys compared with the liver (Roberts et al. 1994; Zerilli et al. 1995). **This massive induction of CYP2E1 in the kidneys results in oxidative stress that modifies phospholipids in cell membranes**. Such modified phospholipids may in turn activate immune cells called neutrophil granulocytes, which further aggravates oxidative stress, promoting a vicious cycle (Latchoumycandane et al. 2015).

Studies suggest that ethanol consumption may increase renal expression of other potential sources of free radicals involving a family of enzymes called nitric oxide synthases (Tirapelli et al. 2012).

Nitric oxide synthase stimulates the production of nitric oxide, which, if produced excessively, can react with other molecules and create free radicals that trigger tissue damage in the kidneys (Pacher et al. 2007; Szalay et al. 2015).

Tirapelli and colleagues (2012) showed that ethanol consumption increased the expression of two nitric oxide synthases.

Alcohol-Metabolism Derived Intermediaries

Along with oxidative stress, increasing evidence suggests that some nonoxidative mechanisms also factor into alcohol related organ damage. Specifically, **ethanol metabolism produces fatty acid ethyl esters** in various organs (Laposata and Lange 1986), **which can cause ethanol-induced organ damage**. Calabrese and Rizza (1999) found that ethanol induced a significant increase in the levels of fatty acid ethyl esters. They measured the highest levels in the heart, followed by kidney, brain, and liver. Due to the metabolism of ethanol, significant amounts of acetate are produced and subsequently incorporated into acetyl-coenzyme-A, a molecule that participates in metabolism of proteins, lipids, and carbohydrates. This leads to the reprogramming of systemic metabolism

Alcohol-Induced Intestinal Damage

Alcohol-induced intestinal damage and increased mucosal translocation of bacterial endotoxin are crucial in the initiation and progression of alcoholic liver injury and in the pathogenesis of other alcohol-related diseases (Bala et al. 2014; Purohit et al. 2008).

The direct role of alcohol-related endotoxin release in alcoholic kidney injury has not yet been studied.

However, **it is possible that activation of the innate immune system due to endotoxins released by a leaky gut plays a central role in the development of renal damage, as it does for liver damage** (Zhang et al. 2008).

Substantial experimental and clinical evidence suggests that increased intestinal permeability and endotoxin release caused by excessive alcohol consumption leads to higher levels of circulating immunoglobulin A (IgA), an antibody critical to the immune response of mucous membranes.
The kidney is particularly sensitive to an increased IgA load.
Experimental studies suggest that heavy alcohol consumption induces IgA kidney disease (Smith et al. 1990).

In addition, rats given intragastric infusions of a commercial whiskey (1.5 ml/100 gm body weight) 3 times a week along with a nutrient-deficient diet develop a more severe form of IgA nephropathy (Amore et al. 1994).

Evidence also exists that alcohol related damage to the liver, in particular advanced liver cirrhosis, leads to hepatorenal syndrome (HRS)—a deterioration in renal function related to impaired circulation.

Alcoholic Skeletal Myopathy:

A Potential Indirect Mechanism **Severe AUD is frequently associated with various acute or chronic muscle symptoms, including difficulties with gait, muscle cramps, pain, and overall reduced muscle mass.**

In fact, biochemical lesions in the muscles and the resulting myopathy develop independently of any peripheral neuropathy, macro- and micronutrient malnutrition, and overt liver disease in people with AUD. In chronic alcoholic myopathy, a person's entire muscle mass may be reduced by up to one-third. It is the most common skeletal muscle disorder in the industrialized world, present at varying severity in approximately half of alcohol misusers (Preedy et al. 2001). To date, studies have not examined whether there is a direct link between acute alcoholic myopathy and kidney injury. However, several lines of research suggest there might be a

Although the mechanism of alcoholic myopathy is not fully understood, it is likely that **disruption of mitochondria related energy homeostasis** is important in promoting muscle cell (myocyte) injury (Eisner et al. 2014).

In rare cases in malnourished chronic alcoholics, acute alcoholic myopathy, also termed acute alcoholic necrotizing myopathy or alcoholic rhabdomyolysis, also may occur, which may lead to reversible or irreversible acute kidney injury (Haller and Knochel 1984; Hewitt and Winter 1995; Muthukumar et al. 1999; Sofat et al. 1999).

Alcoholic Cardiomyopathy:

Another Potential Confounder Several epidemiological studies have shown that mild alcohol consumption benefits cardiovascular health (Coate 1993; Kannel and Ellison 1996) by reducing the risk of coronary heart disease (Mukamal et al. 2006).

In contrast, heavy drinking leads to the development of nonischemic dilated cardiomyopathy (Klatsky 2007) and significantly increases the risk of sudden cardiac death (Hookana et al. 2011).

Chronic or acute heart failure can lead to chronic or acute dysfunction in the kidneys, known as cardiorenal syndrome (Cleland et al. 2012). The complex renal pathophysiological response leads to fluid buildup in tissues, ischemic injury, peripheral vasoconstriction, and activation of the hormone system that helps regulate blood flow (called the renin– angiotensin–aldosterone system,

The overactivation of RAAS further aggravates oxidative stress in chronic alcoholism (Ungvari et al. 2004).

As a consequence, oxidative stress not only propagates kidney failure, but it also contributes to the progression of chronic heart failure (Pacher et al. 2005) and leads to a vicious cycle in alcohol induced cardiovascular complications

Thank you