TOXIC MUSHROOM INGESTIONS

A Toxidrome Based Approach

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OBJECTIVES

• Ability to recognize specific toxidromes
  • Requires minimal knowledge of mushrooms!

• Recognize the importance of interval from ingestion to onset of symptoms

• Ability to describe basic mushroom anatomy

• Approach to triage and treatment
OUTLINE

• Brief introduction to mushrooms

• Review of specific toxins/toxicidromes and the mushrooms that cause them

• Case reviews
SCOPE OF THE PROBLEM

• 6,000 reported toxic mushroom ingestions reported in US in 2013

• Represent <1% of poisonings reported to poison control

• 4-5 deaths per year in US over the last decade

• Majority of exposures involve gastrointestinal toxins only

• UPHSM sees average 1-2 serious poisonings per year
SCOPE OF THE PROBLEM

- Poisonings may result from
  - Mistaken identity
  - Inadvertent ingestion of mushroom (toddlers)
  - Intentional poisoning
  - Increase in foraging over the past decade leads to increasing problems with inexperienced foragers
The Mushroom Life Cycle
Gills
Pores
Teeth
Scales and ring
Volva
Staining
IMPORTANT CHARACTERISTICS

- Color/staining
- Substrate (if known)
- Ring present/absent
- Volva present/absent
- Scales present/absent
- Gills, pores or teeth on underside of cap
- If not a cap mushroom, describe the shape, etc.
  - Club shaped, brain-like, coral-like, shelf, etc.
- Odor
Important Questions to Ask

• Symptoms at presentation?

• Any alcohol consumed?

• How many specimens were consumed?

• Had patient consumed this mushroom before?

• Is a specimen of the mushroom available?

• Photograph of mushroom?

• How long after ingestion did symptoms begin?
TOXINS/TOXIDROMES

• Early onset
  • 1-6 hours post ingestion

• Delayed onset
  • > 6 hours post ingestion
EARLY ONSET

- GI Irritants
- Muscarine
- Coprine
- Isoxazoles
- Psylocybin/hallucinogens
GI Irritants
GI IRRITANTS

• Heterogeneous group of toxins

• Some are idiosyncratic—i.e., some people do not tolerate morels

• Characterized by abdominal pain, nausea, vomiting and diarrhea

• Onset: 30 minutes to 3 hours post ingestion
Gastrointestinal Irritants
Treatment

• Hydration and electrolyte replacement are most important aspect of treatment

• Anti-emetic medications (odansetron, prochlorperazine) may be helpful

• Anti-diarrheal medications may also help

• No long term sequelae of toxicity
MUSCARINE
Ach vs Muscarine

Muscarine
**Muscarine receptors**

<table>
<thead>
<tr>
<th>Locations</th>
<th>Muscarinic receptors (M-receptor)</th>
<th>Nicotinic receptors (N-receptor)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>smooth muscle, gland and cardiac muscle</td>
<td>skeletal muscle -- motor ending-plate (N2 N2), ganglia-postsynaptic membrane(N1),</td>
</tr>
<tr>
<td></td>
<td>• M--- smooth muscle, gland</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• M1 -- ganglia, gland</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• M2 -- heart</td>
<td></td>
</tr>
<tr>
<td>Effect</td>
<td>inhibiting the cardiac muscle, <strong>exciting the smooth muscle &amp; gland</strong></td>
<td>N2: exciting skeletal muscle, N1 exciting the postsynaptic neuron in ganglia</td>
</tr>
<tr>
<td>Antagonist</td>
<td>Atropine</td>
<td>N1: hexamethonium, N2: decamethonium</td>
</tr>
</tbody>
</table>
Muscarine clinical correlation

- Causes a syndrome of cholinergic excess with symptom onset within 30-60 minutes of ingestion
  - Salivation
  - Lacrimation
  - Urinary incontinence
  - Diarrhea
  - Gastrointestinal upset
  - Eye (blurred vision)
  - B/Bradycardia/bronchorrhea
Muscarine treatment

- Supportive care with fluid resuscitation
- Bronchodilator
- If significant symptomatic bradycardia, atropine at routine therapeutic doses
- Atropine is also indicated for severe bronchorrhea
- Expect complete recovery without long term sequelae
Coprine
Coprine Structure
Coprine--Clinical

- Inhibits aldehyde dehydrogenase leading to accumulation of aldehydes upon metabolism of ethanol

- Disulfuram-like reaction requires *co-ingestion of alcohol*

- Onset of symptoms within 30-60 minutes

- Symptoms include agitation, palpitations, tachycardia, diaphoresis, gut cramps
Coprine--Treatment

• Supportive care with fluids

• May develop dysrhythmias (usually supraventricular) that can be treated as one would normally approach

