Ethylene Glycol Poisoning

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Questions to Answer

- How does ethylene glycol present
- How does the presentation differ from uremia
- How do you treat it?

Outline

- Sources
- Pharmacology
- Metabolism
- Lab Findings
- Diagnosis
- Treatment

Sources

- Antifreeze
- Brake fluids
- Industrial solvents

Pharmacology

- Dihydric alcohol
- Odorless, colorless, water soluble, sweet tasting (“the sweet killer”)
- Molecular Weight 62 kDa

Metabolism

- Absorption
- Excretion

Absorption

- Readily absorbed from the GI tract within 30-60 minutes
- Maximal blood concentration reached in 1-4 hours
- 1/2 life is 3-8 hours
- Lethal dose is estimated as 1-1.5 mls/kg or 100mls

Metabolism / Excretion

- Liver
- Kidney

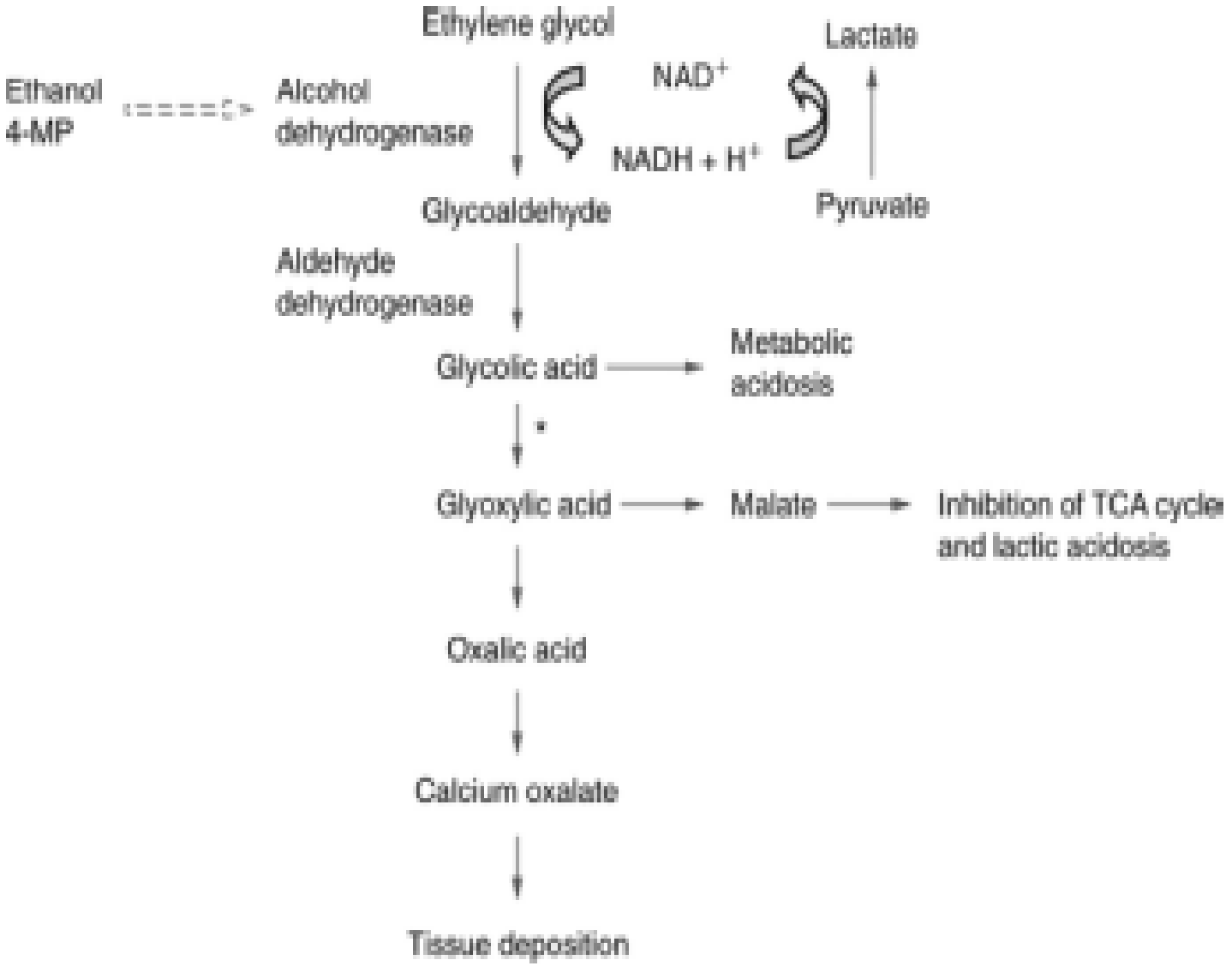
Liver

- Metabolizes 80% of what is absorbed
- Half life with liver metabolism is 3-8 hours

Liver Continued

- Broken down in the liver by alcohol dehydrogenase to four compounds

- Glycoaldehyde which is metabolized by aldehyde dehydrogenase to glycolic acid, which is metabolized to glycoxylic acid, which is metabolized to oxalic acid


