University of Anbar
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Clinical Toxicology 5th stage

BOTANICALS AND PLANTS-DERIVED TOXINS

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Herbal products:

Herbal product is constituted in general from leafy plant, animal products, and mineral products.

While many herbal products are harmless or possess minimal toxicity, some contain toxic ingredients that may not be identified on the label.

These unidentified ingredients may be unintentionally included in the product (e.g misidentification of a toxic plant as a desired non-toxic plant or contamination with pesticide residues or heavy metals) or introduced for increased effect (e.g addition of a pharmaceutical agent to an herbal preparation).

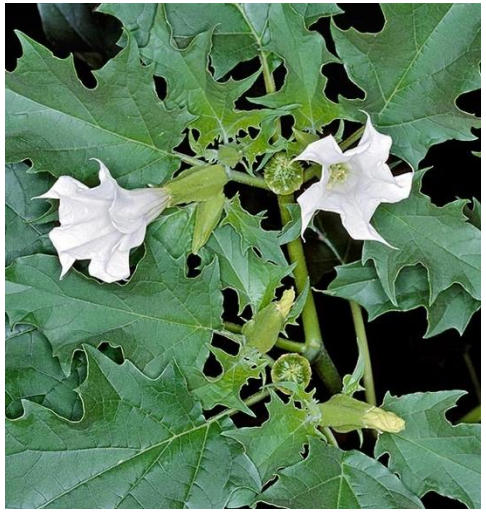
- Dietary supplements, including herbal products are regulated as a food product, thus does not require to be effective or safe prior to marketing.
- The FDA has little control over the marketing of herbal products but may prohibit sales of herbal products containing pharmaceutical agents.
- The FDA also may prohibit sale of an herbal product proven to have serious or unreasonable risk under conditions of use on the label or as commonly consumed.

Pathophysiology:

- Herbal products are generally heterogeneous, may produce multiple effects, and may affect multiple organ systems, including the CNS, CVS, GIT, hepatic, renal, and hematologic systems.

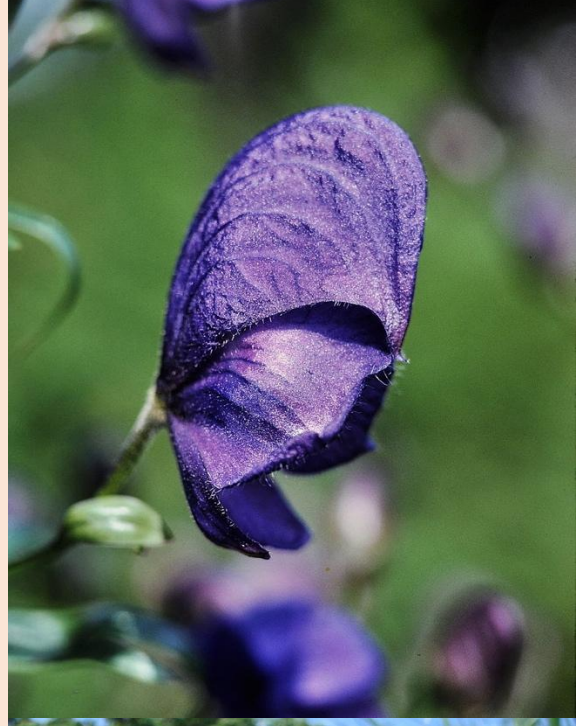
1. CNS:

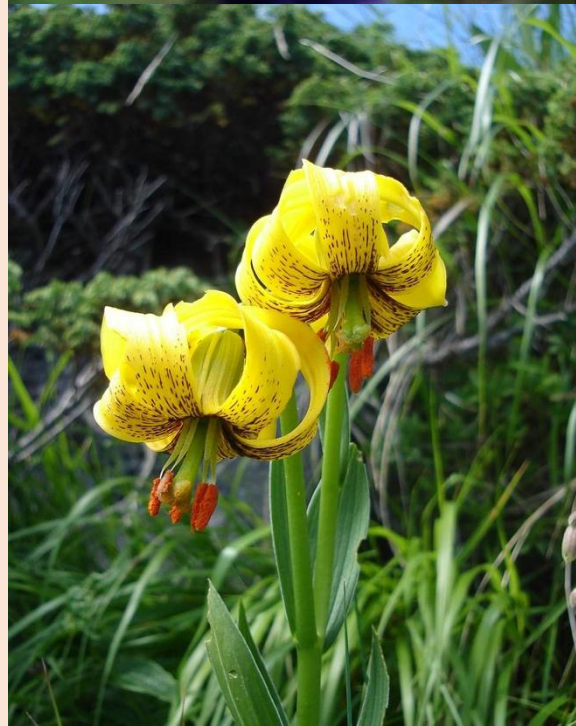
- Several herbal products can produce anticholinergic symptoms as (Atropa belladonna, Datura stramonium, Hyoscyamus niger)
- Kava-kava (Piper methysticum) is a herbal preparation that may be fermented into a beverage. Methysticin and kawain (a local anesthetic) are its main constituents; however, primary effects of kava- kava are anxiolytic, myorelaxant, and sedation and also has been associated with hepatotoxicity.
- Lobelia inflata and Nicotiana cause nicotine toxicity via Symp. ST. and release of NEP. Lead to CNS excitation and hypertension. Severe cases may progress to neuromuscular paralysis.