• No long term sequelae
ISOXAZOLE
Isoxazole—Structure
Ibotenic acid  Muscimol
Isoxazoles--Clinical

Onset of action 30-60 minutes post ingestion

• Two types of isoxazole are present
  • Muscimol: sedating (stimulates GABA receptors)
  • Ibotenic acid: excitatory (stimulates glutamic acid receptors)

• May cause significant agitation, muscle fasciculations and seizures if Ibotenic acid is predominant

• May induce coma if Muscimol is predominant

• Concentrations of components varies from specimen to specimen
Isoxazoles--Treatment

• Supportive care and reassurance if hallucinations are bothersome

• Seizures may respond to benzodiazepines, although may require higher than normal doses

• Although generally not considered a deadly toxin, protracted seizures may lead to aspiration and death
Hallucinogens
Psilocybe cubensis
Psilocybin--Structure
Psilocybin -- Clinical

- Onset of action is 30-90 minutes post-ingestion
- Produces hallucinations
- May cause transient nausea and vomiting
- Resolves without intervention
- Benzodiazepines may help with agitation and disorientation
Psilocybin--Treatment

- Treatment is purely supportive—reassurance, benzos may help if agitation is present

- Hallucinations usually subside after 3-6 hours

- No long term sequelae (flashbacks are reported with less frequency than with other hallucinogens).
DELAYED ONSET TOXINS

- Gyromitrin
- Amatoxin
- Orellanine
- Allenic norleucine
- Tricholoma myotoxin
Gyromitrin
Gyromitrin--Clinical

- The parent compound is metabolized to monomethylhydrazine
- Adverse effects include hemolysis and seizures
- Toxin is water soluble and heat labile
Gyromitrin $\rightarrow$ Monomethylhydrazine
GYROMITRIN

- MMH inhibits Glutamate dehydrogenase
- Glutamate (excitatory NT)≠GABA (inhibitory)
- Results in hyperexcitability and seizures
- Inhibits Phosphofructokinase
- Multiple toxic metabolic intermediaries-hydrazones, etc. that injure lipid molecules in cell walls
Gyromitrin—Clinical

• Initial symptoms: severe nausea, vomiting, diarrhea, headache and may also include seizures
  • Symptom onset 8-12 hours post ingestion

• May develop methemaglobinemia

• In severe intoxication there is a progression of illness to hepatic injury and renal failure (pigment induced)

• Symptoms are similar to those of toxicity from INH, also a hydrazine

• Seizures are the most serious acute manifestation of toxicity
Gyromitrin--Treatment

- Supportive care with fluid and electrolyte replacement
- Methemaglobinemia can be treated with methylene blue
- Seizures respond to routine anticonvulsants
- Check glucose and provide D50 if hypoglycemia present
- May require dialysis and possibly liver transplantation
Amatoxin
Amanitin Structure
Amatoxin Clinical

- Inactivates DNA dependent RNA polymerase
- Requires active transport into the cell by organic anion transporting polypeptide 1B3 and sodium taurocholate co-transporter
- Symptom onset: at least 6 hours after ingestion, often longer
- Initial symptoms include vomiting, diarrhea and gut cramps
- Asymptomatic period of latency may occur lasting several days
- May lead to massive hepatic necrosis and hepatic failure
Amatoxin treatment

• Initial treatment is supportive

• Activated charcoal may be of some benefit as the toxin undergoes enterohepatic circulation

• Liver transplantation is definitive treatment for those with hepatic injury that do not recover
Amatoxin treatment-New Horizons

- IV Sylbinin (Legalon®)
  - Inhibits transmembrane transport of toxin
  - Study is ongoing, but early results appear favorable
  - 50% reduction in mortality compared with historical controls

- Biliary drainage

Orellanine
Orellanine
Orellanine Clinical

• Causes acute interstitial nephritis and kidney failure

• Nature of the insult is unclear

• Initial mild gastroenteritis-type illness that passes spontaneously

• More severe symptoms are delayed for days after ingestion.
Orellanine Treatment

- No specific antidote known

- Initial management the same as for any presentation of acute renal failure

- Patients with persistent renal failure may require long term dialysis and/or transplantation
Tricholoma myotoxin
Tricholoma Myotoxin Clinical

Little is know about the structure of this toxin or it’s mechanism of toxicity

First described in France in the 1990s

The mushrooms have been commonly eaten for many years

Effect (rhabdomyolysis) appears to be cumulative and to require repeated exposure to cause toxicity

Wild-Mushroom Intoxication as a Cause of Rhabdomyolysis. Bedry, et. al NEJM, 345, 11, 9-13-01 798-802
Tricholoma Myotoxin Treatment

