Mushroom Poisoning Cases in Dogs and Cats: Diagnosis and Treatment of Hepatotoxic, Neurotoxic, Gastroenterotoxic, Nephrotoxic, and Muscarinic Mushrooms

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KEYWORDS

- Amanita • Amanitins • Hepatotoxic mushrooms
- Gastrointestinal irritation • Liver failure • Neurotoxicosis
- Toxicosis

There is no simple test that distinguishes poisonous from nonpoisonous mushrooms, and accurate mushroom identification will require consultation with an experienced mycologist. Although it is estimated that only a few species are lethal, it is not clear how many of the mushrooms worldwide contain potentially toxic compounds. New species are being discovered continuously, and for many species, toxicity data are unavailable. In the United States, mushroom poisonings of humans and animals continue to be a medical emergency and demand extensive efforts from clinicians and toxicologists. It is challenging to establish a confirmed diagnosis of mushroom poisoning in animals because of limited diagnostic assays for toxin detection. Currently, only the detection of amanitins, psilocin, and psilocybin is available at select veterinary toxicology laboratories. Thus, only limited data on confirmed mushroom poisonings in animals exist. Because the risk of animals to ingest toxic mushrooms, particularly in dogs due to their indiscriminant eating habits, is much

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The authors have nothing to disclose.

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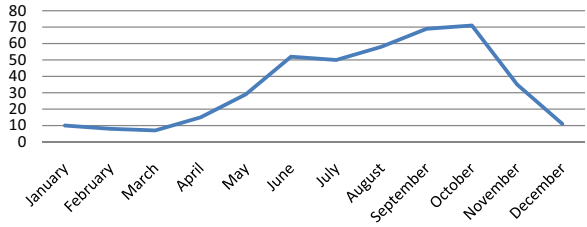

Fig. 1. ASPCA APCC average number of reported mushroom exposure cases by month (January 1, 2006–January 1, 2011).

greater than the risk for humans, mushroom poisoning in animals is likely underreported.

Human and animal mushroom poisoning cases can be reported to the North American Mycological Association's Mushroom Poisoning Case Registry. Reports may be submitted online at www.sph.umich.edu/~kwcee/mpcr. In addition, the website provides a list of volunteers willing to assist in the identification of mushrooms. The volunteers are listed by region. Alternatively, many universities have lists of mycologists available for assistance.

INCIDENCES

The ASPCA Animal Poison Control Center (APCC) received 2090 incident reports of potential mushroom exposures in animals between January 1, 2006, and December 31, 2010. A majority of these exposures were reported in dogs. These cases on average involved 433 canine and 6 feline exposures per year (some incidents involved multiple animals). During this period, there were also reports of mushroom exposure in 7 caprine, 2 mustelid, 1 avian, 1 lagomorph, and 1 marsupial case. The fall months (September and October) had the highest number of cases reported to the APCC (**Fig. 1**). Regionally, in the continental United States, the Northeast region had the largest annual average number of reported potential exposures (**Fig. 2**). In the majority (94.6%) of the reported exposures, the type of mushroom ingested was unknown at the time of the original call to the APCC; thus, the agent was classified as "unknown mushroom." These data reflect overall trends, but due to reporting and identification constraints, they are not representative of confirmed exposures/diagnoses of mushroom poisonings. Improved identifications and reporting in small animals may increase the accuracy of incidence data in the future.

HEPATOTOXIC MUSHROOMS

The majority of confirmed mushroom poisoning cases reported in animals are caused by hepatotoxic mushrooms that contain cyclopeptides. While a number of mushroom genera (*Amanita*, *Galerina*, *Lepiota, Cortinarius, Conocybe* spp) contain the hepatotoxic cyclopeptides,[1] *Amanita phalloides* is considered most toxic worldwide. *A phalloides*, also known as Death Cap (**Fig. 3**), is found throughout North America with 2 distinct ranges: one on the West Coast from California to British Columbia and one on the East Coast from Maryland to Maine.[2] The mushroom grows commonly in association with oaks, birch, and pine and is the species most frequently resulting in fatalities in humans[3] and probably also in dogs. *A phalloides* is particularly common in the San Francisco Bay area and is most abundant in warm, wet years. The large fruiting bodies appear in the late summer and fall and have a smooth, yellowish-green