2. CVS:

- Cardiac glycosides and other cardioactive steroid contaminants may cause toxicity e.g. Digitalis lanata. Ephedra (Ma Huang) and ephedrine-containing products may produce cardiac stimulation, hypertension, peripheral vasoconstriction, chest pain, myocardial infarctions, and intracerebral hemorrhage.
- Aconitum species (contain aconitine) and Veratrum species (contain Veratrum alkaloids). These toxins block sodium channels in cardiac myocytes, resulting in conduction blockade, bradycardia, ventricular dysrhythmias and cardiovascular collapse.





3. Hepatic system:

- Hepatic toxicity has been reported with pyrrolizidine alkaloids, hepatomegaly and cirrhosis can caused by Heliotropium, Senecio, and Symphytum.
- **Jin Bu Huan** is a Chinese herbal preparation (a mixture of 5 herbs) with a long history of use as a sedative, analgesic and decongestant. Some preparations have caused fatal hepatic injury.

4. Hematologic system:

- Ginkgo biloba has been reported to increase bleeding times and may have contributed to intracranial hemorrhages.
- Yohimbine use associated with agranulocytosis.
- Jui, a Chinese herbal for detox and wt. loss associated with thrombocytopenia.

Contamination and adulteration:

- Some herbal products contain high concentrations of heavy metals, such as lead, mercury, and arsenic.
- Use of ayurvedic medications should arouse suspicion of heavy metals contamination.
- Some herbal preparations have been found to be adulterated with drug ingredients. For example, Caffeine, Acetaminophen, Hydrochlorothiazide, Ephedrine, Chlorpheniramine and cortisones.

- Chinese herbal medications have been an incredible source of contamination, with one study showing that, out of 247 traditional Chinese medicines investigated, a proportion were contaminated with arsenic (5-15%), lead (5%), and mercury (approximately 65%).

Adverse effects:

Classified into the following 4 types:

- **Type-A:** Pharmacologically predictable, dose dependent, and preventable by dose reduction.
- **Type-B:** Idiosyncratic, pharmacologically unpredictable, toxicity not correlated with dose, often immunologically mediated, often serious and potentially fatal.
- **Type-C:** Developed over long-term therapy, well-described, and may be anticipated.
- **Type-D:** Delayed effects (e.g, carcinogenicity, teratogenicity)

Physical Examination:

Evaluate the patient for the following:

- **Anticholinergic syndromes:** (ie, mydriasis, dry mucous membranes and axilla, urinary retention, tachycardia, disorientation, hallucinations suspect Atropa belladonna, Datura stramonium, Hyoscyamus niger).
- **Cardiac dysrhythmias:** (suspect cardiac glycoside e.g Digitalis or aconite toxicity).
- **Hepatomegaly** and jaundice: (suspect pyrrolizidine alkaloids and herbal teas).
- **Hematological assesment.**

Treatment:

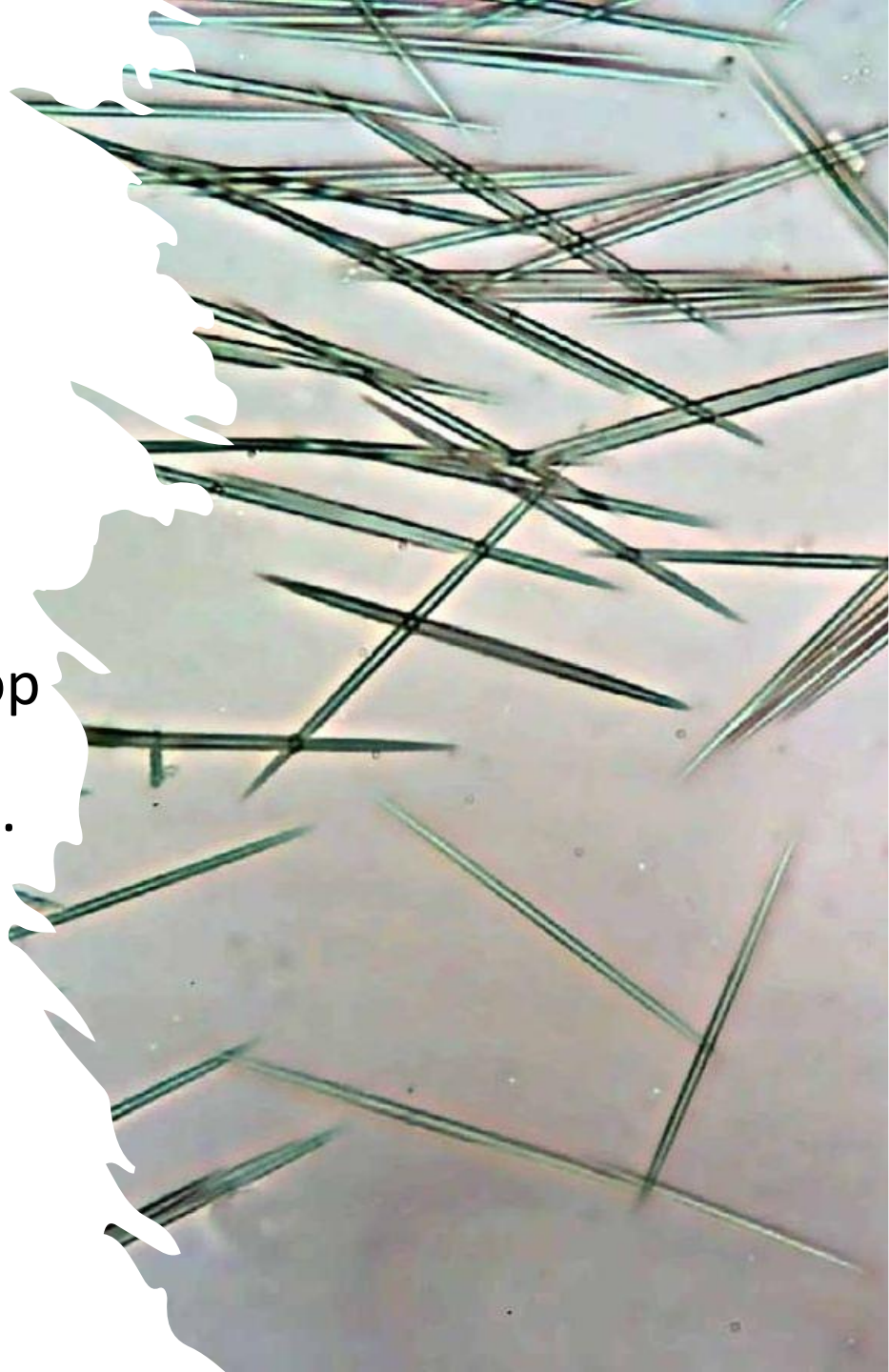
1. Stabilize the airway, assess respiration, and initiate respiratory assistance - Assess blood pressure and pulse.
2. Supportive care.
3. Decontamination protocols.
4. Specific treatments depend on the substance ingested e.g. specific antidotes for suspected cardiac glycoside toxicity (immune fab), N-acetylcysteine for hepatotoxicity, chelating agent for heavy metal poisoning.

Decorative plant poisoning:

- The plant species most frequently reported in human exposures were Philodendron, Caladium and Dieffenbachia species. they are commonly found in homes, offices, and waiting rooms.

Pathophysiology:

- Philodendron, Dieffenbachia, and Caladium contain calcium oxalate crystals packaged into bundles called raphides.
- Also the presence of proteolytic enzymes, in addition to specialized cells that forcibly expel the raphides, seems to be cause injury.
- When child accidentally eat the plant leaf, will develop immediate burning, irritation and swelling of the oral mucosa, which generally deters any further exposure.
- Cutaneous exposure can cause redness and irritation but is not nearly as common as oral exposure caused by chewing.
- Ocular exposure may result in eye pain, redness, and lid swelling.



