

Compendium

Tremorgenic Mycotoxicosis in Dogs

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Abstract: Ingestion of tremorgenic mycotoxins formed in spoiled food can cause an acute tremor syndrome, the severity of which can range from mild to life-threatening. Swift recognition of the likely cause is required for accurate prognostication and rapid institution of appropriate therapy, which leads to complete resolution in most cases.

Clinical Signs

Tremorgenic mycotoxicosis in dogs typically presents as an acute onset of generalized tremors, sometimes of sufficient severity to resemble a seizure; animals occasionally present in status epilepticus.¹ Such cases usually present as emergencies. Affected animals may also salivate, pant excessively, be pyrexic (body temperature may exceed 107°F [41.7°C]), and show mydriasis, nystagmus, and hypersensitivity to noise and touch.²⁻⁵ The time to onset of convulsions or tremors after ingestion varies from ~30 minutes to several hours.^{1,4} Nonneurologic signs can include vomiting, diarrhea, flatulence, and tachycardia,⁴ and severely affected animals may be recumbent and unable or unwilling to raise their head. At presentation, it can be difficult to elicit an accurate history from owners, but, occasionally, access to garbage or other sources of decaying food is known. Access to rotten material is significant because there are few reports of tremorgenic mycotoxicosis, despite the ubiquity of mycotoxin-producing molds in the environment.

Etiology

Ingestion of a variety of moldy foods, including grains, walnuts, almonds, and peanuts, as well as nonspecific garbage, has been associated with tremorgenic mycotoxicosis.² Dogs are more commonly affected than other species of domestic animals, probably because of their tendency to scavenge⁶; intoxication of several dogs within the same household has also been reported.⁵

The most common sources of tremorgenic mycotoxins are fungi of the genus *Penicillium*,^{7,8} which are found in decomposing food and vegetable matter. Many tremorgenic compounds are known, including penitrem A, thomitrem A, aflatoxin, cyclopiazonic acid, and roquefortine. It is believed that different tremorgenic mycotoxins produce clinical signs of varying severity, but consumption of more than one toxin is common in clinical cases.³

The major tremorgens in domestic dogs are penitrem A and roquefortine, with *Penicillium crustosum* contamination the most commonly identified source (first reported by Wilson et al in

1968⁷). Experimental intoxication of mice and rats produced dose-dependent signs, including tremors, behavioral changes, seizures, and death. Examination of different isolates of *P. crustosum* found that 100% produced penitrem A in addition to roquefortine.⁸ Roquefortine is mainly produced by *Penicillium roqueforti* (the same species used in making Roquefort cheese) but may also be produced by several other types of *Penicillium* fungi, including *P. crustosum*.⁶

Mode of Action

The mode of action of the tremorgenic mycotoxins is variable and not fully understood, although access to the brain across the blood-brain barrier is facilitated by their lipophilia.⁶ Rats injected with penitrem A show marked increases in the release of glutamate, GABA, and aspartate at cerebrocortical synapses.⁹ A similar interference with neurotransmission within the cerebellum is thought to cause the characteristic tremor.⁴ Penitrem A also increases gastric smooth muscle activity in vitro,¹⁰ probably through sensitizing it to acetylcholine, and similar effects may also occur within the central nervous system.

In one study, focal tremors developed within 7 to 10 minutes of intraperitoneal injection of penitrem A in rats¹¹ and changes were detected only within the cerebellum at necropsy. Initial changes were seen as ischemic changes in Purkinje cells. Animals that were not euthanized returned to near-normal behavior within 1 week.¹¹ Areas of necrosis within the cerebellar granule cell layer and vacuolization of the molecular layer have also been reported.¹²

The minimum oral toxic dose of penitrem A, aflatoxin,

Key Points

- The propensity of dogs to ingest rotting material exposes them to the risk of tremorgenic mycotoxicosis.
- Rotting foodstuffs often consist of many different potential fungal growth substrates and may contain a variety of fungal toxins.