Ethylene glycol
Lactate
Ethanol
4-MP
Alcohol
dehydrogenase
NAD+
NADH + H+
Glycoaldehyde
Pyruvate
Aldehyde
dehydrogenase
Glycolic acid
Metabolic
acidosis
Glyoxylic acid
Malate
Inhibition of TCA cycle
and lactic acidosis
Oxalic acid
Calcium oxalate
Tissue deposition

Liver Continued

- The conversion of glycolic acid to glycoxylic acid is the rate limiting step
- These metabolites are oxidative phosphorylation toxins that cause CNS depression and cardio-pulmonary and renal failure

Kidney

- The proximal tubule reabsorbs 80% of what is filtered
- Half life with renal metabolism is 18-20 hours
- The remaining 20% is excreted unchanged from the kidneys

Clinical Presentation

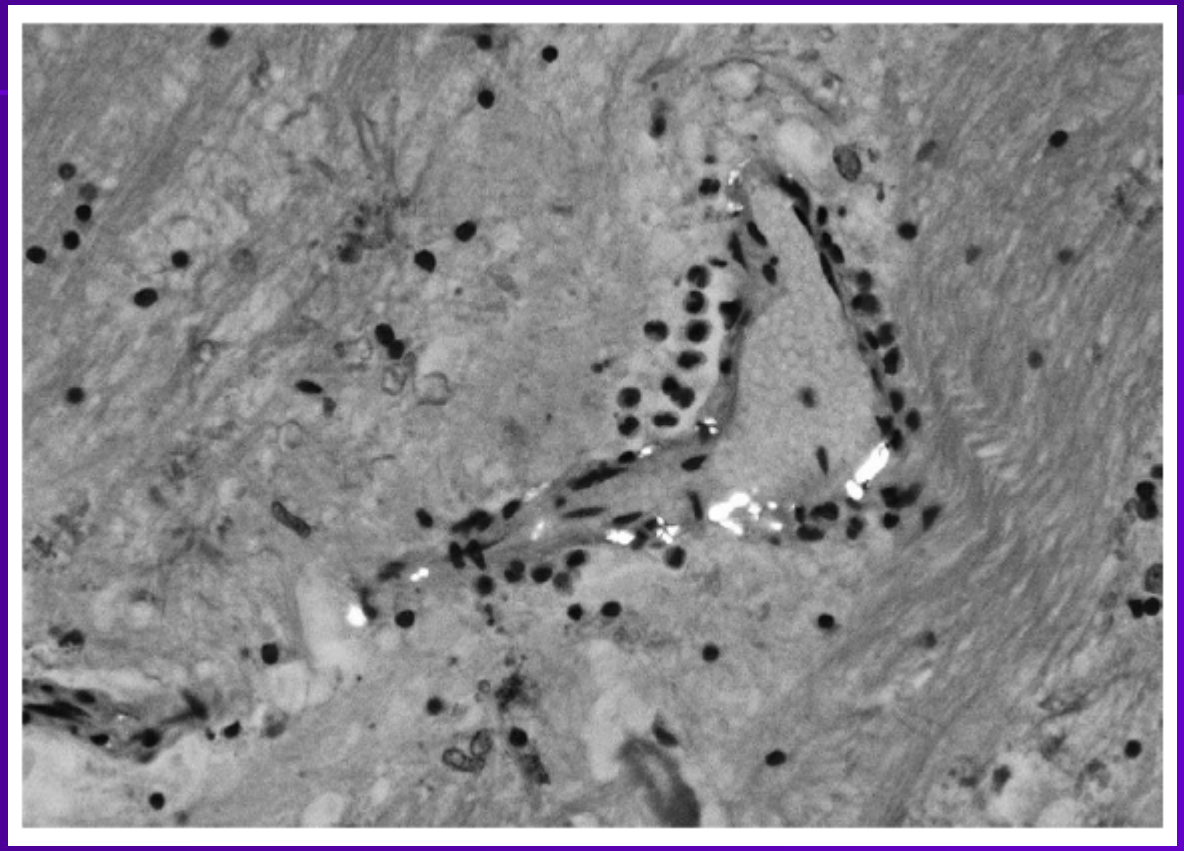
- Neurologic: 30 minutes to 12 hours
- Cardiopulmonary: 12-36 Hours
- Renal: 24-72 Hours

Neurologic

- CNS manifestations: Somnolence, Disorientation, agitation, confusion, ataxia (pt may appear drunk)
  - Pathophysiology: Initially a direct effect of ethylene glycol, which in low doses causes euphoria and in high doses causes CNS depression

Cardiopulmonary

- Deeper CNS Symptoms: Stupor, coma, nystagmus, ocular paresis, myoclonus and focal or universal seizures
  - Results from high dose of ethylene glycol
  - Results from calcium oxalate desposition in the brain



Cardiopulmonary Cont.

