

# Compendium

## Sago Palm Toxicosis in Dogs

Leyla Fatourechi, DVM

Louis A. DelGiudice, DVM, DACVECC

Animal Emergency Medical Center  
Torrance, California

Nadrea Sookhoo, DVM

Animal Eye Clinic of Waterloo Region

Cambridge, Ontario  
Canada

**Abstract:** Cycads (also known as sago palms) are popular ornamental and landscaping plants that have historically been both a food source and a cause of toxicosis in humans and animals. This article summarizes the history of cycad toxicosis and reviews the available literature on the pathogenesis, clinical aspects, treatment, and prognosis of this toxicosis in dogs. Clinical signs of cycad ingestion are referable to the gastrointestinal, hepatic, and central nervous systems. Diagnosis of cycad ingestion must rely on clinical signs and historical information. Treatment consists of decontamination and supportive care, and the prognosis is variable. Because cycads are a cause of morbidity and mortality in dogs, clinicians should be aware of their toxic properties.

Cycads (also known as *sago palms*) are popular decorative plants that have long been associated with toxicosis in humans and animals. Because cycads are a cause of morbidity and mortality in dogs, clinicians should be aware of their toxic properties.

### Plant Biology

Cycads are hardy, slow-growing, palm-like plants that are the evolutionary intermediates between ferns and flowering plants.<sup>1</sup> Cycads have a tubular trunk that varies in height and consists of a thin layer of wood surrounding a large central pith. Pinnate leaves arise from the top of the trunk and vary in length from several inches to several feet.<sup>1,2</sup> Cycads have either seed-bearing or pollen-bearing cones<sup>1</sup> (FIGURE 1).

All cycads belong to the class Cycadopsida, which includes a single order, Cycadales. This order contains two families (Cycadaceae and Zamiaceae),<sup>3</sup> although some references classify the order into three families.<sup>4</sup> Cycadaceae consists of one genus (*Cycas*). Zamiaceae consists of nine genera (including *Encephalartos*, *Macrozamia*, *Bowenia*, *Stangeria*, and *Zamia*).<sup>3</sup> The term *cycad* is a general term and, in this review, refers to any member of the class Cycadopsida.

Today, cycads are native to the tropical and subtropical regions of the world.<sup>5,6</sup> In the United States, *Cycas circinalis* and *Cycas revoluta* (also known as *queen sago* and *sago palm*, respectively) are naturalized in Puerto Rico, southern Florida, and Georgia.<sup>7</sup> These cycads and those of the Zamiaceae family are also popular ornamental plants that can be found throughout the United States.<sup>6</sup>



Figure 1. *Cycas revoluta*.

### History of Cycad Toxicosis in Humans and Livestock

Despite a long history of recognized toxic effects, cycads have been a commercially and culturally significant food source for numerous human populations,<sup>1</sup> including groups in South Africa, Australia, and Guam. These populations used similar methods of fermentation and drying to detoxify the plant.<sup>1,8</sup> Acute poisonings in humans usually occur during times of food shortage and when the plants are inadequately processed for ingestion.<sup>1,4,9,10</sup> Such poisonings have been reported as early as the 17th and 18th centuries and as recently as the end of the 20th century.<sup>1,4,10</sup> Symptoms of acute intoxication include “violent retching,” abdominal pain, diarrhea, vertigo, stupor, and muscle paralysis.<sup>1,4,10</sup>

**Box 1. Cycad Toxins<sup>5,6</sup>**

- Azoxyglycosides (e.g., cycasin, macrozamin, neocycasin)  
—Toxic metabolite: methylazoxymethanol
- $\beta$ -Methylamino-L-alanine (BMAA)
- Unidentified high-molecular-weight compound

Similarly, acute poisonings of cattle and sheep have occurred throughout the tropical and subtropical regions, including Puerto Rico, the Dominican Republic, Mexico, the Japanese islands of Okinawa, and Western Australia.<sup>1,11–13</sup> Severe acute hepatic and gastrointestinal signs have been described in these species, resulting in anorexia, hyperthermia, bloody diarrhea, icterus, and death.<sup>11–13</sup> A chronic form of toxicosis (incorrectly called *ricketts* in the past) has been reported to result in partial posterior paralysis and muscle wasting in cattle.<sup>10</sup>