Box 1. Common Etiologies of Tremors in Dogs

Primary neurologic disorders

- Steroid-responsive tremor syndrome (“little white shaker syndrome”)
- Episodic tremors (idiopathic)
- Cerebellar disease
- Congenital action-related tremors

Endocrine/metabolic disorders

- Hypoglycemia
- Hypocalcemia/eclampsia
- Hepatic encephalopathy

Toxin ingestion

- Tremorgenic mycotoxins
- Metaldehyde
- Organophosphates/carbamates
- Strychnine
- Xanthines (e.g., caffeine, theophylline, theobromine)
- Bromethalin
- Macadamia nuts
- Marijuana
- Cocaine

- Amphetamines/pseudoephedrine
- Paintballs
- Ethylene glycol
- Heavy metals (aluminum, lead)
- Ivermectin

Iatrogenic

- Blood transfusion reactions

Infectious diseases

- Distemper
- Rabies

or roquefortine has not been determined; however, since the amount of the compounds ingested cannot be quantified in practice, it is not possible to determine if a dog has ingested a toxic dose.

Differential Diagnosis

Tremors are a nonspecific clinical sign; the Cornell University Veterinary Consultant Web site (www.vet.cornell.edu/consultant/consult.asp) lists almost 200 different causes of tremors in dogs. Some of the more common causes are listed in **BOX 1**. Therefore, a detailed history and typical additional clinical signs (e.g., vomiting, seizures) associated with mycotoxin ingestion may be helpful in rapid identification of the etiology (**FIGURE 1**).

In view of the acute onset of nonspecific signs and history of these patients, toxicosis is often suspected. Common toxins resulting in tremors, seizures, and similar neurologic signs include metaldehyde (slug bait), organophosphates and carbamates, strychnine, xanthines, and bromethalin. Strychnine toxicosis cannot always be differentiated from tremorgenic mycotoxicosis based on clinical signs,¹³ although it is generally associated with tetanic spasms rather than tremor, and exposure is relatively rare. Similar considerations apply in ruling out exposure to bromethalin (rodenticide), xanthines (caffeine, theophylline, theobromine), and macadamia nuts.¹⁴

In dogs in which a nontoxic etiology of tremors merits consideration, the differential diagnosis includes idiopathic tremor syndromes, hypoglycemia, hypocalcemia, eclampsia, and cerebellar disorders. Many of these

conditions can be differentiated from acute toxicoses based on history, clinical progression of the disease, and routine blood tests. For instance, hypoglycemia and hypocalcemia are easily recognized during routine investigation of emergency patients, and while eclampsia can cause acute tremors,¹⁵ the signalment (pregnancy or lactation) should aid recognition. Idiopathic tremor syndrome (previously called *little white shaker syndrome*) is the most prominent diagnostic differential for a small-breed dog with acute-onset tremors and no other significant clinical signs. Although most common in young members of small, white breeds, idiopathic tremor syndrome can occur in many dog breeds. Importantly, affected animals have normal neurologic and physical examination findings apart from the tremors, which can be acute in onset but frequently become progressively severe over a period of days, which aids in differential diagnosis. In addition, tremors usually occur only when the animal is stimulated and affected

