Toxicology Times

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Mushrooms

Delicious, magical, intoxicating, “food of the gods”; but, also deadly. We are talking about Mushrooms, deemed “food of the gods” by ancient Egyptians and used throughout history for ceremonies and medicinal purposes. Hippocrates is known to have used the amadou mushroom as early as 450 BCE as an anti-inflammatory. Mushrooms recently are becoming more “in vogue” and being researched for their medicinal properties. UCLA Health reports 7 benefits from edible mushrooms including: decreased risk of cancer, lower cholesterol, protecting brain health, source of vitamin D, healthier gut and immune system, and lowering sodium. With recent shows on Netflix™ and Crave™ showcasing mushrooms and fungi coupled with the upcoming autumn season, this is a very relevant topic for consideration.

For all their potential benefits as medicine and food, foraging and ingesting mushrooms also comes with risks. First, it is very difficult as a lay individual to identify mushrooms appropriately and safely. Even Mycologists can have difficulties identifying them without close microscopic observation or even DNA analysis. Mushrooms at different stages of growth appear differently; toxic and non-toxic mushrooms may have very similar phenotypes; and the same mushroom growing on different soils can accumulate rare materials from one environment and not the other to allow toxin production. It is also important to know that toxic mushrooms can grow right beside non-toxic edible mushrooms. This creates a risk for accidental exposures toxic mushrooms even for knowledgeable foragers.

There are multiple different species of toxic mushrooms, a few of which are extremely toxic and possibly deadly. Types of toxicity can range from mild GI upset, and hallucinations, to more severe renal failure, SLUDGE symptoms, seizures, liver failure and death.

Mushroom classifications:

There are many other ways of classifications of mushrooms in the literature. The following is a simplified list for reference.

1) *GI irritants*- typically cause GI effects with 30mins-2hrs post ingestion with spontaneous resolution.
2) *Cyclopeptides (amatoxin)* –cause a later onset (6-24 hours post ingestion), Phase 1 toxicity, of GI symptoms of nausea, vomiting, & diarrhea which can be bloody lasting hours, progressing to Phase 2 (quiescent) where there is apparent recovery but a rise in liver enzymes, and finally Phase 3 (2-4 days post ingestion) with abdominal pain, jaundice, renal failure, liver failure, seizures, coma and death.
3) *Psilocybin ("magic mushrooms")* –symptoms usually start within 30mins-3hrs post ingestion with signs of mood alterations, impaired judgement, hallucinations, drowsiness.
4) *Muscarine* –symptoms of cholinergic toxicity including diaphoresis, salivation, lacrimation, bradycardia, abdominal pain, diarrhea, increased respiratory secretions with onset usually within 15-30 minutes.
5) *Ibotenic & Muscimol* (the "Mario" mushroom) – symptom onset is usually within 30mins-3hrs post ingestion with signs of intoxication and drowsiness followed by a state of confusion, euphoria, delirium, hallucinations (lasting 4-12hrs).
6) *Gyromitrin (Monomethylhydrazine)* (the "false morel")– symptoms have a latent period of 6-12hrs starting with a feeling of fullness progressing to watery diarrhea and vomiting. There is the potential for seizures, intense abdominal pain, jaundice, and cyanosis unresponsive to oxygen.
7) *Coprine* (the "inky cap") – onset within 20mins-2hrs after an ingestion of Alcohol up to 5 days after this mushroom has been ingested. Symptoms include flushing, tachycardia, swelling to hands, nausea, vomiting and sweating.

Mushroom Case:

A husband and wife present to the hospital with severe GI upset, nausea, vomiting and diarrhea with abdominal pain starting approximately 9 hours after they ingested a meal which contained mushrooms they picked earlier in the day. On presentation to ED both patients were tachycardic, diaphoretic and borderline hypotensive. They were unable to tolerate fluids by mouth due to vomiting.

They were immediately started on IV fluids and given antiemetics. Lab work included electrolytes, liver enzymes, creatinine, urea, venous blood gas and lactate. There were no concerns regarding the patients' ECGs. The ED physician had already ordered an ultrasound due to their symptoms. A sample of the dinner contents was being brought into the ED by family.

The Poison Centre was contacted approximately 1 hour after arrival in ED because of the history involving an ingestion of foraged mushrooms. The late onset of symptoms in the setting of a foraged mushroom meal was of immediate concern for the Poison Centre. This is the classic story of an amanita poisoning where liver failure can result in a liver transplant, or even death.

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Initial recommendations given by the Poison Centre included fluid resuscitation, monitoring electrolytes, managing GI symptoms and additional laboratory investigations to include an INR and group and screen. The Poison Specialist also recommended taking a urine sample and drawing extra tubes of blood for more specialized testing to be done upon the request of toxicologist on-call. The Specialist then consulted the Toxicologist on-call for more specific treatment recommendations.