In humans, chronic ingestion of cycad products has been proposed to play a role in the development of amyotrophic lateral sclerosis and parkinsonism-dementia complex (ALS/PDC). This slowly progressing neurodegenerative disease was first noted in the 1950s among the indigenous Chamorro population of Guam, the residents of West New Guinea, and the Japanese residents of the Kii peninsula.<sup>14,15</sup> An association with processed cycad flour (a component of traditional food among the Chamorro and other populations) has been proposed but not proven.<sup>14–16</sup>

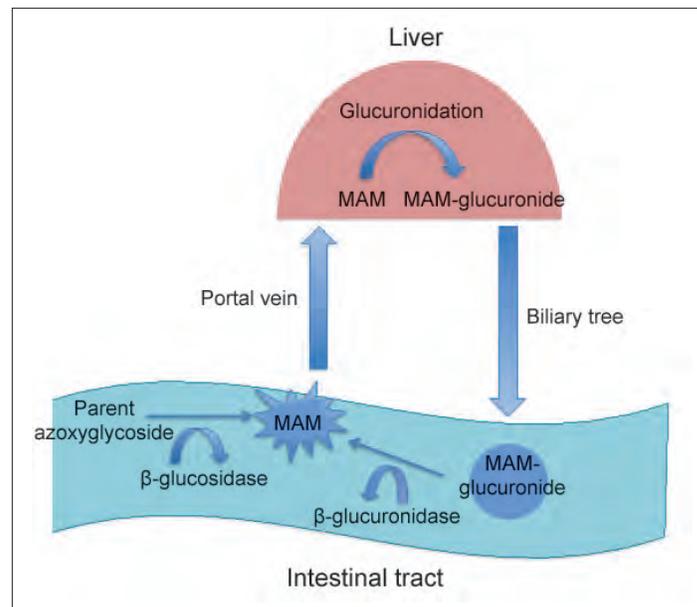
**Toxicokinetics and Mechanisms of Action**

Three types of toxin are present in cycad species: azoxyglycosides,  $\beta$ -methylamino-L-alanine (BMAA), and an unidentified high-molecular-weight compound (**BOX 1**).<sup>5,6</sup> Azoxyglycosides are the compounds responsible for gastrointestinal signs, hepatotoxicity, and carcinogenicity. The latter two compounds have been implicated in the development of neurologic signs.<sup>6</sup>

The toxic agents of cycads are present in all parts of the plant, but seeds contain the highest concentrations.<sup>4,5</sup> A 1998 study of National Animal Poison Control Center (NAPCC; now known as the ASPCA Animal Poison Control Center) records revealed that although most affected dogs (38.7%) ingested the seeds, clinical signs developed in patients that ingested any part of the plant (including the leaves and roots).<sup>5</sup> Ingestion of as few as one or two seeds resulted in severe toxicosis and death.<sup>5</sup>

Of the three toxins, azoxyglycosides are perhaps the most extensively researched. These water-soluble compounds are amino sugars that consist of a sugar component bound via a glycosidic bond to an aglycone, methylazoxymethanol (MAM).<sup>4,14,17</sup> The specific azoxyglycosides identified in cycad species include cycasin, macrozamin, and neocycasin. While the sugar component varies among cycad species, the aglycone component (MAM) is constant.<sup>8,17</sup>

Early studies of azoxyglycosides in mammals established that in vivo hydrolysis of the glycosidic bond must take place for toxic effects to occur. For example, researchers noted that parenteral administration of the parent azoxyglycoside did not result in toxic



**Figure 2.** Intestinal liberation and enterohepatic circulation of MAM. The enzyme  $\beta$ -glucosidase, which is produced by intestinal bacteria, liberates MAM from the cycad azoxyglycoside. MAM undergoes enterohepatic circulation: after glucuronidation by the liver, it is released as a conjugate via the biliary tree into the bowel, where the conjugate is broken down to rerelease the toxin. This second reaction is catalyzed by the enzyme  $\beta$ -glucuronidase, also produced by bacteria.