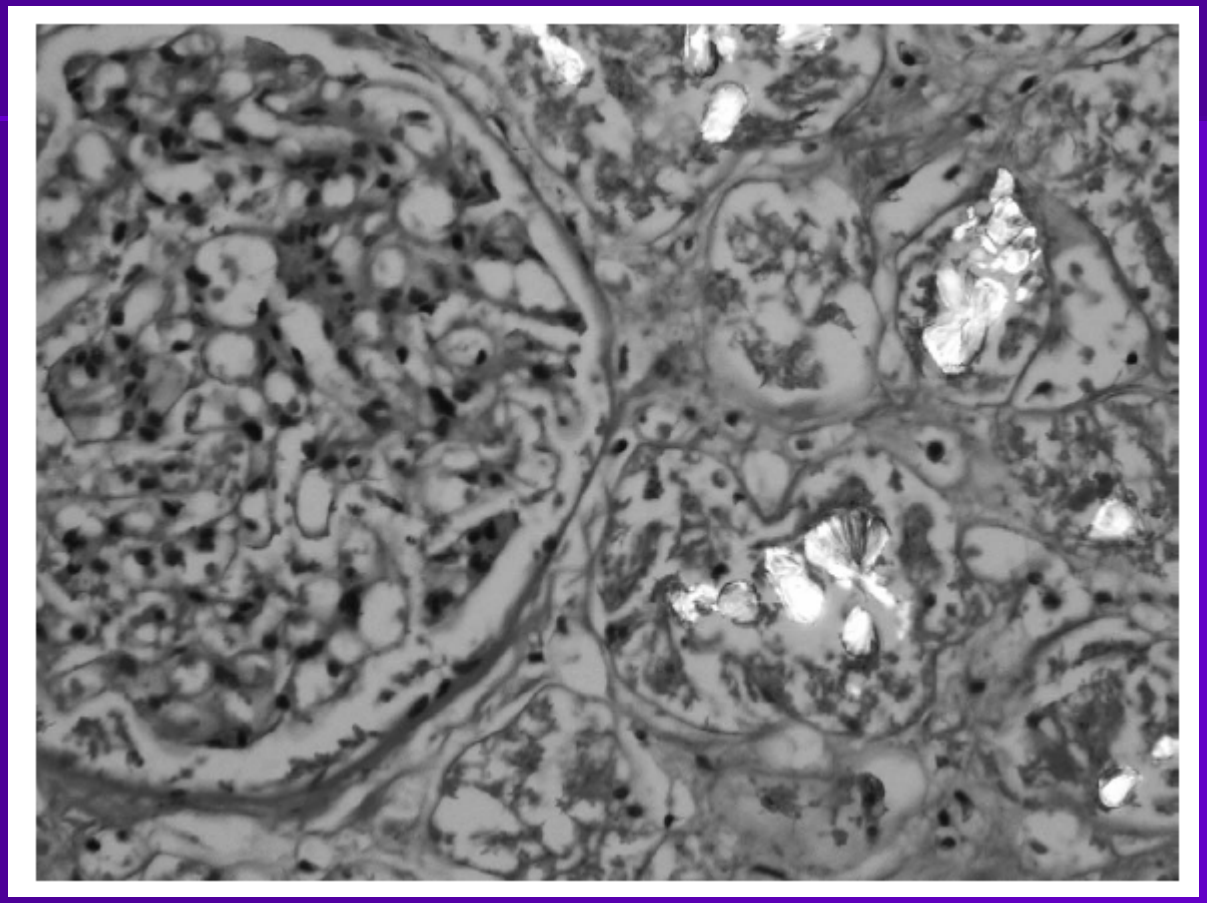
- Leukocytosis
- Seizures
  - Direct effect of the calcium oxalate
  - May also result from hypocalcemia
- Heart failure
  - Arrythmias result from hypocalcemia and acidosis