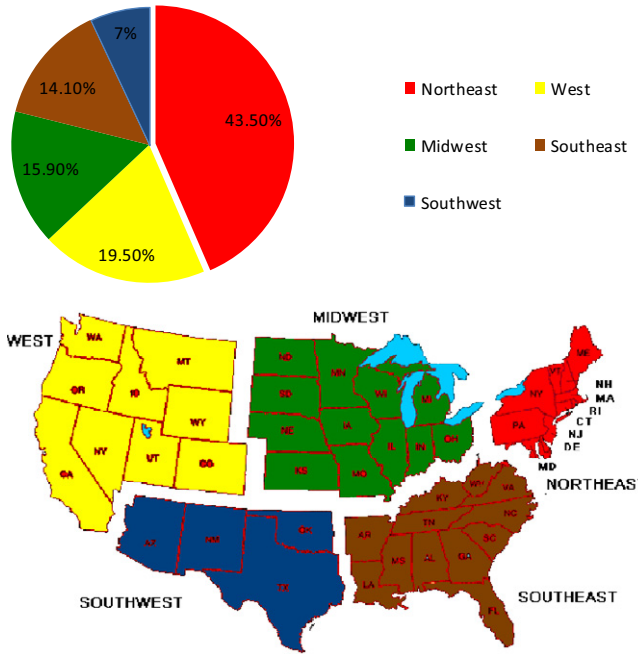

Fig. 2. ASPCA APCC average annual number of reported mushroom exposures by region (January 1, 2006–January 1, 2011).

to yellowish-brown cap, white gills, a white ring around the upper part of the stem (veil), and a white cup-like structure around the base of the stem (volva). *A ocreata,* also referred to as the Western North American destroying angel (**Fig. 4**), grows exclusively along the Pacific Coast from Baja California to Washington and is commonly found in sandy soils under oak or pine. *A ocreata* occurs commonly in

Fig. 3. *Amanita phalloides.* (*Courtesy of* Dr R. Michael Davis, UC Davis.)

Fig. 4. *Amanita ocreata.* (*Courtesy of* Dr R. Michael Davis, UC Davis.)

California. The fruiting bodies are usually found in later winter and spring and have a white or cream-colored cap, white, short gills, a white stem with a white, thin, broken, partial veil, and a white, thin volva.

These toxic species contain a number of different toxins, most notably the amatoxins, which include the hepatotoxic amanitins responsible for most poisonings and fatalities. In humans, the estimated oral LD_{50} of α-amanitin is 0.1 mg/kg body weight, which is similar to an oral LD_{50} for methyl-γ-amanitin in dogs of 0.5 mg/kg body weight.[4] On average, species of *A phalloides* and *A ocreata* contain 1.5 to 2.3 mg amanitins per gram of mushroom dry weight.[5] Therefore, one mushroom cap can contain a lethal dose for an animal or a human.

Amanitins inhibit RNA polymerase II, which shuts down transcription and leads to decreased protein synthesis.[6] Cells with a high metabolic rate, including hepatocytes, crypt cells, and proximal convoluted tubules of the kidneys, are most prone to the toxic effects. Apoptosis of hepatocytes[7] and amanitin-induced insulin release[8] are additional effects that contribute to the pathogenesis.

Differences in bioavailability account for differences in species sensitivities. The rate of gastrointestinal (GI) absorption of amanitins is estimated to be much greater in dogs than in mice and rabbits; rats appear relatively resistant to the toxic effects of amanitins. Once absorbed, α-amanitin is taken up by hepatocytes via OATP1B3, an organic anion-transporting polypeptide.[9] Amanitins do not undergo metabolism and are primarily excreted unchanged in urine with a small amount (up to 7%) eliminated in bile. Amanitins are detectable in serum and urine well before any clinical sign of poisoning, whereas routine laboratory tests such as complete blood count and serum chemistry profiles are unremarkable until liver or kidney damage has occurred. In humans with *A phalloides* exposure, α- and β-amanitins are present in plasma for up to 36 hours and in urine for up to 72 hours post exposure.[10] The plasma half-life of amanitins in dogs is short ranging from 25 to 50 minutes. Plasma and urine amanitin concentrations do not seem to correlate with the clinical severity or outcome.