effects, whereas the isolated compound MAM did result in toxic effects when administered via parenteral routes.<sup>4</sup> Researchers further found that the parent azoxyglycoside was toxic and carcinogenic only after passage through the gastrointestinal tract. Studies of germ-free mice ultimately established that enzymatic conversion of the parent compound by intestinal bacteria resulted in the hydrolysis of the glycosidic bond and release of MAM.<sup>18</sup> The enzyme responsible for hydrolysis of the glycosidic bond is  $\beta$ -glucosidase, which is produced by bacteria of the mammalian gastrointestinal tract.<sup>5</sup> The role of bacterial conversion is further illustrated by the finding (in mice) that neoplasms induced by azoxyglycosides occurred almost exclusively in the large bowel, where bacterial enzymatic production of MAM would be greatest.<sup>8</sup>

Once absorbed, MAM undergoes enterohepatic circulation and is taken up by the liver via the portal vein. It is oxidized by cytochrome P450–dependent enzymes and then conjugated via glucuronidation.<sup>19</sup> The conjugate is excreted via the bile into the small intestine, where it is hydrolyzed by  $\beta$ -glucuronidase (also produced by intestinal bacteria). The parent compound is subsequently released, thereby increasing exposure to the toxin<sup>19</sup> (**FIGURE 2**).

MAM causes acute hepatic failure, which was found to be dose dependent in one experimental study in rats.<sup>20</sup> In this study, MAM was injected intraperitoneally at dosages of 20  $\mu$ g/g, 50  $\mu$ g/g and 200  $\mu$ g/g. Hepatotoxicity did not occur at 20  $\mu$ g/g, but fulminant hepatic failure occurred at the two higher dosages. Greater hepatic injury may therefore be expected with ingestion of greater quantities of plant material. According to studies in animals, cycasin toxicosis results in hepatocellular necrosis, hepatic mitochondrial injury, and

breakdown of the hepatocyte endoplasmic reticulum.<sup>20,21</sup> In addition, studies in rodents have revealed that MAM decreases mitochondrial and adenosine triphosphatase activity and decreases glucose-6-phosphatase activity in the liver.<sup>22</sup> Because glucose-6-phosphatase is essential in gluconeogenesis and glycogenolysis, MAM may also interfere with carbohydrate metabolism.<sup>22</sup>

MAM is also carcinogenic, mutagenic, and teratogenic.<sup>5</sup> These effects have been well demonstrated in rats and nonhuman primates.<sup>6,17,23,24</sup> MAM causes in vitro methylation of nucleic acids (RNA and DNA) within the hepatic cells of rats.<sup>21</sup> Tumors of the renal, hepatic, biliary, intestinal, and central nervous systems have occurred in rats after even small doses of the toxin.<sup>8,24,25</sup> This mutagen also crosses the placenta and disrupts embryonic and fetal development.<sup>8</sup>

Although MAM can lead to neurologic signs from hepatic encephalopathy, it does not cause the specific neuroparalytic effects seen with cycad ingestion. Cows experimentally fed whole leaves of *C. revoluta* developed spinal cord lesions, but those fed the isolated azoxyglycoside (MAM precursor) did not develop these lesions.<sup>12</sup> This finding suggested that other toxic agents within the plant are responsible for the neuroparalytic signs of cycad toxicosis. One such toxin is BMAA, which is present in unprocessed cycad flour and in variable concentrations in the processed flour. This amino acid is an *N*-methyl-D-aspartate (NMDA) agonist that produces neurodegeneration in animal models.<sup>14</sup> BMAA is also the agent that has been implicated in the development of ALS/PDC. The other neurotoxin present in cycad species, an unidentified high-molecular-weight compound, has been associated with hindlimb paralysis and axonal degeneration in the central nervous system (CNS) of cattle that have ingested cycads.<sup>5,6,11</sup>

### Epidemiology in Dogs

Some have speculated that reports of cycad toxicosis in dogs are infrequent because cycad seeds are unpalatable to dogs.<sup>9,26</sup> In a 2012 report, *C. revoluta* ingestion accounted for a very small percentage of all cases of toxin ingestion reported to the NAPCC.<sup>27</sup> However, among toxic plant ingestions (as reported to the NAPCC and in an Australian study), cycad ingestion was relatively common.<sup>27,28</sup>