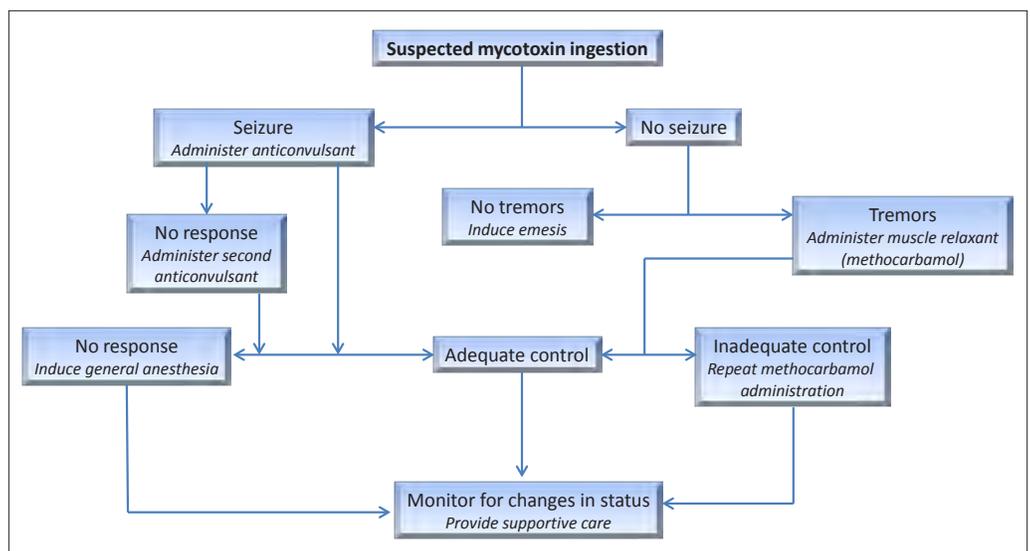


Figure 1. Diagnostic tree for acute tremors in dogs, based on initial assessment and emergency/cage-side tests.

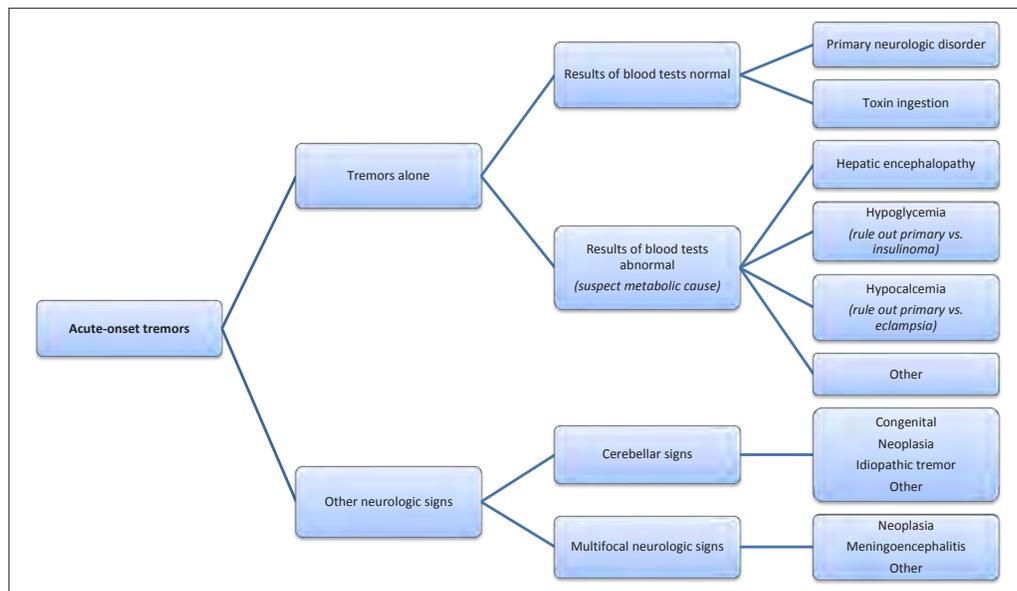


Figure 2. Flow chart of treatment options for suspected tremorgenic mycotoxin ingestion. The choice of treatment depends on the severity of clinical signs. Active cooling should be instituted in animals that are severely pyrexic; the technique used should be appropriate to the status of the dog.

mycotoxicosis. Known ingestion of, or possible access to, moldy food, garbage, or compost is highly suggestive.

Definitive diagnosis is made by analysis of vomitus or stomach contents, blood, urine, or the suspected contaminated material. Analytic methods include identification of the mold through culture of the organism or detection of the toxins themselves,^{1,4,17} although the presence of mold does not necessarily mean mycotoxin will be present. Liquid chromatography–mass spectrometry has also been used to screen for the specific toxins penitrem A and roquefortine in serum¹⁸ and urine samples.³ These tests are available from some specialized diagnostic laboratories.