Amanitin poisoning is clinically divided into 4 phases, although not all cases present with those 4 consecutive stages. The initial phase is a latency period of approximately 6 to 12 hours, during which no clinical signs of illness occur after the ingestion. During the second phase, poisoned animals develop GI signs (vomiting,

diarrhea, evidence of abdominal pain, lethargy, anorexia) between 6 and 24 hours after ingestion. After a period of "false recovery" of 12 to 24 hours, which signifies the third phase of poisoning, fulminant liver failure develops. During this third phase, close monitoring of liver and kidney function is essential in order to prevent misdiagnosis. After the GI phase, severe hypoglycemia as a result of breakdown of liver glycogen can occur.[11] Fifty percent of dogs given lethal doses of amanitins or pieces of *A phalloides* died from hypoglycemia 1 to 2 days after exposure.[4] The fourth and final phase begins 36 to 48 hours after exposure and is characterized by fulminant hepatic failure with subsequent coagulation disorders, encephalopathy, and renal failure. Significant elevations in serum of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and bilirubin are commonly observed.[12] Puppies, or dogs that ingest large amounts of amanitins, can die of amanitin poisoning rapidly, within 24 hours.[13]

A tentative diagnosis of hepatotoxic mushroom toxicity can be made based on history of exposure (witness or suspected exposure), a latency period of 6 to 12 hours before clinical signs are seen and the types of clinical signs present. Confirmatory diagnosis is made by detection of α-amanitin in serum, urine, gastric contents, suspect mushroom, liver, or kidney.[14] This testing is provided by select veterinary toxicology laboratories. The well-known Meixner test (also known as the newspaper test of Wieland) should not be relied on alone for amanitin identification.[15] Rapid confirmation of amanitins in suspect exposures assists in the early recognition of exposure and timely therapeutic intervention, while a negative result can prevent unnecessary hospitalization. Serum and urine samples should be collected and frozen at various time points beginning as early after exposure as possible. Amanitin has been detected in livers and kidneys of dogs dying from amanitin poisoning. In humans, amanitin concentrations have been detected in liver and kidney up to 22 days post ingestion and at later time points. Kidneys appear to contain higher concentrations than liver. At necropsy, the liver is often swollen, without any other significant gross abnormalities. Histopathologically, the liver shows massive hepatocellular necrosis with collapse of hepatic cords[11] and acute tubular necrosis in dogs that developed renal failure.

There is no specific antidote to treat amanitin intoxication. Despite the evaluation of numerous treatment options, no specific therapy has proved to be effective and the mortality rate in dogs is high. The key elements of treatment are close monitoring, fluid replacement, and supportive care. Activated charcoal at 1 to 2 g/kg PO with or without a cathartic like sorbitol (do not use a cathartic if diarrhea is present) followed by 2 or 3 half-doses within 24 hours of exposure is recommended. In the past, multidose activated charcoal was recommended. However, recent data indicate that interruption of the enterohepatic circulation of amanitin is unlikely to be effective after 24 hours.[16] Dextrose, vitamin K_1, blood products, and intravenous fluids must be considered as beneficial therapeutic agents for case management. In Europe, a silibinin-containing product (Legalon-Sil; Madaus Inc, Cologne, Germany) is a well-established and approved treatment for amanitin poisonings in humans.[17] Silibinin, or silybin, the main component of silymarin, which is extracted from the common milk thistle, *Silybum marianum*, reduces the uptake of amanitins into hepatocytes.[18] In dogs, 50 mg/kg of silibinin IV given at 5 and 24 hours after exposure to *A phalloides* was shown to be effective.[19] Other options may include use of nonspecific hepatoprotective agents like *N*-acetylcysteine (Mucomyst; Bristol-Myers Squibb Company, New York, NY, USA) or *S*-adenosylmethionine (SAMe), although their efficacy remains undetermined. Penicillin G at 1000 mg/kg IV given at 5 hours after dogs were exposed to *A phalloides* was also effective in reducing amanitin uptake into the hepatocytes. However, the efficacy of penicillin G in humans with amanitin

poisoning is questionable. Manage vomiting as needed with metoclopramide (0.2 to 0.4 mg/kg subcutaneously or intramuscularly every 6 hours or maropitant 1 mg/kg subcutaneously once a day).