In contrast to the numerous reports of poisonings in livestock and laboratory animals, descriptions of cycad toxicosis in dogs are limited to three case reports and two retrospective studies.<sup>4-6,9,26</sup> A 10-year retrospective study of records from the NAPCC identified 60 cases of known or suspected cycad toxicosis in dogs.<sup>5</sup> A recent 7-year retrospective study of cases presenting to the Louisiana State University Veterinary Teaching Hospital (LSU VTH) identified 36 cases of known cycad ingestion.<sup>6</sup> A 1985 report describes two dogs that ingested *Zamia floridana* and presented to the University of Florida Veterinary Teaching Hospital.<sup>26</sup> Another 1991 report describes illness in three dogs that presented to the Faculty of Veterinary Science at the University of Pretoria in South Africa after ingesting *C. revoluta*.<sup>4</sup> The third report, from the Murdoch University Veterinary Clinic in Australia (published in 1996), describes poisoning in a dog that ingested *Macrozamia riedlei*.<sup>9</sup>

In the two retrospective studies, age (ranging from 2 months to 11 years) and sex were not predictors of ingestion and toxicosis.<sup>5,6</sup> Doberman pinschers and pugs were overrepresented in one study, but a small sample size might have contributed to this overrepresentation.<sup>6</sup> Most cases of cycad toxicosis presenting to LSU VTH occurred during the spring and summer.<sup>6</sup> A study of toxicosis among cattle in Japan revealed a similar temporal distribution.<sup>12</sup> This pattern might exist because the plant develops palatable young sprouts during these seasons and because the seeds are likely to be present on the ground.<sup>6,12</sup> In the United States, 89.7% of all affected dogs were from southern states or Hawaii, with 55.1% from Florida.<sup>5</sup>

### Pathogenesis

The pathogenesis of cycad toxicosis (particularly the toxic effects of MAM) reflects the consequences of gastrointestinal insult, hepatocellular necrosis, and cholestasis. Coagulopathy is suspected to be a result of decreased hepatic synthesis of coagulation factors as well as of severe cholestasis. Cholestasis interferes with the activation of coagulation factors by disrupting enterohepatic circulation of bile acids, thus decreasing intestinal absorption of vitamin K<sub>1</sub>. The combination of coagulation abnormalities, hepatopathy, and gastrointestinal insult can subsequently lead to disseminated intravascular coagulation (DIC) or sepsis.<sup>6</sup> The direct hepatocellular injury from MAM is exacerbated by concurrent hypovolemia and oxidative damage.<sup>6</sup> Hypoproteinemia is mainly due to gastrointestinal hemorrhage and gastrointestinal protein loss.<sup>9</sup> Hypoproteinemia may be exacerbated because MAM directly decreases protein synthesis via hepatocellular injury, mitochondrial damage, ribosomal damage, and alkylation of hepatic RNA and DNA.<sup>8</sup> In some cases, proteinuria may also contribute to protein loss. Hypocholesterolemia occurs due to a combination of decreased hepatic production and decreased gastrointestinal absorption.<sup>9</sup> The development of acute renal injury is probably due to a combination of bilirubinuria, coagulopathy, and reduction in renal perfusion rather than to direct nephrotoxicity.<sup>9,26</sup>

### Clinical Presentation

The onset of clinical signs in dogs can be as soon as 15 minutes and as late as 3 days after ingestion.<sup>5</sup> The duration of signs has been reported to range from 24 hours to 9 days.<sup>5</sup> In the two veterinary retrospective studies, 85% and 91.6% of dogs experienced vomiting.<sup>5,6</sup> A smaller percentage in both studies (about 30% in each) experienced diarrhea, and a few of these dogs experienced melena or hematochezia.<sup>5,6</sup> Many dogs also presented with lethargy (68%) and anorexia (38%).<sup>6</sup> Some dogs (53.5% reported to the NAPCC and 21% presented to LSU VTH) experienced neurologic signs.<sup>5,6</sup> These signs included weakness, ataxia, conscious proprioception deficits, coma, seizures, and altered mentation.<sup>5,6</sup> Physical examination findings included abdominal pain, icterus, hypersalivation, petechiae, and neurologic abnormalities<sup>6</sup> (**BOX 2**).