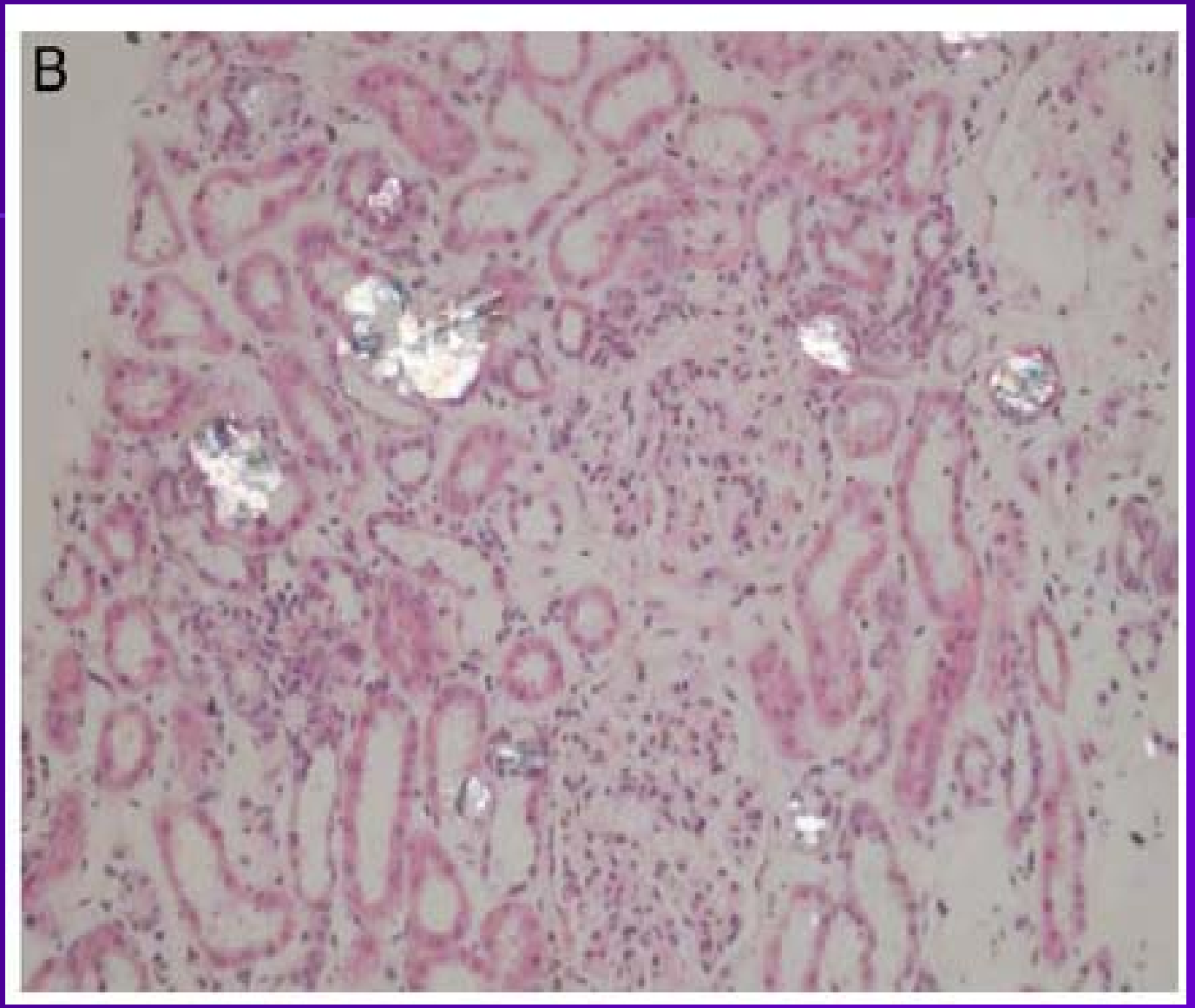
Cardiopulmonary Cont.

- Respiratory Distress
  - As compensation for metabolic acidosis and from the hypoxia
- Tachycardia, HTN, Dyspnea, Tachypnea, Kussmaul's Respiration
  - As compensation for metabolic acidosis and from hypoxia

Renal

- Will get flank pain, renal tubular necrosis, hematuria, proteinuria, anuria or oliguria
  - Thought to result from calcium oxalate blocking the renal tubules
  - Calcium oxalate is internalized by the proximal tubule causing mitochondrial damage, and resulting in ATN




B

Renal Continued

- Calcium oxalate monohydrate crystals adhere to the proximal tubule membrane and are endocytosed within 30 minutes
- Once they enter the proximal cell, calcium oxalate can inhibit the electron transport chain

Renal Continued

- COM can also lead to the mitochondrial permeability transition (MPT) which increases the permeability of mitochondria
  - Molecules up to 1500 kDA can enter the mitochondria
  - Causes depolarization, inhibition of ox phos, and ATP depletion