NEUROTOXIC MUSHROOMS

Hydrazines

Hydrazines are toxins in false morels, *Gyromitra* spp, which are found throughout the North America, especially under conifers and aspens. Gyromitrin, the toxin, is estimated to be present at 0.12% to 0.16% in fresh *G esculenta*. While the estimated lethal dose of gyromitrin in humans is 20 to 50 mg/kg for adults and 10 to 30 mg/kg for children,[20] such data are unavailable for dogs or cats. But gyromitrin poisoning is rarely reported in veterinary medicine; only one case report, in a 10-week-old dog, exists.[21] The dog vomited 2 to 3 hours after chewing on a mushroom later identified as *G esculenta,* became lethargic and comatose 6 hours post-ingestion, and died 30 minutes later. Gyromitrin is a direct irritant resulting in vomiting and diarrhea within 6 to 12 hours after exposure. The toxin is hydrolyzed in the stomach to monomethylhydrazine, which depletes pyridoxal 5-phosphate, ultimately resulting in decreased γ-aminobutyric acid (GABA) concentrations and increased glutamic acid concentrations.[22] Clinically, seizures can develop. Additional metabolites of gyromitrin can also result in hemolysis and liver and kidney failure. Diagnosis of gyromitrin poisoning is primarily based on the identification of the mushroom as detection of gyromitrin is not routinely available. Treatment of gyromitrin poisoning is mainly supportive, including correction of fluid and electrolyte imbalances. Pyridoxine can be given intravenously to dogs at 75 to 150 mg/kg body weight during acute phases of seizure activity.[23] Diazepam can also be considered for seizure control at 0.5 to 1.0 mg/kg IV to effect.

Isoxazoles

Ibotenic acid and muscimol are chemically classified as isoxazoles, which are most commonly associated with exposures to *Amanita pantherina* (panther cap, panther agaric) and *Amanita muscaria* (fly agaric). These mushrooms are found throughout the United States but are most abundant in the Pacific Northwest in the summer and fall, where they are often found in coniferous and deciduous forests. Clinical signs of poisoning in humans are seen with exposures greater than 6 mg of muscimol or 30 to 60 mg of ibotenic acid.[24] The concentration of ibotenic acid in *A muscaria* is estimated to be at 100 mg/kg fresh, while the concentration of muscimol is less than 3 mg/kg fresh weight. Therefore, an average-size, 60- to 70-g fruiting body of *A muscaria* can contain a toxic concentration of isoxazoles. While the toxicity of isoxazoles is not well documented in dogs, postmortem examination of puppies indicated that the ingestion of a single *A pantherina* can be lethal.[25] Although both muscimol and ibotenic acid are present in the mushrooms, muscimol is further derived from ibotenic acid by spontaneous decarboxylation, which can occur during drying of the mushroom, during digestion in the stomach, or after absorption in a variety of tissues. Therefore, muscimol is considered the major toxin responsible for causing clinical signs of toxicosis. Muscimol increases the membrane permeability for anions resulting in a slight, short-lasting hyperpolarization and associated decreased excitability of the receptive neuron. Muscimol also acts on $GABA_A$ receptors and has a depressant action.[26] Neurologic signs in animals include disorientation, opisthotonus, paresis, seizures, paddling, chewing movements, miosis, vestibular signs (ataxia, head tilt, nystagmus, circling, etc), respiratory depression, and, in severe cases, coma. In humans, muscimol intoxication is referred to as the “pantherine-muscaria”

syndrome, which is characterized by mydriasis, dryness of the mouth, ataxia, confusion, euphoria, dizziness, and tiredness within ½ to 2 hours of ingestion, followed by full recovery within 1 to 2 days. Similar clinical signs have been described in cats,[27] while favorable[28] and lethal outcomes have been described in dogs with isoxazole exposure.[25,29] Diagnosis of isoxazole poisoning is primarily based on the history of exposure to a mushroom, quick onset of clinical signs (within hours of exposure), the type of clinical signs (hallucinations and other central nervous system [CNS] effects), and identification of the mushroom. While muscimol and ibotenic acid are excreted in urine shortly after exposure, routine diagnostic tests are not available. Treatment of isoxazole poisoning is mainly supportive, with special focus on seizure control. Early decontamination (induction of emesis and administration of activated charcoal) can be tried in asymptomatic animals. Because of the GABAergic effects of muscimol and ibotenic acid, medications with GABA agonist effects such as diazepam or phenobarbital should be used with caution. The use of these medications in a poisoned animal to control seizuresmay further aggravates CNS and respiratory depression. Thus, if such drugs are used, the animal's respiration should be carefully monitored for need of mechanical ventilation.