The clinical findings described in the three veterinary case reports were similar to those reported in the larger retrospective studies and also included vomiting, abdominal pain, depression,



**Box 2. Common Clinical Signs of Cycad Toxicosis**

- Vomiting
- Diarrhea (± melena or hematochezia)
- Abdominal pain
- Anorexia
- Icterus
- Neurologic signs (weakness, ataxia, seizures)
- Hypersalivation
- Depression

**Box 3. Clinical Pathology of Cycad Toxicosis**

- Hypocholesterolemia
- Elevated ALT and ALP
- Hyperbilirubinemia
- Hypoalbuminemia
- Hyperglycemia/hypoglycemia
- Thrombocytopenia
- Elevated PT/PTT
- Azotemia
- Anemia

ALP = alkaline phosphatase, ALT = alanine aminotransferase, PT = prothrombin time, PTT = partial thromboplastin time

hypersalivation, icterus, melena, and ecchymoses.<sup>4,9,26</sup> In addition, dogs in two of these reports experienced polydipsia.<sup>4,26</sup> The dogs in the case reports did not exhibit neurologic abnormalities such as ataxia, seizure, or conscious proprioception deficits but did experience weakness, prostration, and profound depression.<sup>4,9,26</sup>

**Clinical Pathology**

In some cases, the clinical signs of cycad toxicosis developed quickly, but laboratory and clinical pathologic abnormalities did not become apparent until 24 to 48 hours after ingestion.<sup>5</sup> Commonly observed clinical pathologic abnormalities included hyperbilirubinemia (45.5% in one study and 28% in the other), elevated alanine aminotransferase (ALT; about 50% in both studies) levels, and elevated alkaline phosphatase levels (about 35% in both studies).<sup>5,6</sup> Most dogs had mild to moderate elevations in ALT,<sup>5,6</sup> although severe elevations in ALT have also been reported.<sup>9</sup> Hypocholesterolemia at the time of presentation was a common finding (61% of dogs).<sup>6</sup> Some patients were hypoalbuminemic at presentation (25% of dogs) and many more (44% of dogs) ultimately became hypoalbuminemic.<sup>6</sup> Other biochemical abnormalities that occurred in these dogs included hypoglycemia (12%), hyperglycemia (18%), and thrombocytopenia.<sup>6</sup> According to the NAPCC survey, thrombocytopenia was rarely reported.<sup>5</sup> Among dogs presenting to the LSU VTH, 34% were thrombocytopenic and more than half (56%) had elevations in both prothrombin time (PT) and partial thromboplastin time (PTT).<sup>5,6</sup> Inconsistently reported clinical pathologic findings included hemorrhage, severe anemia, and azotemia.<sup>9,26</sup> One dog was reported to have developed renal failure with severe azotemia, isosthenuria, pigmenturia, and cylindruria within 6 days of toxin ingestion.<sup>9</sup> In contrast, the NAPCC study found that renal failure and elevated blood urea nitrogen (BUN) were rare.<sup>5</sup> Among the dogs presenting to

LSU VTH, 9% had elevations in BUN on presentation, but none had a concurrent increase in creatinine. The authors concluded that renal azotemia was unlikely in these patients because concurrent elevations in creatinine did not occur.<sup>6</sup> However, the initial biochemical data obtained in this study might not account for the development of acute renal failure during the course of hospitalization (**BOX 3**).

**Gross Pathology and Histopathology**

Gross necropsy findings in dogs have included generalized icterus, petechiae, generalized and gastrointestinal hemorrhage, hepatomegaly, and gastric wall edema and congestion.<sup>9,26</sup> Histopathology revealed progressive and dose-dependent hepatic lesions.<sup>8,13,20</sup> In the acute phase,<sup>6</sup> centrilobular hemorrhage and hepatocellular coagulative necrosis, vacuolar degeneration, hepatic venous congestion, pigmentary bile duct distention, bile duct plugging, and intracanalicular cholestasis were commonly seen.<sup>6,8,9,11,13,17,20,26</sup> Midzonal coagulation necrosis and vacuolar degeneration have also been described.<sup>9,26</sup> Subacute and chronic regenerative changes such as nodular regeneration, periportal and bridging fibrosis, stromal collapse, and bile duct proliferation have been reported.<sup>6,11,13,17</sup> Fibrosis occurred mostly around the central veins and extended into the parenchyma to varying degrees.<sup>11,13</sup> Most hepatic lesions also had inflammatory infiltrates.<sup>6,11,13,17,20,26</sup> In one study, chronic lesions (up to 53 days after ingestion) were reported to be more extensive and diffuse.<sup>6</sup> At this stage, one dog in the study had acquired portosystemic shunting.<sup>6</sup>

