METHANOL

Synonyms
Methyl alcohol, methyl hydrate, carbinol, wood alcohol.

Description
Volatile alcohol found in windshield washer antifreeze, gas line antifreeze, air brake antifreeze, fondue fuel, lacquer thinner, shellac, varnish, paint removers and copy machine fluid. May be present in illicitly produced alcohol mixtures ("moonshine") and some denatured ethanol preparations.
See also ANTIFREEZE, ETHANOL monographs.

SI Unit Conversion
methanol (mg/dL) = 3.204 x methanol (mmol/L)

Toxicity
Initial CNS and GI effects may occur. Onset of anion gap metabolic acidosis and visual impairment are delayed. Death within hours to days, usually due to respiratory failure or cardiovascular collapse. Survivors of severe poisoning may suffer permanent blindness and/or neurologic impairment. Toxicity may occur following all routes of exposure.
Risk factors for fatal outcome include delayed initiation of treatment, arterial pH < 7, coma, seizures or respiratory failure at time of admission.

Mechanism of Toxicity
Methanol is less intoxicating than ethanol, but high serum levels can cause *CNS depression*. Accumulation of metabolite *formic acid (formate*) causes severe anion gap *metabolic acidosis*, and is responsible for toxic effects to eye, brain and other organs. Tissue penetration and injurious effects of formate are enhanced in presence of acidemia. *Lactic acid* may contribute to acidosis later in clinical course, secondary to tissue hypoxia.

Toxic Dose
Minimum toxic dose not established; individual susceptibility may vary. Ingestion of 30-60 mL is potentially lethal to an adult; ingestion of 2.5-5 mL could produce serious toxicity in a young child. Patients have survived massive ingestions with prompt treatment.
Minimum toxic serum methanol level not established. Peak serum levels > 6.2 mmol/L (20 mg/dL) are considered potentially toxic; > 15.6 mmol/L (50 mg/dL) may cause severe toxicity.
Prognosis may be better predicted by serum level of toxic metabolite than methanol; however, formate levels are not usually measured. Formate level correlates well with arterial pH, anion gap and serum bicarbonate.

Case Reports
A 6-year-old presented to hospital with a 3-hour history of ataxia and "not feeling well". On admission, serum electrolytes, glucose were normal, and drug and toxin screens were negative. Child was initially somnolent but "woke up" within 3 hours, complaining of headache, dizziness and weakness. He developed a metabolic acidosis with arterial pH 7.21, anion gap 23 and osmole gap 112. Admission methanol level was 109 mmol/L. Child received folic acid, sodium bicarbonate, IV ethanol and hemodialysis, and was discharged on day 3 without sequelae.
A 32-year-old was brought to hospital comatose and hyperventilating several days after ingesting methanol-contaminated liquor. Admission labs showed arterial pH 7.09, anion gap 31.8, osmole gap 28. CT scan revealed cerebral edema and bilateral putamenal lesions. Fundus examination showed optic neuritis. Treatment included ethanol, IV sodium bicarbonate, folic acid and hemodialysis. Metabolic abnormalities resolved within 12 hours and patient slowly regained consciousness over 2 weeks. Sequelae on discharge included residual visual impairment and Parkinsonian symptoms.

Pharmacokinetics
Rapidly absorbed following ingestion, inhalation and dermal application. Peak plasma levels usually occur within 0.5-1.5 hours of ingestion but may be delayed with large ingestions.
Extensively metabolized via pathways similar to ethanol metabolism. Methanol is initially oxidized to *formaldehyde* via *alcohol dehydrogenase* (*ADH*). Formaldehyde does not accumulate, is rapidly oxidized to *formic acid (formate)* via aldehyde dehydrogenase. Formate is slowly detoxified via folate-dependent enzymatic pathways. Small portion of methanol is excreted unchanged in urine (< 5%) or exhaled through lungs (10-20%).
Elimination half-life of ***methanol*** is 2.5-3 hours at low doses; up to 14-30 hours in high doses. Treatment with antidote (ethanol or fomepizole) *prolongs* elimination half-life to approximately 50 hours. Hemodialysis plus antidote *reduces* methanol half-life to approximately 3-3.5 hours.
Elimination half-life of ***formate*** is 2.5-20 hours during antidote therapy (ethanol or fomepizole). Hemodialysis plus antidote *decreases* formate half-life to 0.75-2.8 hours.