Psilocin and Psilocybin

Mushrooms in the genera *Psilocybe*, *Panaeolus*, *Conocybe*, and *Gymnopilus* contain primarily psilocybin, with some also containing psilocin. These mushrooms grow predominantly in fields and animal pastures in the Northwestern and Southeastern United States. The toxin concentrations in these mushrooms are affected by location, growing conditions, storage conditions, and species. Species common to the Pacific Northwest contain between 1.2 and 16.8 mg/kg psilocybin on a dry weight basis.[30] Oral doses of 10 to 20 mg of psilocybin result in hallucinations in people. Toxicity data for domestic animals do not exist. Psilocin is pharmacologically the most active metabolite of psilocybin after dephosphorylation in plasma, liver, and kidney.[31] Psilocin is structurally similar to serotonin and activates some serotonin receptors in the CNS,[32] leading to lysergic acid diethylamine (LSD)-like clinical effects. In the United States, United Kingdom, and Germany, psilocybin and psilocin are classified as controlled substances, and mushrooms containing those substances are called magic or hallucinogenic mushrooms. People consuming those mushrooms generally have hallucinations for approximately 1 hour, and have full recovery within 12 hours. In dogs, exposure to psilocybin containing mushrooms can result in aggression, ataxia, vocalization, nystagmus, seizures, and increased body temperature.[33] Exposure can be confirmed by detection of psilocin and psilocybin in urine by select veterinary diagnostic laboratories. Because of the short-lasting effects, mild cases may resolve themselves without treatment. Symptomatic and supportive treatment may be necessary when severe clinical signs are present. Seizures can be controlled with diazepam or phenobarbital.

MUSCARINE-CONTAINING MUSHROOMS

The most common muscarine-containing mushrooms include *Inocybe* spp and *Clitocybe* spp. The largest numbers of mushroom species that contain significant amounts of muscarine belong in these 2 genera.[34] These mushrooms are often described as nondescript little brown mushrooms, although some may be other colors such as white or cream.[34] They can be found in forests, lawns, and parks. These mushrooms most commonly fruit in summer and fall, although some fruit year round.[34] Several other genera such as *Mycena*, *Boletus*, *Entoloma*, and *Omphalotus*

are suspected to contain significant muscarine levels.[34–36] Muscarine is also present in low concentrations in other mushrooms such as *Amanita muscaria.*[34]

Muscarine is a thermostable muscarinic receptor agonist that binds to acetylcholine receptors in the peripheral nervous system.[34] Stimulation of postganglionic neurons results in parasympathomimetic effects. Unlike acetylcholine, it is not degraded by acetylcholinesterase and toxicity results from unregulated stimulation at the receptors.[34,37] Organophosphates and carbamates can produce similar muscarinic signs; however, they act by binding acetylcholinesterase, which increases the amount of acetylcholine at the receptors. There may also be muscarinic compounds that produce a histaminic effect resulting in flushing, hypotension, and wheezing.[36]

Clinical signs can occur rapidly (often within 5 to 30 minutes) and mostly within 2 hours of ingestion.[34,36,37] Signs may include **s**alivation, **l**acrimation, **u**rination, **d**iarrhea, **d**yspnea, and **e**mesis (often described by the acronym SLUDDE). Dyspnea may develop in response to increased bronchial secretions and bronchoconstriction. Bradycardia, miosis, hypotension, and abdominal pain are also possible. In the author's experience, dogs suspected of ingesting muscarinic mushrooms often present with a history of acute onset of vomiting, severe diarrhea, and ptyalism. The saliva may be described as thick and ropey. Differential diagnoses include exposure to pesticides such as organophosphates, and carbamates and mycotoxins like slaframine. Exposure to cholinesterase-inhibiting pesticides such as organophosphates and carbamates may also result in nicotinic signs such as tremors, muscle weakness, and seizures. Unlike these pesticides, muscarine does not stimulate nicotinic receptors or cross the blood-brain barrier.[34,36,37] Consequently, nicotinic and direct CNS effects are not expected. Depression may develop as a result of hypotension or hypoxia.[34]

Diagnosis is based on rapid onset of clinical signs, the type of clinical signs (SLUDDE), and response to treatment. Muscarine has been detected in urine and analysis could be considered for confirmation of exposure.[36] Identification of the mushrooms from the environment and/or vomitus may also be used to support the diagnosis.