Cranial Nerve Abnormalities

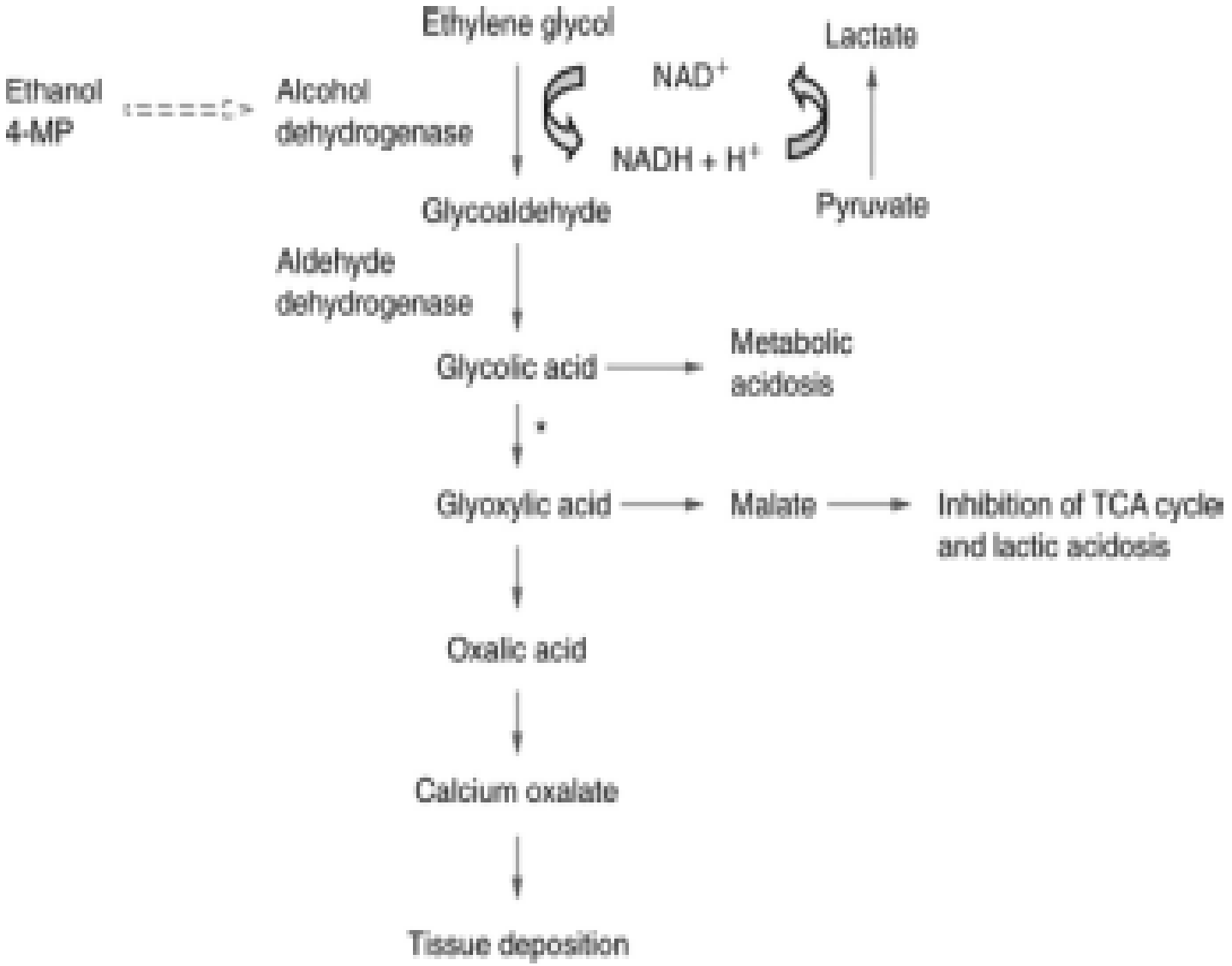
- Occur with the ingestion of at least 100 cc of ethylene glycol
- Occur 6-18 days after the ingestion of ethylene glycol
- Postmortem studies attribute this to inflammation around the nerve from oxalate microcrystal deposition

Cranial Nerve Abnormalities Cont.

- Type of treatment is immaterial in terms of
- Full recovery may take a year

Laboratory Findings

- High osmolarity with osmolar gap
  - Ethylene glycol and glycoaldehyde increase serum osmolarity
  - Occurs early on, may disappear later as ethylene glycol and glycoaldehyde are metabolized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Tissue deposition

High anion gap metabolic acidosis

- Partially because of glycolic acid
  - Because the conversion of glycolic acid to glycoxilic acid is the rate limiting step, glycolic acid is able to build up

High anion gap metabolic acidosis

- Partially because lactic acidosis
  - The first two steps in ethylene glycol metabolism cause the reduction of NAD to NADH. The elevated NADH to NAD ration causes the conversion of pyruvate to lactate

Calcium oxalate crystals

- Appear in the urine 4-8 hours after ingestion
- May appear as either an elongated crystal (monohydrate) or octahedral like a pyramid
- Will deposit in almost every tissue of the body including the brain, heart, lungs, kidneys, and urine