Clinical Effects
- **Topical**: Local irritation. Possible systemic toxicity.
- **Ocular**: Possible local irritation; effects usually transient. Ocular toxicity is normally associated with ingestion, not with brief, direct eye contact.
- **Inhalation**: Irritation. Possible systemic toxicity.

- **Ingestion**:
  General: Initial symptoms (onset about 2 hours) may resemble ethanol intoxication. Latent period of 4-12 hours prior to onset of metabolic acidosis and associated symptoms. Massive exposure results in early onset of acidosis; co-ingestion of ethanol will delay onset of toxicity.
  HEENT: Characteristic ocular effects begin 8-36 hours after exposure. Early symptoms include blurred vision, decreased visual acuity, sensation of "being in a snowstorm". Findings range from normal to decreased pupillary light reactions, hyperemia or pallor of optic disc, retinal edema. Bilateral blindness may develop. Retinal and optic nerve damage can be permanent; partially or fully reversible in some cases.
  CVS: Cardiovascular effects may be seen in severely poisoned, moribund patients. Sinus bradycardia indicates a poor prognosis.
  Respiratory: Tachypnea or Kussmaul respirations secondary to metabolic acidosis are common. Respiratory arrest may occur.
  Neurologic: Symptoms resembling ethanol intoxication may be present shortly after a large exposure; may be of short duration. Progressively worsening headache, vertigo, weakness, apprehension, confusion begin to develop within hours, progressing to coma, convulsions in severely poisoned patients. Late onset symptoms (> 12-24 hours) include cerebral edema, cerebral hemorrhage and/or necrosis; basal ganglia infarcts. Putamenal necrosis is characteristic of severe methanol poisoning.
  GI: Nausea, vomiting, abdominal pain (may be severe).
  GU: Renal failure is uncommon; may be secondary to rhabdomyolysis.
  Fluids/Lytes/Acid-Base: Progressive metabolic acidosis with elevated anion gap is characteristic. Onset usually within 12 hours; may be delayed with ethanol co-ingestion. May be rapid following massive exposure.
  Musculoskeletal: Rhabdomyolysis may occur.
  Other: Elevation of serum amylase with or without pancreatitis has been reported.
  Late Sequelae: Partial or complete visual impairment, Parkinsonian-like symptoms, pseudobulbar palsy, cognitive defects.

Treatment

1. **Topical**: Remove contaminated clothing, wash skin thoroughly with soap and water. Monitor for systemic toxicity with large exposures.

2. **Ocular**: Flush eyes for 5 minutes with a gentle stream of tepid water. Obtain ophthalmologic opinion if irritation persists.

3. **Inhalation**: Remove from exposure. Treat respiratory tract irritation symptomatically. Monitor for systemic toxicity with large exposures.

4. **Ingestion: Initial risk assessment and patient disposition:**
   Sub-toxic exposure: No intervention required for unintentional exposures to following quantities, if history is reliable:
   - *Adult or adolescent*: ≤ 5 mL of 100% methanol or equivalent.
   - *Child*: very minor exposure, such as licking residue from a finger. If there is POTENTIAL for ingestion of a toxic dose (e.g. child found with an open container of antifreeze), refer to health care facility.

   Low risk exposure (**see** Figure 1): Monitor in hospital without antidote treatment, if *asymptomatic* patient with unintentional ingestion of approximately 1 mouthful:
   - *Adult or adolescent* ~5-20 mL of 100% methanol or equivalent.
   - *Child* < 0.3 mL/kg (< 5 mL max) of 100% methanol or equivalent are likely at low risk for developing toxicity.

   High risk exposure: Intentional exposures, *symptomatic* patients, or patients who have ingested:
   - *Adult or adolescent* > 20 mL of 100% methanol or equivalent.
   - *Child* > 5 mL of 100% methanol or equivalent.

   Antidote treatment may be indicated while awaiting laboratory confirmation of poisoning.

5. Gastrointestinal decontamination may be considered if patient has consumed a large quantity of toxin and presents within 1 hour post ingestion.

6. **Laboratory monitoring: *Initial assessment:*** simultaneous measurement of serum sodium, potassium, chloride, bicarbonate (total CO_2), glucose, urea, creatinine, osmolality, ethanol. Add blood gases if patient is *symptomatic*. Calculate anion gap and osmole gap. Repeat every 4-8 hours depending on clinical condition (**see** Figure 1). **See also** FOMEPIZOLE, ETHANOL antidote monographs.
   Methanol levels: Quantitative (gas chromatography) serum methanol level(s) are recommended for all high risk patients. Also, measure serum ethylene glycol with initial sample. N.B. Qualitative (colorimetric) methanol assay is prone to false positive results.