Decontamination includes induction of emesis and administration of activated charcoal in asymptomatic animals following ingestion of mushrooms. The rapid onset of signs (which may include vomiting) following muscarinic mushroom ingestion often makes decontamination unfeasible. Atropine competes with muscarine at the receptors and is the recommended treatment. In dogs and cats, the beginning dosage is 0.04 mg/kg with one fourth of the dose given intravenously and the remainder given subcutaneously or intramuscularly (American Society for the Prevention of Cruelty to Animals, Animal Poison Control Center, Antox™, unpublished data, 2011). The dosage can be titrated up and repeated if needed to control severe signs. Overatropinization should be avoided and can result in anticholinergic signs, including tachycardia, hyperthermia, behavior changes, and GI stasis. Signs typically respond well to atropine and resolve within 30 minutes of administration. Without treatment, signs may persist for several hours. Supportive care (intravenous fluids) should be provided as needed. The prognosis, in most cases, is good and long-term effects are not expected.

MUSHROOMS RESULTING IN GASTROINTESTINAL IRRITATION

Mushrooms that result in primarily GI signs are grouped under this category. Specific genera include *Agaricus*, *Boletus*, *Chlorophyllum*, *Entoloma*, *Gomphus*, *Hebeloma*, *Lactarius*, *Naematoloma*, *Omphalotus*, *Ramaria*, *Rhodophyllus*, *Russula*, *Scleroderma*,

Tricholoma, and others. These mushrooms have a wide distribution and variation in appearance and substrate.

The toxins in most species have not been identified. Illuden S is thought to be a toxic component in some *Omphalotus* and *Lampteromyces* species.[38] Illudens can be cytotoxic and have produced hemorrhagic lesions in animal studies.[36,38] *Omphalotus illudens* also produces a muscarine-like effect although muscarine has not been isolated from this mushroom.[39] Suspected toxins in other species include Monoterpenes, norcaperatic acid, hebeleomic acid A, cucurbitane trierpene glycosides, lectins, marasmane/lactarane sesquiterpenes, and phenolethylamines. Proposed mechanisms include hypersensitivity, idiosyncratic reactions, some enzyme deficiencies, and local GI irritation.[40] Some of the mushrooms in this category are considered edible, although even the edible species can result in GI signs in sensitive individuals. Some of the toxins may be inactivated by cooking.

The onset of clinical signs is fairly fast and signs are expected within 15 minutes to several hours after ingestion. Vomiting, diarrhea, and abdominal discomfort are common signs. Other signs may include lethargy, hypersalivation, hematemesis, and hematochezia. Secondary electrolyte abnormalities and hypovolemia may develop. A 1-year-old cat ingested one-half of an *Agaricus* spp cap and developed foaming, vomiting, diarrhea, and disorientation. Hematemesis developed in another cat that ingested an unknown species of *Russula*. The mushroom was described as having a shellfish odor, which may have attracted the cat.[40] There is also a report of a 7-month-old pot bellied pig that developed vomiting, weakness, hypothermia, abdominal pain, tachycardia, and tachypnea within 1 hour of ingestion of *Scleroderma citrinum*. The pig died within 5 hours despite treatment with fluids and dexamethasone.[40] Differential diagnoses for GI irritant mushrooms include many other causes of acute gastroenteritis such as dietary indiscretion, garbage poisoning, foreign body ingestion, pancreatitis, bacterial or viral gastroenteritis, ingestion of corrosive or irritating agents, and ingestion of GI irritant plants.

Diagnosis is supported by the history, clinical signs, and evidence of mushrooms in the vomitus. The mushrooms should be saved for identification. It is important to note that GI upset is also an initial sign following ingestion of more dangerous hepatotoxic and nephrotoxic mushrooms, although the onset is typically more delayed. A complete blood count, chemistry panel, and radiographs may be performed to assess the clinical picture and help rule out other causes for the signs. In severe cases, electrolyte and acid-base status should be monitored and corrected as needed.