• No specific treatment is known

• Muscle enzyme abnormalities normalize with abstinence from the mushroom

• With severe rhabdomyolysis may develop pigment induced acute tubular necrosis

• Fluids and alkalinization of the urine, as for rhabdo of any cause, may help to minimize risk of renal injury
Allenic Norleucine
Allenic Norleucine Clinical

- **Late onset of toxicity** although may cause early (within 6 hours) gastroenteritis

- Ultimately causes renal failure from interstitial nephritis

- May take 10 days or more to cause symptomatic renal failure

- Temporal link between ingestion and onset of renal failure may be missed
Allenic Norleucine Treatment

- Treat as for any cause of acute renal failure
- Dialysis is appropriate with severe oliguric renal failure.
- May recover normal renal function

*Amanita Smithiana Mushroom ingestion: A Cause of Delayed Renal Failure and Literature Review. West, et al. Journal of Medical Toxicology 5,1, 2009 32-38*
Encephalopathic mycotoxicity
Encephalopathic mycotoxicity

- Mechanism of toxicity is poorly understood

- Toxicity occurred in people in Japan who had known chronic renal failure and ingested Pleurocybella

- Causes a syndrome of acute encephalitis
Case #1

• 64 yo man presents to the ED stating he ate poison mushrooms and is now sick. His family have a picture of *Amanita virosa* and believe this is the mushroom he has ingested. He ate a “handful” of the mushroom. He did not consume alcohol proximate to the ingestion.

• Patient notes onset of nausea, vomiting and diarrhea approximately **12 hours after ingestion**.

• He is taking multiple medications: hydrochlorothiazide, celecoxib, omeprazole, allopurinol, fluoxetine, rosuvastatin, amlodipine, lisinopril.

• PMHx significant for mild aortic stenosis and osteoarthritis.
Case #1

- Exam: Uncomfortable man with orthostatic blood pressure changes and dry mucous membranes
- There is no scleral icterus
- Cardiac exam reveals a 2/6 systolic murmur
- Remainder of exam is stated to be normal
Case #1
Case #1

- Labs:
  - AST: 60
  - ALT: 59
  - BUN: 59
  - Creatinine: 5.7
  - INR: 1.1
  - CK: 1383
  - Myoglobin: 3293
Case #1

• Clinical course:

• Patient hydrated with return of BUN and creatinine to normal within 48 hours

• Transaminases, bilirubin, INR remained normal

• Discharged from the hospital in good and stable condition

• Transaminases remained normal 2 and 6 weeks post discharge
Case #2

- 75 yo man seen at a local emergency department after eating “beefsteak” (*Gyromitra esculenta*) mushrooms. He stated that he had eaten large amounts of these mushrooms for several days in a row (he had eaten them before without ill effect) and became ill with vomiting, profuse diarrhea, abdominal pain and bloating and passage of red urine after the third meal.
Case #2

- PMHx significant for hypertension, hyperlipidemia, atrial fibrillation

- PSHx significant for bioprosthetic aortic valve replacement

- Meds: coumadin, hydrochlorothizide, Lipitor, diltiazem

- Exam: VS normal at time of my exam. Marked scleral icterus, dry mucous membranes and a soft systolic murmur.
Case #2

- Labs:
  - WBC: 8.6 with normal differential
  - Hb/Hct: 12.2/37.5
  - Peripheral smear: Anisocytosis and Shistocytosis noted
  - INR: 2.1
  - Bilirubin: 6.6
  - AST: 1141
  - ALT: 747
  - Alk Phos: 61
  - No evidence of hepatitis A,B or C infection
  - UA: Dipstick positive for blood with no RBCs seen
Case #2

Hospital Course:

- Patient was aggressively hydrated and liver functions slowly returned to normal
- Discharged with normal kidney function and improved transaminases
- 6 month follow-up: complete recovery
Summary

• Early onset of symptoms suggests a less serious ingestion (beware multiple ingestions)

• Delayed onset of symptoms suggests a more serious ingestion

• Few specific antidotes other than Atropine for muscarine intoxication and sylbinin for amatoxin ingestion

• Early recognition and intervention is the most important prognostic factor
The ugliest mushroom I have ever seen?
References and Resources


• Addison, James. *An Interesting Case of Mushroom Poisoning*. McIlIlvainea 23, 1-5.
References and Resources

- Beug, Michael W., Marilyn Shaw and Kenneth Cochran. *Thirty-Plus Years of Mushroom Poisoning: Summary of Approximately 2,000 Reports in the NAMA Case Registry*. McIlvainea 16:2, Fall 2006. 47-68.
References and Resources


• Kirchmar, Martin, et. al. *Amanita poisonings resulting in acute, reversible renal failure: new cases, new toxic Amanita mushrooms*. Nephrology Dialysis Transplantation 2012. 27. 1380-1386.