7. Calculate Anion and Osmole Gaps
   Anion Gap (AG): Elevated AG indicates accumulation of toxic acid metabolite. AG may remain normal for several hours after exposure, or with ethanol co-ingestion.

   $AG = Na^+ - (Cl^- + HCO_3^-)$
   reference range ~ 6-12

   Osmole Gap (OG): OG gives an imprecise estimate of serum methanol concentration, has poor sensitivity for detecting low methanol levels, and may be within normal limits in late presentation cases. Serum

osmolality (O_m), sodium, urea, glucose and ethanol must be measured *simultaneously*.

SI Units:
OG = O_m – ([2 x sodium] + urea + glucose + (1.25 x ethanol))
all values in mmol/L
reference range -10 to +10

Conventional Units:
OG = O_m – ([2 x sodium] + BUN/2.8 + glucose/18 + ethanol/3.7)
all values in mg/L
reference range -10 to +10

8. Treat metabolic acidosis aggressively. Administer IV sodium bicarbonate for arterial pH < 7.25-7.3. Prompt correction of acidosis reduces tissue penetration of formate and improves outcome. Monitor serum sodium and potassium closely. Maintain fluid and electrolyte balance.

9. **Antidote therapy**: Begin fomepizole (preferred) or ethanol therapy if:
   - Serum methanol level ≥ 6 mmol/L, ***OR***
   - Osmole gap > 10 (corrected for ethanol) with history of methanol exposure, ***OR***
   - History or strong clinical suspicion of methanol poisoning with at least *two* of the following criteria:
     - Serum bicarbonate < 20 mmol/L
     - AG > 16
     - arterial pH < 7.3
     - Osmole gap > 10

   If there is strong clinical suspicion of methanol poisoning but health care facility is unable to measure OG and AG, or if results cannot be obtained promptly, initiate antidote while awaiting lab results or patient transfer. **See** FOMEPIZOLE and ETHANOL antidote monographs.

10. **Folate** therapy: Administer either folic acid or leucovorin to enhance detoxification of formic acid. Indicated for all high risk patients. Continue supplementation until antidote course is completed. **See** FOLIC ACID/LEUCOVORIN antidote monograph.

11. ***Hemodialysis*** removes both methanol and formate, and corrects metabolic acidosis and electrolyte balance. Indications for hemodialysis include:
    - Arterial pH < 7.25 that fails to rapidly normalize with treatment, ***OR***
    - Visual defects, ***OR***
    - Other serious clinical effects (e.g. coma, seizures, severe electrolyte imbalance, renal impairment), ***OR***
    - Clinical condition deteriorates during antidote treatment, ***OR***
    - Initial measured or estimated methanol serum level > 15 mmol/L. Methanol is eliminated slowly during antidote therapy (serum level of 15 mmol/L would require ~ 3 days of treatment with antidote alone to reach sub-toxic levels).

    Continuous renal replacement therapy such as CVVHD clears the toxins more slowly than conventional hemodialysis (limited data). Conventional hemodialysis is preferred for rapid detoxification, if the patient can tolerate the procedure.

12. ***Therapeutic endpoint:*** Continue antidote with or without hemodialysis until metabolic acidosis is corrected, ***AND***
    - Serum methanol level is < 6 mmol/L, ***OR***
    - Osmole gap < 10 for 2 consecutive measurements (measured at least 1 hour apart during dialysis or 6 hours apart without dialysis). Post-dialysis rebound of serum methanol is usually not clinically significant.