Decontamination includes emesis and activated charcoal in asymptomatic animals following ingestion of mushrooms. The potential rapid onset of vomiting may make decontamination following ingestion of GI irritant mushrooms less feasible. Treatment is symptomatic and supportive and depends on the extent of signs. Intravenous fluids are recommended to maintain hydration. Sucralfate, H2 blockers (famotidine), and/or proton pump inhibitors (omeprazole) may be used to reduce mucosal irritation. Vomiting should be controlled with antiemetics such as maropitant and metoclopramide. Many cases are self-limiting and resolve without treatment. The severity of signs depends on the type of mushroom, amount ingested, and individual sensitivity. In most cases, the prognosis is good and full recovery is expected within a few hours to days.

NEPHROTOXIC MUSHROOMS

Some species of mushrooms in the genus *Cortinarius* are nephrotoxic. These mushrooms were first noted to be toxic in Poland in the 1950s.[34,36,41] Although they

are found throughout Europe and North America, reports of toxicity have been rare in North America. There is a report of a woman who developed renal failure after ingesting *Cortinarius orellanosus* mushrooms from under an oak tree in Michigan.[42] To the author's knowledge, there have been no confirmed cases of accidental animal poisoning resulting from nephrotoxic mushrooms in North America.

The mushrooms are often a rusty or reddish brown color.[36] Webcap is a common name used for some of these nephrotoxic mushrooms due to the presence of a cortina or spider-web like veil that connects the edge of the cap to the stem in the immature stages. The cortina is not recognizable in adult mushrooms.[35,36] *Cortinarius* sp grows in forests and mountains and is rare in urban areas.[34] These mushrooms most commonly fruit between August and October.[43]

The bipyridyl toxin orellanine is thought to be the main toxin in *Cortinarius* sp mushrooms. Orelline and orellinine are 2 thermal and photo degradation products that have been identified. These toxins are thought to inhibit protein synthesis in renal tubular epithelium. Another theory is that the toxins reduce cellular NADPH, which results in free radical damage, lipid peroxidation, and membrane destruction.[34] There is a lag time between ingestion and development of signs, which suggests metabolism to an active form of the toxin.[34] Another toxin, a cyclopeptide named cortinarin has been isolated from some species. Cortinarins A, B, and C have been described. In the liver, cortinarin A is thought to be metabolized to cortinarin B, which is then converted to its sulfoxide form via cytochrome P450 enzymes. Cortinarins A and B sulfoxide are nephrotoxic. Females seem to be more resistant to the toxin than males. This may be due to differing binding capacities in the cytochrome P450 system.[34] There is still some controversy over the toxins present in *Cortinarius* sp and their relationship to each other and the nephrotoxicity associated with these mushrooms. Toxicity is not affected by cooking, canning, or drying of the mushrooms.[34] Interestingly, experimentation in rats has shown significant individual variation in susceptibility. In one study, 20% to 30% of rats were resistant to toxicity even at high dosages.[44]

There is a latent phase between ingestion and onset of signs. GI signs may occur within 72 hours. Within 3 to 20 days, signs of renal failure may develop. In humans, increased thirst, flank pain, chills, and night sweats have been described. Oliguria followed by diuresis and recovery or chronic renal failure may occur.[36] *Cortinarius orellanus* resulted in signs similar to those noted in humans when given orally to the cat, guinea pig, and mouse experimentally. The main damage was to the renal tubular epithelium.[40] In animals, vomiting, diarrhea, polyuria, polydipsia, abdominal pain, and depression may be noted. Differential diagnoses include other causes for GI upset and acute renal failure such as grape or raisin ingestion, NSAIDs, ethylene glycol, lily ingestion (cats), and leptospirosis.