Individuals do not present with hyperthermia. Episodic tremors of the head and neck have also been observed in young Doberman pinschers, English bulldogs, French bulldogs, and boxers.¹⁶ The tremors are idiopathic, only occur when the dog is standing, and disappear when the dog is lying down or distracted by objects or food. These tremors can therefore be easily differentiated from mycotoxic tremors, which are continuous. Several types of congenital action-related tremors have been recorded, but since they are present from birth,¹⁶ they should be unlikely to be confused with acute toxicosis. Cerebellar disorders can cause intention tremors, but they disappear at rest, in contrast to tremors observed in tremorgenic mycotoxicosis. Many cerebellar disorders are associated with additional neurologic signs such as postural reaction deficits, which are inconsistent with tremorgenic mycotoxin ingestion.

Diagnosis

A minimum database for suspected toxin ingestion includes a complete blood count, serum chemistry panel, and urinalysis, as well as evaluation of the patient's acid-base status.¹⁵ These tests may aid in ruling out mycotoxin ingestion but cannot identify mycotoxicosis. Hematologic values in mycotoxicosis may be altered, but they are nonspecific⁴ and often explained by dehydration. Renal damage has been suspected in dogs exposed to *Penicillium* toxins, but whether it was due to primary tremorgenic toxicosis, drugs given as treatment, or secondary injury because of increased muscle activity is unclear⁴; nevertheless, monitoring of renal function and repeated urinalysis may be indicated.

Neurologic examination cannot definitively diagnose tremorgenic mycotoxicosis, but the absence of neurologic signs other than consistent tremor aids in ruling out other neurologic diseases. History is the key factor in forming a presumptive diagnosis of

Treatment

Identifying the specific responsible mycotoxin is frequently difficult in emergency patients and may not be possible; furthermore, there is no specific treatment or antitoxin available for these toxins. Treatment of these patients is therefore symptomatic, focusing on control of seizures and hyperthermia and correction of circulating volume deficits (FIGURE 2 and BOX 2).

Primary treatment should, if possible, include elimination of the toxin from the body, although affected individuals do not always present at an early enough stage. Induction of emesis can be considered for asymptomatic patients that present within 15 to 30 minutes after suspected or confirmed ingestion of moldy food or noncorrosive waste material. Induction of vomiting in a recumbent animal is potentially hazardous and should not be attempted. Apomorphine is the emetic of choice; however, hydrogen peroxide is a reasonably reliable alternative. Gastric lavage can be considered if ingestion occurred within ~60 minutes but requires anesthesia and intubation,² which are often contraindicated because animals with neurologic disease are at increased risk of aspiration pneumonia.¹⁹

Activated charcoal with or without a cathartic can be administered to reduce toxin absorption. There is evidence that the common tremorgenic mycotoxins are excreted in bile, suggesting the possibility of hepatic recirculation^{6,13} and the need for repeated treatment with activated charcoal over 2 to 3 days. However, affected animals rarely show clinical signs for so prolonged a period, and those that do are not usually safe candidates for oral medications.

Although seizures are not seen in all cases of tremorgenic toxicosis, seizure control is the most crucial aspect of emergency care, and many anticonvulsant drugs can also be used to reduce tremors. Intravenous anticonvulsants such as diazepam, midazolam, and phenobarbital are routine first-line treatments for persistent seizures.