Only a few studies describe the CNS lesions in dogs. Necropsy of one dog that had generalized weakness revealed mild nerve fiber degeneration in the cranial cerebellar peduncle.<sup>26</sup> More detailed histopathologic descriptions of CNS lesions exist in reports of ruminant and laboratory animal toxicoses. Some of these lesions, such as astrocyte swelling and CNS edema, may have resulted from the hepatic encephalopathy associated with fulminant hepatic failure.<sup>20</sup> Primary CNS lesions associated with cycad toxicosis included vacuolation, demyelination, and spongiform degeneration of the brain and spinal cord.<sup>1,8,11,12</sup> Additional studies are needed to characterize the CNS effects of cycad ingestion in dogs. Other histopathologic findings in animals have included hypertrophy and desquamation of the renal tubular epithelium with tubular casts, pulmonary changes, and bone marrow dyserythropoiesis.<sup>9,17,26</sup>

**Diagnosis**

A tentative diagnosis of cycad toxicosis must rely on a known history of exposure and on the presence of expected clinical signs.<sup>5</sup> As of April 2012, specific blood testing for the detection of MAM was not available through the major veterinary diagnostic laboratories or toxicology laboratories. In some cases, plant material can be found in the stool and vomitus. Even postmortem diagnosis with necropsy in the absence of historical evidence may be challenging because of the nonspecific pathologic findings. The centrilobular pattern of necrosis and destruction of hepatic veins is supportive of the diagnosis, but toxins other than MAM can cause a similar distribution of changes.<sup>6,26</sup> Thus, cycad intoxication

may be underdiagnosed in the canine veterinary population. The index of suspicion should be high in geographic areas where cycads are common and when the clinical signs and historical information are supportive of the diagnosis.

**Treatment**

**Decontamination**

Given the severity of the clinical signs, the lack of any specific antidote, and the dose-dependent nature of cycad toxicosis, treatment of patients that have ingested cycad plant material hinges on decontamination and supportive care. Patients presenting with cycad toxicosis can be unstable or critically ill and should be stabilized before any attempt at decontamination.<sup>29</sup> Decontamination generally consists of a combination of emesis, adsorption, and, in some cases, gastric lavage or colonic irrigation with enemas (FIGURE 3).

Induction of emesis is most effective when performed within several hours of toxin ingestion but may be effective after this time frame if the substance coalesces in the stomach.<sup>29</sup> Ingestion of plant material (such as leaves, bark, seeds, or cones) can delay gastric emptying. Therefore, induction of emesis is justifiable in a stable, alert, and neurologically unimpaired patient, even when the patient presents to the hospital longer than a few hours after ingestion. In such cases, survey abdominal radiography may help the clinician determine if material is present in the stomach.

Agents typically used to induce emesis in dogs include apomorphine and 3% hydrogen peroxide; these agents are successful in most dogs (>90%).<sup>29</sup> Alternative methods of inducing emesis, such as administration of salt or syrup of ipecac, are not recommended. Furthermore, syrup of ipecac is no longer available and can cause cardiotoxicity.<sup>29</sup>

Induction of emesis is contraindicated in unstable patients, hypoxic patients, those with pharyngeal/laryngeal dysfunction, and those with severe CNS dysfunction. Emesis is also contraindicated in patients that have already vomited, especially if they have vomited repeatedly.<sup>29</sup>

Gastric lavage is sometimes performed in patients that do not vomit or in which emesis cannot be safely induced or those in an obtunded or comatose state. Gastric lavage should not be performed as a primary method of decontamination if emesis can be safely induced.<sup>29</sup> Furthermore, gastric lavage should not be performed in a patient that has already vomited because compared with the mean recovery rate with emesis (40% to 60%),<sup>29</sup> the recovery rate with gastric lavage is low (<20% after 1 hour) and decreases greatly with time.<sup>30</sup> The recovery rate of ingested plant material via gastric lavage may be even lower. The risks associated with gastric lavage include aspiration pneumonia, esophageal and gastric perforation, hypoxia, cardiac dysrhythmia, electrolyte