Diagnostic tests to monitor renal values and a complete clinical assessment include a complete blood count and serum chemistry. In addition, urinalysis may reveal isosthenuria, glucosuria, pyuria, proteinuria, cylinduria, and hematuria. Acid-base status and electrolytes should also be monitored. Liver enzymes are expected to remain normal.[36] Orellanine can be detected in the urine within 24 hours of the exposure. Unfortunately, due to the lag time between ingestion and onset of signs, this may not be clinically useful.[34] The clinical signs and laboratory findings are not specific for *Cortinarius* sp ingestion. Due to the rarity of animal poisoning in North America, diagnosis should be made based on the history, mushroom identification if possible, and ruling out more likely causes of renal failure/damage. Renal biopsy may also be useful. In humans, renal biopsies have revealed interstitial edema, interstitial nephritis, and acute tubular necrosis.[42] Thin-layer chromatography has detected

orellanine in renal biopsy samples up to 6 months post ingestion. Orellanine has also been measured in human plasma.[36]

Decontamination includes emesis and activated charcoal in asymptomatic animals following ingestion of mushrooms. However, due to the long latent period, patients may not be presented until days after the exposure and the opportunity for decontamination is missed. Treatment consists of supportive care for renal failure and GI signs. Intravenous fluids, GI protectants (sucralfate, famotidine, rhinitidine, or omeprazole), and antiemetics (maropitant, metoclopramide) may be used. In humans, chronic hemodialysis is often necessary and, in some cases, renal transplant is performed. In humans, forced diuresis is not recommended due to increased renal damage.[41] Furosemide increased toxicity, in rats, when injected prior to *C orellanoides* ingestion.[44] In animals, peritoneal or hemodialysis could be considered. Experimental treatments, in humans, include use of corticosteroids, *N*-acetylcysteine, and selenium. The results have not been conclusive.[36]

The prognosis, following ingestion of nephrotoxic *Crotinarius* sp, varies. There appears to be a dosage-dependent aspect as well as individual variation. In humans, renal failure has been reported to occur in 30% to 40% percent of cases. This may be followed by a slow return to normal function or development into chronic renal failure, which requires hemodialysis and/or transplantation. A shorter latent period usually indicates a worse prognosis.[36]

SUMMARY

There are numerous types of mushrooms that may be ingested by small animals, mostly by dogs. Although many mushrooms are not toxic, there are some types that can result in hepatotoxic, neurologic, cardiovascular, hemolytic, muscarinic, GI, and/or nephrotoxic effects. Gross identification by nonmycologists is often not effective, so it is safest to assume that any mushroom ingested may potentially be toxic until or unless identification is accomplished. It should also be assumed that more than one kind of mushroom could be ingested in a single exposure.

Following ingestion of an unknown mushroom in small animals, decontamination should consist of induction of emesis (3% hydrogen peroxide or apomorphine in dogs and xylazine in cats) followed by administration of activated charcoal (1 to 2 g/kg) orally in asymptomatic animals. The vomitus should be examined for the presence of mushrooms. Mushroom specimens from the vomitus and/or other similar mushrooms from the animal's environment should be saved for identification. Do not save mushrroms in plastic bags. Instead, place them in a paper bag, towel, or a newspaper. Refrigerate the specimen until shipped out for identification. Specimen should be labeled and dated properly. Information regarding a brief history of exposure, chronology of onset time and types of clinical signs, blood and chemistry changes, treatment used, and response to treatment should be sent to the veterinary diagnostic laboratory when needed.

Baseline complete blood count and chemistry panels should be obtained and repeated as needed. The animal should be monitored at the clinic for several hours for the onset of CNS, cardiovascular, muscarinic, and GI signs. Also, during this time, the animal can be monitored for hypernatremia that may occur following administration of activated charcoal. If signs develop, or are present at the time of presentation, the animal should be treated accordingly. If no signs develop, the animal can be monitored on an outpatient basis for the development of delayed (often beyond 6 to 8 hours) GI signs that often precede more severe effects associated with the hepatotoxic, hemolytic, and nephrotoxic mushrooms. Typically signs are expected within 4 hours following ingestion of isoxazoles, GI irritants, muscarine, and psilocybins. If the

onset of vomiting, diarrhea, and abdominal pain are delayed beyond 6 to 8 hours, it increases the suspicion that the more serious amatoxin, gyrometrin, or orellanine (rare) toxins have been ingested. In asymptomatic animals, serum chemistries could be monitored daily for up to 4 days post ingestion. SAMe could be initiated as a potential liver protectant in case amatoxin was ingested.

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