A
B
C
D

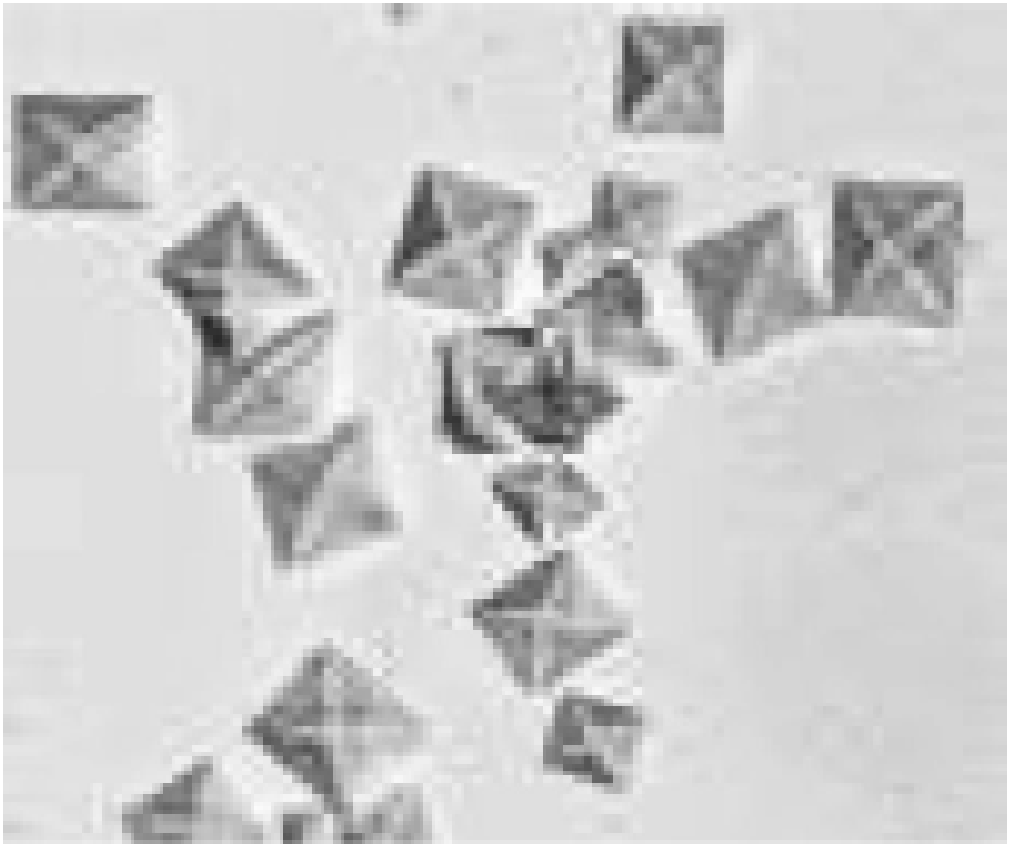


FIGURE 3. Calcium oxalate dihydrate crystals.

FIGURE 2. Calcium oxalate monohydrate crystals.

Table 2. Comparison of Laboratory Features Seen in Patients Presenting Early and Later in the Course of Ethylene Glycol Poisoning

Laboratory	Early	Late
Anion gap	Normal or mildly increased	Increased
Osmolal gap	Increased	Normal
Serum ethylene glycol	Detectable	Not detectable
Oxalate crystalluria	May be present*	May be present†
Kidney function	Normal or mild AKI	Severe AKI

*May be seen 4 to 8 hours after ethylene glycol ingestion, up to 40 hours in the absence of acute kidney injury (AKI).

†Present up to 4 days with AKI.

Further Metabolic Abnormalities

- Hypocalcemia:
  - Caused by precipitation of oxalate
- Hyperkalemia:
  - Caused by renal failure

Diagnostic Tests

- Flourescin is added to antifreeze and can be detected by Wood's light, but is cleared within 4 hours of ingestion

- Serum ethylene glycol levels can disappear after 5 days, whereas urine ethylene glycol levels persist for 17 days

Treatment

- Inhibit Absorption
- Correct Acidosis
- Inhibition of Metabolism
- Elimination of parent compound and the metabolites

Inhibit Absorption

- Gastric Treatment:
  - Gastric aspiration followed by lavage useful up to 1 hour after ingestion
  - Syrup of ipecac contraindicated because of aspiration
  - Activated charcoal: Not helpful