Treatment:

1. All pieces of plants should be removed, and the mouth gently rinsed with water to eliminate all residual components.
2. Induced emesis and gastric lavage usually are not indicated.
3. Ingesting demulsifying agents, such as cold milk or ice cream, may help.
4. Based on severity of pain, analgesics, including acetaminophen, ibuprofen, or codeine derivatives, may be necessary.
5. Steroids may be beneficial for severe cases.
6. Antihistamines may improve patient comfort in moderate or severe cases.
7. Ophthalmology follow-up should be arranged for ocular injuries. Antibiotic eye drops, steroids, or both may be prescribed.

Mushroom poisoning:

- Mushrooms are the fruiting bodies of a group of higher fungi, toxicity occurs after ingestion of toxic mushrooms that similarly appearing to non-toxic one.
- There are thousands of species of mushrooms, but only about 100 species of mushrooms cause symptoms when eaten by humans, and only 15-20 mushroom species are potentially lethal when ingested.
- No simple rule exists for distinguishing edible mushrooms from poisonous.

- **The severity and clinical spectrum of mushroom poisoning depending on:**

1. Geographic location.
2. Genetic characteristics of the mushroom.
3. Growth conditions (Season).
4. The amount of toxin delivered.
5. Species consumed.
6. Preparation method (Boiling, cooking, freezing).
7. Individual response to the toxins.

- Mushroom poisoning can be classified into the 3 categories based on the timing of toxidrome:

1. **Early symptom category** – Symptoms generally appear within the first 6 hrs of mushroom ingestion and include GIT, allergic, and neurologic syndromes.
2. **Late symptom category** – Signs and symptoms begin to appear between 6 - 24 hrs after ingestion cause hepatotoxic syndromes.
3. **Delayed symptom category** – Symptoms appear more than 24 hrs after ingestion mostly cause nephrotoxic syndromes.

Each poisonous mushroom species contains 1 or more toxins, which may be classified on the basis of the mushroom's physiologic and clinical effects in humans, the target organ toxicity, and the time to symptom onset:

1. Cyclopeptides - Amatoxin
2. Gyromitrins (monomethylhydrazine)
3. Orellanine
4. Muscarine
5. Psilocybin
6. Muscimol and ibotenic acid
7. Coprine
8. Nephrotoxins (norleucine)
9. Myotoxins
10. Immunoactive toxins
11. Hemolytic toxins
12. GI irritants

The most commonly implicated in fatal mushroom poisonings worldwide.

Amanita phalloides

Amatoxins:

- Amatoxins, a highly poisonous mushroom, a cyclic **octapeptides** that are synthesized by Amanita species.
- At least 5 subtypes of amatoxins are known, the only significant human toxin being alpha-amatoxin, which inhibits RNA polymerase II and protein synthesis.
- Antidote: Thioctic acid, N-acetylcysteine and Penicillin-G.

Gyromitrins:

- Volatile hydrazine derivative synthesized by *Gyromitra esculenta*.
- In the stomach, gyromitrin is rapidly hydrolyzed into acetaldehyde and N-methyl-N-formyl hydrazine (MFH), which converted to N-methylhydrazine (MH) that inhibits a number of hepatic systems, including CYP-450 and glutathione, and causes hepatic necrosis.
- MH also inhibits pyridoxine kinase and interferes with all the pyridoxine-requiring enzymes in the body, including those involved in the synthesis of (GABA). The downregulation of GABA receptors in the brain leads to CNS hyperexcitability and convulsions.
- Antidote: Pyridoxine and glutathione.

Orellanine:

- Orellanine is a nephrotoxic compound that is synthesized by *Cortinarius mushrooms*.
- Is a colorless and crystalline in nature and may be converted into orelline, which itself may be toxic.
- Its main effects are on the renal tubular system, where it causes necrosis with relative sparing of the glomerular apparatus.
- No specific antidote but adequate dialysis may prevent renal complication in sever toxicity.

Norleucine:

- These mushrooms cause vomiting and diarrhea 1-12 hours after ingestion, followed by a transient elevation of AST and ALT, then oliguric renal failure in 3-6 days.
- It is important to note that renal failure occurs within days of ingestion, as opposed to orellanine-induced renal failure that has an onset over 1-2 weeks.

Psilocybin:

- Psilocybin and psilocin are serotonin (5-HT2) agonists and, when ingested, cause psychological effects similar to those of lysergic acid diethylamide (LSD).