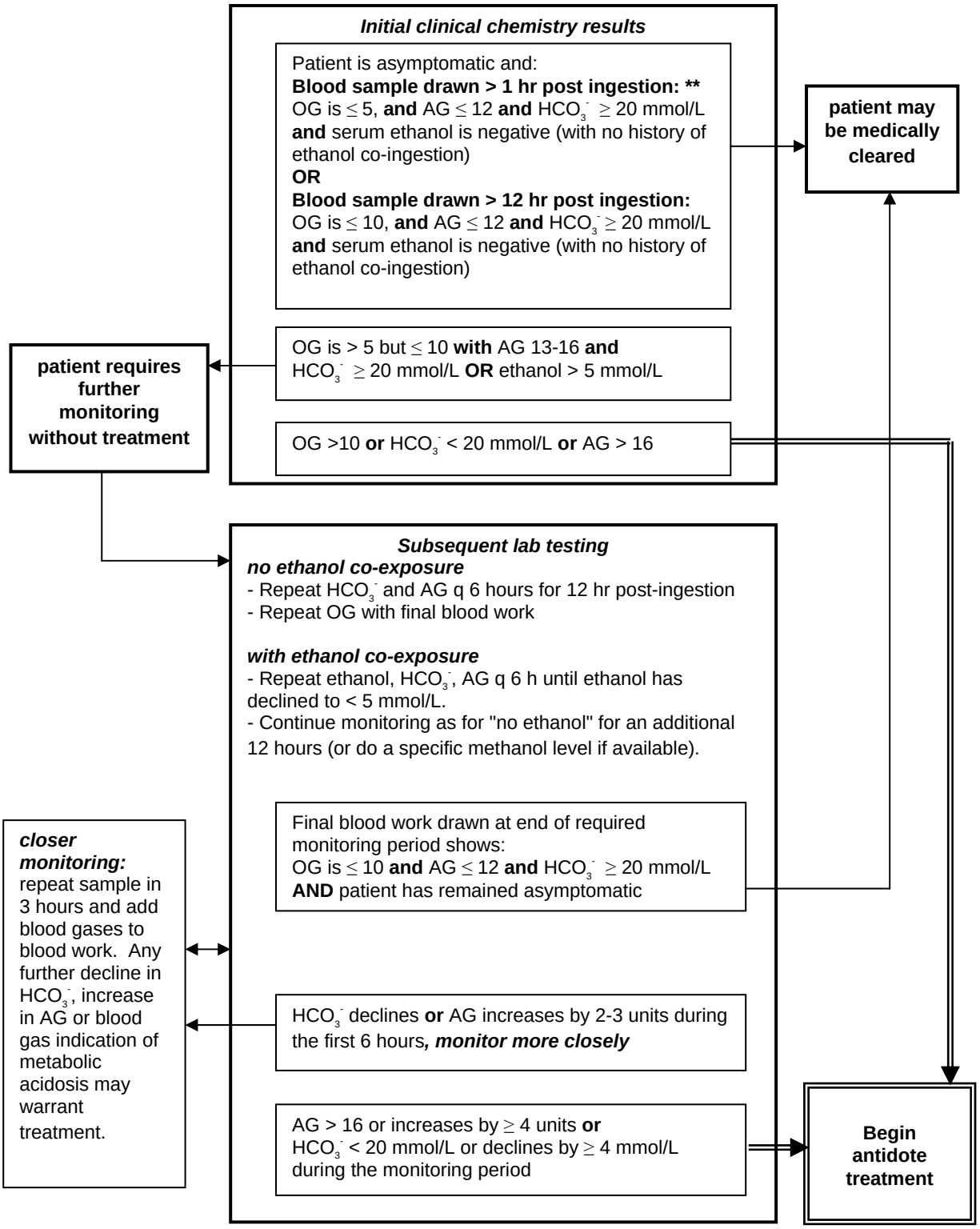
KEY POINTS ON NEXT PAGE

Key Points

- ✓ For *asymptomatic* patients with unintentional, small (~1 mouthful) exposures, see Figure 1 for risk assessment and patient disposition.
- ✓ May see initial intoxication followed by elevated anion gap metabolic acidosis, worsening neurologic symptoms, visual impairment, coma and death.
- ✓ Elevated osmole gap and anion gap. CAUTION: AG may be normal in early presentation, OG may be normal in late presentation.
- ✓ Treatment includes IV sodium bicarbonate for arterial pH < 7.3.
- ✓ Antidote (fomepizole or ethanol) if acidotic and/or serum methanol $\geq$ 6 mmol/L.
- ✓ Hemodialysis for arterial pH < 7.25, severe electrolyte imbalance, or serum methanol > 15 mmol/L.
- ✓ Therapeutic endpoint: Correction of metabolic acidosis AND one determination of serum methanol < 6 mmol/L OR two consecutive measures of OG < 10.

SEE NEXT PAGE FOR FIGURE 1

Figure 1. Monitor LOW RISK methanol exposures <u>without antidote</u>



*****BC DPIC monitoring guidelines for low risk patients are based on medical literature and clinical experience, but have not been formally validated

** Patients with peak OG ≤ 5, normal AG and HCO_3^- are unlikely to have MeOH ≥ 6 mmol/L