Treatment of Acidosis

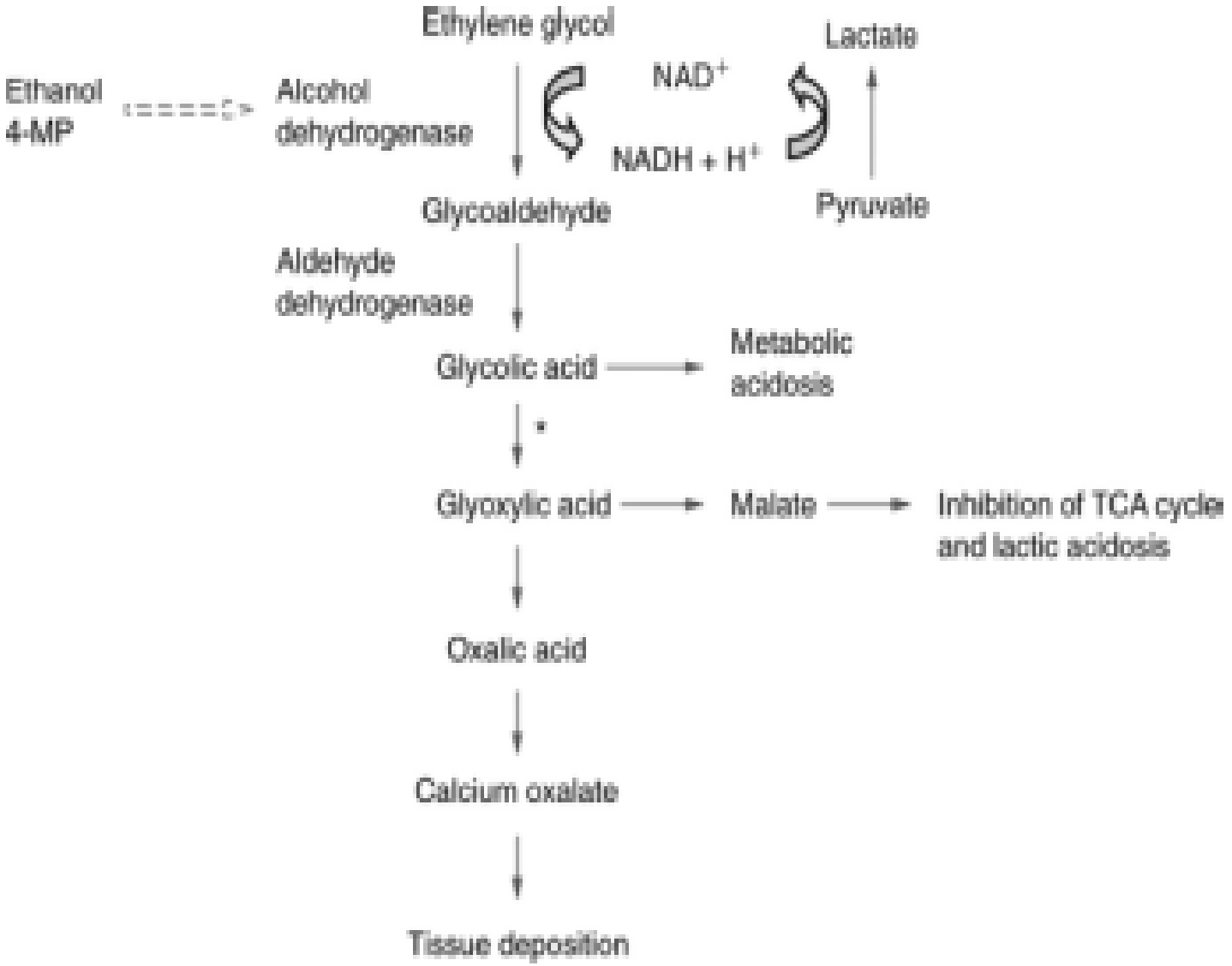
- Bicarb drip:
  - Used to increase the bicarb, but also by increasing the urine pH will promote the excretion of glycolic acid and lactic acidosis

Inhibition of Metabolism

- Fomepizole (4-methylpyrazole)
- Ethanol
- Thiamine
- Pyridoxine

Fomepizole (4-methylpyrazole)

- Mechanism of Action:
  - Competitive inhibitor of alcohol dehydrogenase, alcohol dehydrogenase has 500-1000 times the affinity than for ethylene glycol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Fomepizole (4-methylpyrazole) Cont.