Ibotenic acid and muscimol:

- Both are excitatory neurotoxins and may be mildly hallucinogenic.
- Ibotenic acid is structurally similar to glutamic acid and acts as an agonist at the glutamic acid receptors in the CNS.
- **Ibotenic acid is decarboxylated in vivo to muscimol** which is structurally similar to GABA and acts as a GABA-receptor agonist.

Muscarine:

- Muscarine stimulates M1 and M2 types of postganglionic cholinergic receptors in ANS.
- This action results in parasympathetic stimulation similar to that caused by the release of endogenous Ach at postganglionic receptors of smooth muscle and exocrine gland.
- Cholinergic symptoms included sweating, facial flushing, salivation, lacrimation, vomiting, abdominal cramps, diarrhea, urination, and miosis; occasionally, bradycardia, hypotension, and dizziness develop.
- Symptoms typically occur within 1 hr of ingestion and last for 4-24 hrs.
- In most cases, they resolve without drug therapy or with one dose of atropine.

Coprine:

- Coprine is an a.a that is metabolized to 1-aminocyclopropanol.
- This metabolite blocks acetaldehyde dehydrogenase, and in the presence of alcohol, acetaldehyde accumulates, resulting in a disulfiram reaction.

Involutin:

- Ingestion of *Paxillus involutus* may result in the acute onset of abdominal pain, nausea, vomiting, and diarrhea within 30 minutes to 3 hours of ingestion, followed by an immune complex-mediated hemolytic anemia with hemoglobinuria, oliguria, anuria, and acute renal failure.

GI toxins

- Hundreds of mushrooms contain toxins that can cause just GI symptoms (nausea, vomiting, diarrhea, and abdominal pain) similar to those observed with more dangerous mushrooms. They include Chlorophyllum, Boletus, and Agaricus.

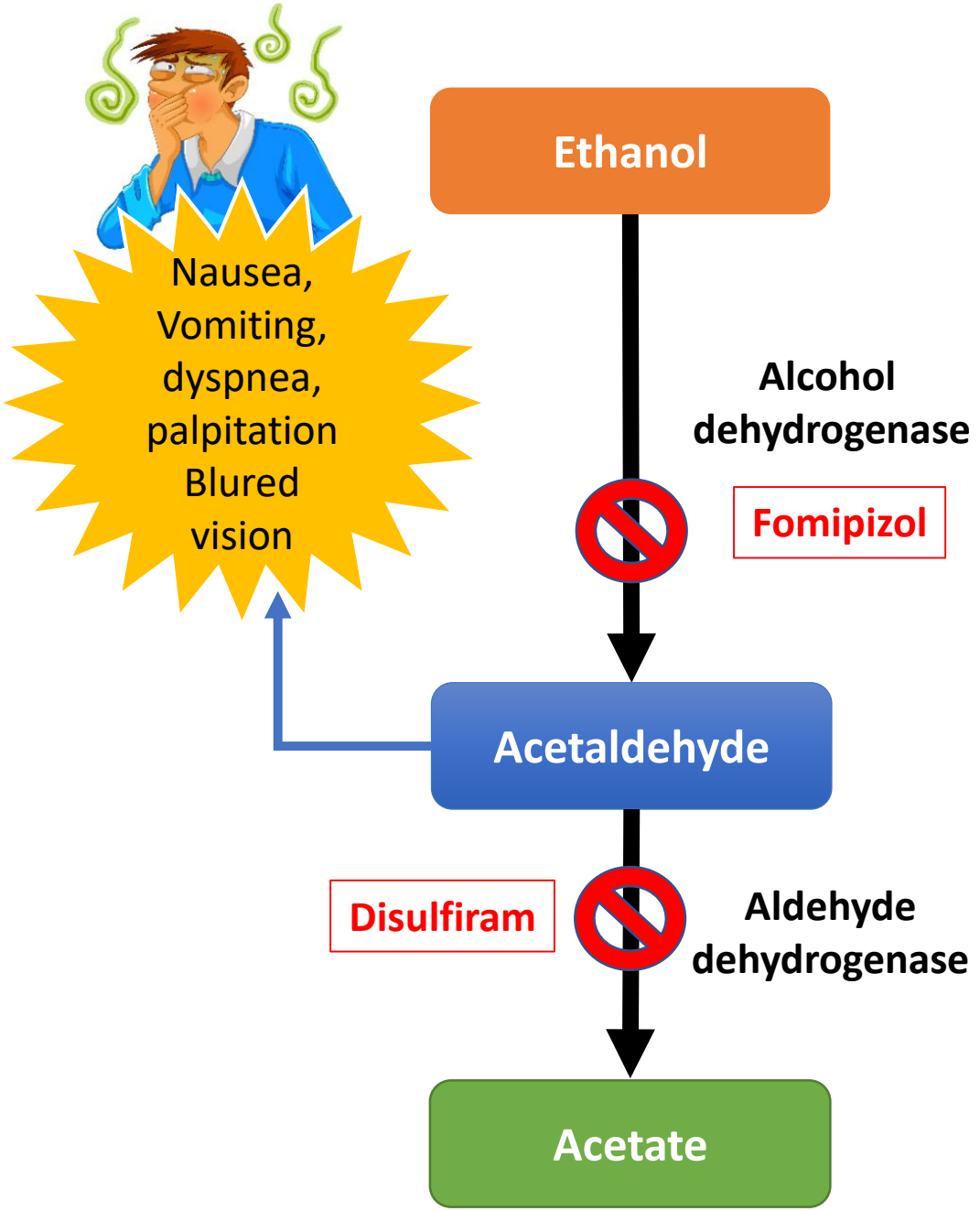
General complications & Predisposing factors:

- Respiratory: Aspiration pneumonia may occur with mushroom poisonings and involves loss of airway protective reflexes that complicated with asthmatic patient.
- Neurologic: Convulsions are common in gyromitrin poisoning, but they also complicated with hypoxia, acidosis, trauma, and hepatic failure and cerebral edema.
- Hepatic: Hepatic disease and hypoglycemia are complicate amatoxin and gyromitrin poisonings.
- Renal: Renal failure and hypoperfusion and shock complicate norleucine and orellanine poisoning.
- Hematologic: Methemoglobinemia and hemolysis may complicate gyromitrin poisoning.
- Trauma may complicate hallucinogenic mushroom poisoning.
- Electrolyte disturbances and hypovolemia can complicate any mushroom poisoning.

General treatment:

1. Early volume resuscitation (fluid rehydration) is important for liver and renal toxicity.
2. Gut decontamination, including whole-bowel irrigation.
3. Multiple doses of activated charcoal (regardless of the timing of presentation) should be administered repeatedly to **interrupt enterohepatic circulation of these toxins**.
4. Endotracheal intubation is recommended in all patients at risk of aspiration, and mechanical ventilation should be initiated in all patients with hypoxia, acidemia, and shock.
5. Agitation, commonly observed with hallucinogenic mushrooms, is treated with benzodiazepines.
6. Severe muscarinic symptoms may be treated with the infusion of small doses of atropine.

6. Patients with severe poisoning from disulfiram containing mushrooms may benefit from fomepizole which blocks alcohol dehydrogenase and, prevent the formation of the toxic aldehyde.



7. Blood transfusions may be required in patients with hemorrhagic diarrhea, blood loss, and severe hemolytic anemia.

8. Renal failure, treated with hemodialysis. Conventional **indications** for dialysis include fluid overload (with pulmonary edema), severe hyperkalemia, and acidosis.

9. Blood pressure support with dopamine and norepinephrine may be required when crystalloids and colloid infusions fail.

10. Hypoglycemia is treated with infusions of 10% dextrose.

Thank You!

- **Fomepizole** is used to treat **ethylene glycol** and **methanol** poisoning. It acts to inhibit the breakdown of these toxins into their active toxic metabolites. Fomepizole is a competitive inhibitor of the enzyme alcohol dehydrogenase,[6] found in the liver. This enzyme plays a key role in the metabolism of ethylene glycol, and of methanol.
- Ethylene glycol is first metabolized to glycolaldehyde by alcohol dehydrogenase. Glycolaldehyde then undergoes further oxidation to glycolate, glyoxylate, and oxalate. Glycolate and oxalate are the primary toxins responsible for the metabolic acidosis, and for the renal damage, seen in ethylene glycol poisoning.
- Methanol is first metabolized to formaldehyde by alcohol dehydrogenase. Formaldehyde then undergoes further oxidation, via formaldehyde dehydrogenase, to become formic acid.[7] Formic acid is the primary toxin responsible for the metabolic acidosis, and for the visual disturbances, associated with methanol poisoning.