Within the first 12 hours, both patients were noted to have a rise in liver enzymes. Over the next 24 hrs, the patients' liver enzymes (AST/ALT) and INR steadily rose, indicating significant liver injury. Both patients had a mild metabolic acidosis. During this time, the patients were given a single dose of activated charcoal. They were started on a Poison Centre protocol that includes IV N-acetylcysteine, Octreotide infusions and Cyclosporin. Both patients continued to receive fluid resuscitation and maintained satisfactory urine output.

On the second day, the husband started to improve. He was continued on treatment for another 24hrs while his liver enzymes trended down, at which point his IV medications were stopped. He was discharged on day 4 after his liver enzymes and INR returned to baseline.

In the meanwhile, it was determined by a mycologist, based on analysis of the meal contents provided, that the suspect mushroom was Galerina Marginata, which contains amatoxin.

Unfortunately, the wife had ingested a larger number of mushrooms than her husband. Her liver enzymes and INR continued to rise, and she developed a metabolic acidosis with elevated lactate.

Over time, she developed a GI bleed and hypotension, requiring fresh frozen plasma and a blood transfusion. Due to a deterioration in her level of consciousness, she was intubated and sedated. In consultation with the toxicologist, it was recommended to consult the liver transplant team. Due to an underlying past medical health history, she was denied transplant.

On Day 5 of the wife's course, her liver enzymes began to improve. She continued on NAC, Octreotide and Cyclosporin. She was extubated and transferred to a medical floor on day 7. With continued improvement of the patient's labs and clinical status, treatments were discontinued and she was discharged home with outpatient follow up on day 10.

Mechanism:

Amatoxin consists of both α-amanitin and phalloidin toxins. They are heat and cold stable and remain toxic whether frozen, raw or cooked.

There are two separate mechanisms of action:

1. *Phalloidin* interrupts actin polymerization and impairs cell membrane function which can result in liver injury through cholestasis, however due to its limited oral absorption contributes more to the GI dysfunction of nausea, vomiting & diarrhea.
2. *α-amanitin* is transported into the liver through an OATP (organic anion transporting polypeptide) transporter and once in the hepatocyte causes inhibition of RNA polymerase. This causes disruption in mRNA transcription and DNA synthesis resulting in cell death. This affects organs with high rates of cell division and replacement, such as the GI epithelium, hepatocytes, and kidneys.

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Clinical Phases:

Phase 1: This phase is a sub-acute phase in which severe GI symptoms develop including nausea, vomiting, diarrhea, and abdominal pain. This typically develops 6-24 hours post ingestion.

Phase 2: Develops 12-48 hours post ingestion and appears to be a "false" recovery period where the patients' symptoms may improve. This lends itself to possible premature discharge, highlighting the importance of accurate history taking and recognition of clinical phases (late onset symptoms) post mushroom ingestion. It is during this phase that α-amanitin causes damage to the hepatocytes with progressive rise in liver enzymes.

Phase 3: Occurs after 48 hours and is characterized by profound hepatic dysfunction with development of coagulopathy, hepatic encephalopathy, renal injury and without adequate treatment can result in death.

Treatments:

There have been many previously documented and proposed treatments in literature in the past. Many have the potential for adverse side effects and/or are ineffective. This is why prompt contact with your Poison Centre should be made for early accurate recommendations and consultation with a Toxicologist for specialized adjunct therapies.

If a suspected liver-toxic mushroom is ingested, aggressive supportive management of initial dehydration related to GI losses, including adequate IV hydration and electrolyte replacement is required. Amatoxin is excreted in the urine and therefore requires significant IV hydration. These patients are often already mildly to severely dehydrated due to severe GI losses and may require liters of fluid. Poor outcomes are associated with significant increases in AST/ALT, INR along with clinical symptoms of low blood pressure, GI bleed, or oliguria-anuria.

A single dose of activated charcoal may still be effective despite late presentation as the α-amanitin undergoes enterohepatic recirculation. Multiple doses are not indicated. Keeping patients NPO decreases the gallbladder's release of bile, limiting the enterohepatic recirculation. Octreotide may also help with this.

No specific antidote exists, however, there are adjunct therapies to improve oxidant effects and decrease or inhibit uptake of the toxin into the liver. Multiple different treatments have been used with varying affects. These treatments are often used in combination.

N-Acetylcysteine has been used due to its low risk profile, antioxidant effects and hepatoprotective properties as seen in acetaminophen toxicity.