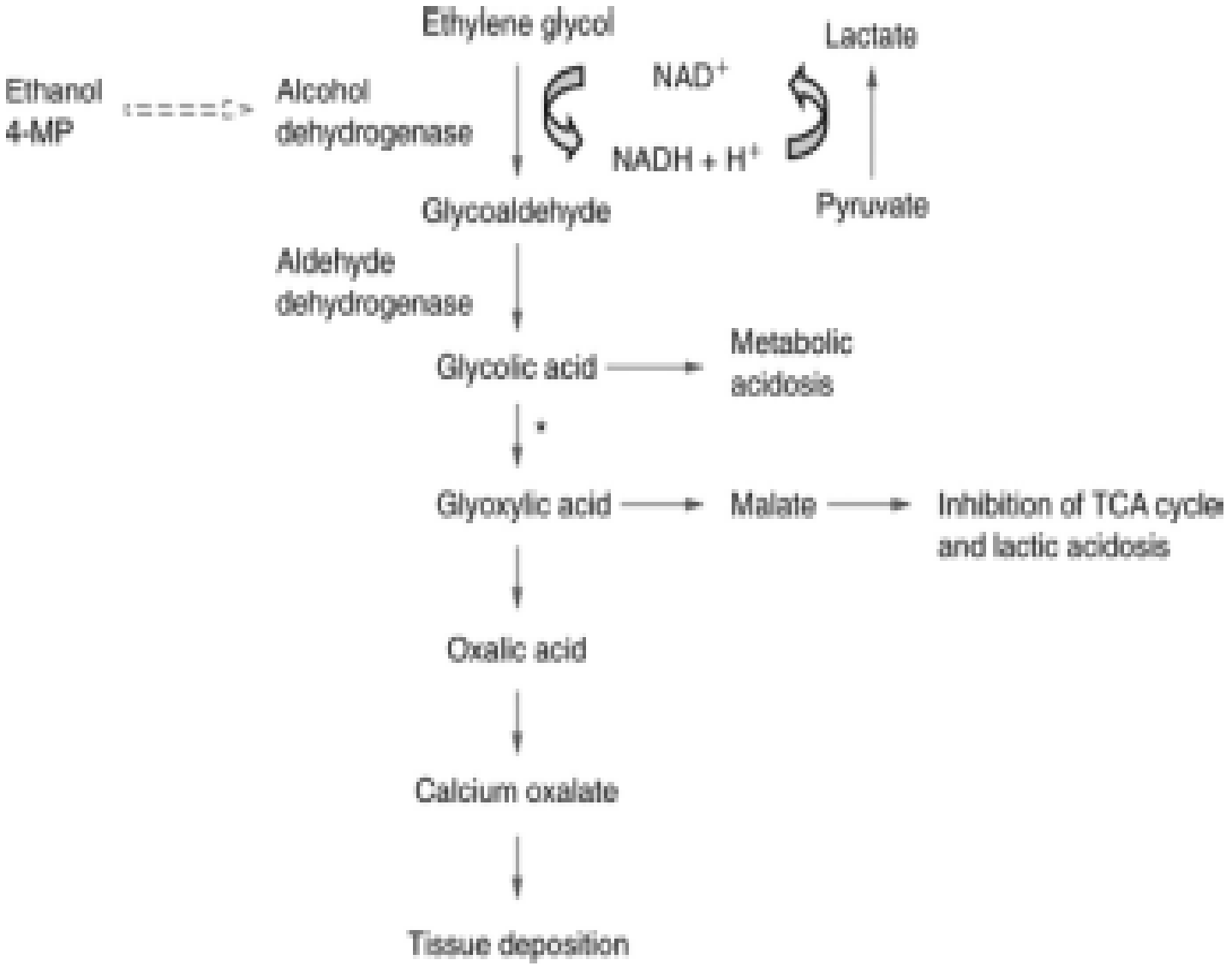
- Loading dose is 15mg/kg in 100 mls of NS or D5W infused over 30 minutes
- Next 10mg/kg every 12 hours for two days
- Next 15mg/kg every 12 hours until the ethylene glycol level is less than 2 and pt. asymptomatic with a normal pH

Fomepizole (4-methylpyrazole) Cont.

- Dializable so administration interval should be reduced to 4 hours during dialysis
- Adverse effects are dizziness, headache, and nausea

Ethanol

- Mechanism of Action:
  - Competitive inhibitor of alcohol dehydrogenase, alcohol dehydrogenase has 100 times the affinity than for ethylene glycol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Ethanol Cont.

- Dosing:
  - Goal ethanol level of 10-12.5 mg/dl, which is enough to saturate the enzyme
  - Loading dos 0.6-0.7 g ethanol/kg, maintenance dose is 66 mg ethanol/kg/hr for nondrinkers and 154 mg/kg/hr for alcoholics
  - Goal is to use until the ethylene glycol level is <2

Ethanol Cont.

- Frequent dose adjustments may be necessary, so the level should be checked every 1-2 hours
- Adverse effects are CNS depression, hepatotoxicity, and hypoglycemia

Thiamine

- Mechanism of Action:
  - Prevents the formation of oxalic acid by facilitating the conversion of glycoxylic acid to alpha-Hydroxy Beta ketoadipic acid.
- Dose:
  - 100 mg IV q6 until ethylene glycol can no longer be measured in the serum

Pyridoxine

- Mechanism of Action:
  - Prevents the oxalic acid by converting gylcoxylic acid to hippuric acid metabolites and glycine.
- Dose:
  - 50 mg IV q6
- Adverse Reaction:
  - Can cause a toxic sensory neuropathy

Elimination:Hemodialysis

- Mechanism of Action:
  - Removes ethylene glycol and glycolate effectively
- Indications:
  - Ethylene glycol concentration>500mg/L or presence of severe metabolic acidosis, renal failure, severe electrolyte imbalance, or generally deteriorating

TABLE 1. Principles of treatment for ethylene glycol intoxication

Indications for treatment of ethylene glycol poisoning with an antidote

- Documented plasma ethylene glycol concentration >20 mg/dL, or
- Documented recent (hours) history of ingesting toxic amounts of ethylene glycol and osmolal gap >10 mOsm/L, or
- History or strong clinical suspicion of ethylene glycol poisoning and at least 2 of the following criteria
  - Arterial pH <7.3
  - Serum bicarbonate <20 mEq/L
  - Osmolal gap >10 mOsm/L
  - Urinary oxalate crystals present

Indications for hemodialysis in ethylene glycol toxicity[16]

- Deteriorating clinical status despite supportive therapy, metabolic acidosis (arterial pH <7.25–7.30) and/or
- Acute kidney injury with a serum creatinine >3.0 mg/dL (265 mmol/L) or increase in serum creatinine by 1.0 mg/dL (90 mmol/L), or
- Acid-base/electrolyte abnormalities unresponsive to standard treatment