Box 2. Summary of Drugs and Dosages for Treatment of Mycotoxicosis

Anticonvulsants

- Diazepam: 0.5–1 mg/kg IV; 0.5 mg/kg/h as CRI^a
- Phenobarbital: 2–20 mg/kg IV (give as 2- to 5-mg/kg bolus q20min to effect)^b
- Midazolam: 0.07–0.20 mg/kg IV/IM; 0.05–0.5 mg/kg/h CRI^c
- Levetiracetam: 30–60 mg/kg IV over 5 min (loading),^d then 10–20 mg/kg IV q8h^b
- Ketamine: 5 mg/kg as initial bolus; 5 mg/kg/h as CRI^e
- Propofol: 2–8 mg/kg IV; 0.1–0.6 mg/kg/min as CRI^a

Induction of emesis

- Apomorphine: 0.03–0.04 mg/kg IV; 0.04–0.08 mg/kg IM; 0.25 mg/kg into conjunctival sac^f
- Hydrogen peroxide: 1 tsp/2.5 kg of 3% hydrogen peroxide¹⁹

Gastrointestinal absorbents/motility stimulants

- Activated charcoal: 1–4 g/kg^g
- Sorbitol: 1–3 mL/kg 70%¹⁹

Muscle relaxants

- Methocarbamol: 55–220 mg/kg IV; half the dose given at 2 mL/min initially, repeat until tremors are relieved; do not exceed 330 mg/kg q24h^h

CRI = constant-rate infusion.

^aParent J. Cluster seizures and status epilepticus in dogs. In: Mathews KA. *Veterinary Emergency and Critical Care Manual*. Guelph, ON: Lifelearn Inc; 2006:460-464.

^bPlumb D. *Veterinary Drug Handbook*. 7th ed. Wiley-Blackwell; 2011.

^cThomas W. Idiopathic epilepsy in dogs and cats. *Vet Clin North Am Small Anim Pract* 2010;40:161-179.

^dDewey CW, Bailey KS, Boothe DM, et al. Pharmacokinetics of single-dose intravenous levetiracetam administration in normal dogs. *J Vet Emerg Crit Care* 2008;18:153-157.

^eSerrano S, Hughes D, Chandler K. Use of ketamine for the management of refractory status epilepticus in a dog. *J Vet Intern Med* 2006;20:194-197.

Intravenous levetiracetam is also effective in controlling seizures but can be costly, especially in large dogs. There is some evidence that seizures caused by mycotoxins respond poorly to diazepam^{1,5,13}; in fact, it has been suggested that this lack of response is highly suggestive of mycotoxin exposure,¹³ although idiopathic tremor syndrome also responds poorly to diazepam. If the animal is nonresponsive to these initial treatments, intravenous propofol (bolus or constant-rate infusion [CRI]), a ketamine CRI, or general anesthesia with inhalant anesthetics can be instituted. In extreme cases, intubation for ventilator and oxygen support may be required.⁵ Severe respiratory signs in dogs with tremorgenic toxicosis would most likely result from aspiration pneumonia; use of antibiotics, nebulization, coupage, and other standard treatments for pneumonia are indicated in these cases.

For patients in which seizures are controlled or absent, sedatives or muscle relaxants can be used to reduce or eliminate tremors. Methocarbamol appears to be the muscle relaxant of choice²⁰ and can be given to effect with repeat doses as required.

Pyrexic animals should be cooled, although body temperature should be closely monitored to avoid inducing hypothermia. For mild to moderate pyrexia (103.1°F to 105.8°F [39.5°C to 41°C]), the use of fans, intravenous fluids, and wet blankets or towels applied to the animal should be sufficient. Body temperatures in excess of 107.6°F (42°C) require more aggressive therapy, including the use of ice packs around the jugular vein; filling the urinary bladder with room-temperature sterile saline, followed by emptying after 5 minutes; or a room-temperature water enema.²¹ Cooling and intravenous fluids also reduce the risk of kidney damage arising from myoglobinuria secondary to seizure or tremor-induced rhabdomyolysis.²²

Recumbent animals require careful nursing attention, such as turning every 2 to 4 hours to prevent development of decubital ulcers. It is also necessary to monitor urination, prevent urine scald, and consider placement of a urinary catheter (although these are rarely required).