High dose Penicillin G or Ceftazidime has been used in case reports with the proposed effect of interfering with hepatic uptake or intracellular interruption of the toxin. Both treatments have a risk of renal injury due to the high dosing required.

Cyclosporine is another adjunct that is being considered as it is a potent inhibitor of OATP transporters which would inhibit the uptake of the α-amanitin toxin into the liver. In fact, cyclosporin is a better drug for blocking OATP and would now be the recommended treatment.

Other treatments including octreotide (decreases biliary emptying), cimetidine (CYP450 inhibitor), thioctic (α-lipoic) acid and silibinin (competitive inhibitor of OATP transporter) have also been proposed to have positive affects post α-amanitin toxicity. There is limited evidence to support the use of these therapies. Silibinin (milk thistle extract) was available in the US in an open label trial. As this trial has since been terminated, it cannot be accessed in Canada.

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Learning Pearls:

1) Prompt **consultation with Poison Centre** and Toxicologist for specialized treatments must occur as there is no specific antidote.
2) Thorough **accurate history,** including history of mushroom ingestion (foraging history), timing of ingestion and symptom onset are very important in determining potential toxicity of mushrooms ingested.
3) When possible, **obtain samples of the mushroom** ingested (actual mushroom, picture, meal and/or emesis) for assessment by a mycologist.
4) All mushroom ingestions (even magic mushrooms), **with late onset of symptoms**, require liver enzymes be drawn as toxic and non-toxic mushrooms can grow closely together.

There have been recent cases of individuals developing liver injury after use of "magic" mushrooms obtained from dispensaries. This highlights the concern about mushroom ingestions and possible toxic mushrooms being ingested unintentionally with other mushroom use.

Mushrooms

Please unscramble the words below

Created on TheTeachersCorner.net Scramble Maker

1. ICNPREO	Cautious with alcohol.
2. DERTOEITOC	Adjunct therapy
3. ONOPSI NERCTE	Who do you call? (not Ghostbusters)
4. SNIAMURCE	SLUDGE
5. SNYILIPOCB	"Magic"
6. TIMANAA	Deadly
7. BNTIIEOC& IMOMSULC	"It'sa Mario"
8. IOYNGTRMRI	A "false" mushroom
9. NOPCSYCROLI	Adjunct therapy

1. ICNPREO — coprine
2. DERTOEITOC — octreotide
3. ONOPSI NERCTE — poison centre
4. SNIAMURCE — muscarin
5. SNYILIPOCB — psilocybin
6. TIMANAA — amanita
7. BNTIIEOC& IMOMSULC — ibotenic & muscimol
8. IOYNGTRMRI — gyromitrin
9. NOPCSYCROLI — cyclosporin

REFERENCES

Horowitz, B. Z., & Moss., M. J. (2023, January 15). *Amatoxin mushroom toxicity - statpearls - NCBI bookshelf*. Amatoxin Mushroom Toxicity. https://www.ncbi.nlm.nih.gov/books/NBK431052/ Affiliations Oregon Health Science University

Stamets, P., & Zwickey, H. (2014, February). *Medicinal mushrooms: Ancient remedies meet modern science*. Integrative medicine (Encinitas, Calif.). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4684114/

7 health benefits of mushrooms. UCLA Health System. (n.d.). https://www.uclahealth.org/news/7-health-benefits-of-mushrooms

Trabulus, S., & Altiparmak, M. R. (2011). Clinical features and outcome of patients with amatoxin-containing mushroom poisoning. *Clinical Toxicology*, *49*(4), 303–310. https://doi.org/10.3109/15563650.2011.565772

Stein, C. M., Wu, P. E., Scott, J. A., & Weinerman, A. S. (2015). Fulminant hepatic failure following ingestion of wild mushrooms. *Canadian Medical Association Journal*, *187*(11), 822–824. https://doi.org/10.1503/cmaj.150080

Manautou, J. E., Campion, S. N., & Aleksunes, L. M. (2010). Regulation of hepatobiliary transporters during liver injury. *Comprehensive Toxicology*, 175–220. https://doi.org/10.1016/b978-0-08-046884-6.01008-3

Garcia, J., Costa, V. M., Carvalho, A., Baptista, P., de Pinho, P. G., de Lourdes Bastos, M., & Carvalho, F. (2015). Amanita phalloides poisoning: Mechanisms of toxicity and treatment. *Food and Chemical Toxicology*, *86*, 41–55. https://doi.org/10.1016/j.fct.2015.09.008

Goldfrank L, Flomenbaum N, Lewin N, Weisman R, Howland M, Hoffman R (2015). *Goldfrank's Toxicologic Emergencies* (10th ed.), New York: McGraw Hill Education

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