Prognosis

The prognosis is good for mildly affected dogs and those that respond to initial supportive therapy and seizure control. Dogs that experience prolonged seizures or develop aspiration pneumonia have a more guarded prognosis, although there is no study of sufficient size to properly evaluate the mortality rate. Clinical signs generally have a short duration, with full recovery within 24 to 96 hours, but long-lasting cases, in which cerebellar-like signs persist for 2 to 3 months after ingestion, are occasionally reported; one dog was even reported to have ataxia and weakness 3 years after toxin exposure.⁴

Prevention

Avoidance of exposure is the only effective prevention. Dogs that are prone to consuming garbage or plant wastes should have their access to these materials obstructed. Owners should be vigilant in disposing of moldy foods properly and ensuring that compost heaps, waste vegetable matter, and garbage are secured in an area to which dogs are unable to gain access.

Conclusion

Treatment of tremorgenic mycotoxicosis is frequently successful when the syndrome is promptly recognized, so it is important to be aware of this possible diagnosis when dealing with emergency cases of tremors or seizures in dogs. The mainstays of diagnosis and treatment, including routine blood tests, muscle relaxants, and anticonvulsant drugs, are readily available in general practice.

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1. Which of the following toxic substances is commonly associated with acute-onset tremors in dogs?
 - a. metaldehyde
 - b. strychnine
 - c. paintball paint
 - d. all of the above
2. Which of the following characteristics can be used to distinguish tremorgenic mycotoxin ingestion from idiopathic tremor syndrome in dogs?
 - a. age and coat color of the patient
 - b. presence of hyperthermia
 - c. acute onset of tremors
 - d. tremors are limited to the trunk and hindlimbs
3. Nonneurologic signs of tremorgenic mycotoxin ingestion can include
 - a. constipation.
 - b. icterus.
 - c. flatulence.
 - d. bradycardia.
4. The mycotoxins most commonly associated with clinical signs of tremorgenic mycotoxicosis in dogs are
 - a. penitrem A and roquefortine.
 - b. penitrem A and thomitrem.
 - c. roquefortine and aflatoxin.
 - d. aflatoxin and ergot alkaloids.
5. Aggressive cooling should be implemented when a dog's body temperature exceeds
 - a. 100.4°F (38°C).
 - b. 102.2°F (39°C).
 - c. 107.6°F (42°C).
 - d. 113°F (45°C).
6. Which of the following is a negative prognostic indicator for a patient suspected of having tremorgenic mycotoxicosis?
 - a. previous history of mycotoxin ingestion
 - b. development of respiratory distress
 - c. development of concurrent gastrointestinal signs
 - d. progression to seizures that are responsive to anticonvulsants
7. Definitive diagnosis of tremorgenic mycotoxicosis relies on
 - a. analysis of vomitus or stomach contents, blood, urine, or the suspected contaminated material.
 - b. neurologic examination.
 - c. history of suspected ingestion and clinical signs consistent with tremorgenic ingestion.
 - d. culture of fungal organisms from ingested foodstuffs.
8. Treatment for tremorgenic mycotoxicosis may include
 - a. administration of anticonvulsants.
 - b. active cooling.
 - c. administration of gastrointestinal motility stimulants.
 - d. all of the above
9. A dog with a history of dietary indiscretion presents with full-body tremors. The owner reports that the dog escaped from its yard and was missing for several hours before clinical signs were observed. The patient is recumbent, has a temperature of 105.8°F (41°C), and is suspected to be approximately 5% dehydrated; no other evidence of disease is present. Which of the following treatments is contraindicated in this patient?
 - a. active cooling with fans and cool water
 - b. induction of emesis with apomorphine and administration of activated charcoal
 - c. intravenous fluid administration
 - d. administration of intravenous methocarbamol
10. A dog presents after the owner observed it eating from a compost pile. The debris was consumed approximately 15 minutes before presentation. The dog appears normal on physical and neurologic examination and is otherwise in good health. Which of the following would be an appropriate first line of therapy?
 - a. commencement of active cooling to prevent hyperthermia
 - b. prophylactic use of anticonvulsants
 - c. administration of prophylactic antibiotics
 - d. induction of emesis followed by oral administration of activated charcoal