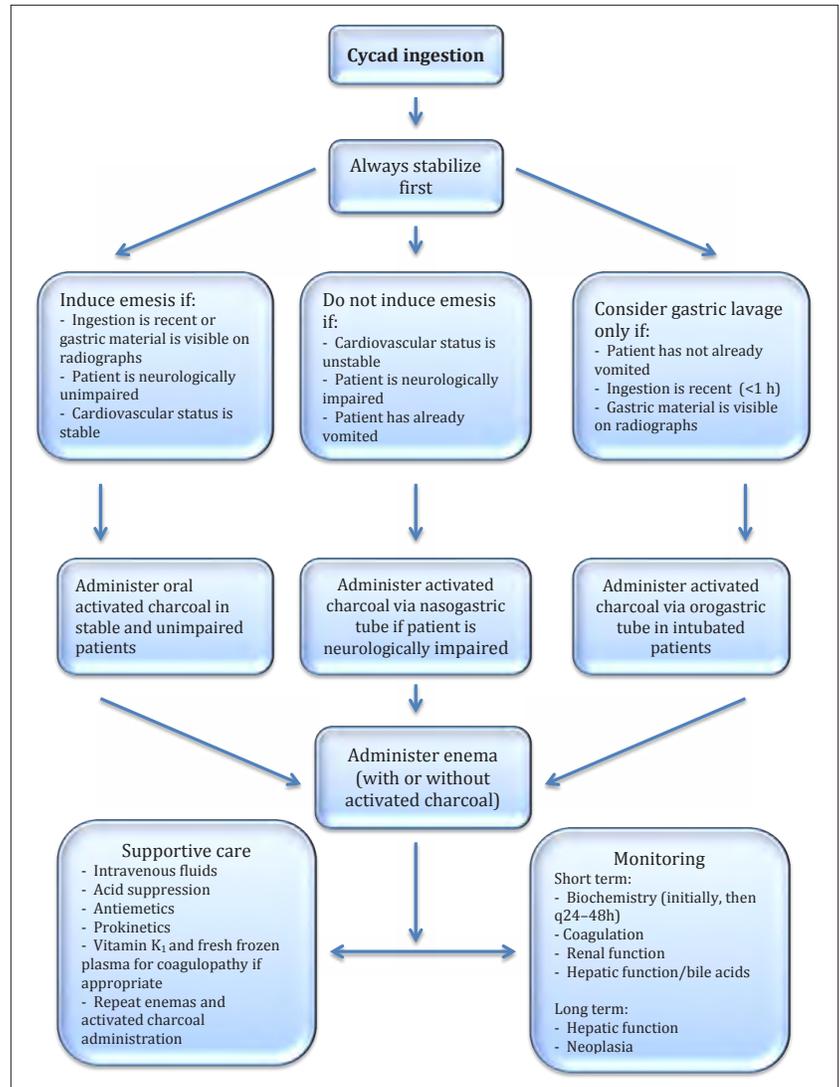


Figure 3. Treatment and decontamination guidelines for cycad toxicosis.

abnormalities (hyponatremia if water is used as the lavage fluid rather than saline), and accidental instillation of fluid into the lungs.<sup>29,30</sup> When emesis is not possible, the clinician must carefully weigh the risks associated with gastric lavage against any potential benefits.<sup>30</sup>

Administration of activated charcoal (with or without cathartic) may be warranted even if emesis is induced successfully and quickly. Adsorption in such cases is recommended because of the suspected potency of cycad seeds<sup>5</sup> and because emesis does not completely empty stomach contents.<sup>29</sup> Oral activated charcoal is an adsorbent with a large surface area that reduces gastrointestinal absorption of toxins by binding toxins with weak chemical bonds.<sup>31</sup> Osmotic cathartics such as sorbitol are often given concurrently with the first dose of activated charcoal because activated charcoal slurries can theoretically slow the gastrointestinal transit time.<sup>31,32</sup>

Activated charcoal best adsorbs toxins that are poorly water soluble and have a high molecular weight. MAM has a low molecular

weight<sup>33</sup> and is highly water soluble. Despite these characteristics, Ferguson et al<sup>6</sup> found that activated charcoal administration had a protective effect in dogs presenting with cycad toxicosis. However, the retrospective nature of the study may have led to a bias, with activated charcoal being administered to less severely affected dogs.<sup>6</sup>

As with emesis, activated charcoal is most beneficial when administered within several hours of toxin ingestion; these benefits diminish greatly with time.<sup>34</sup> Administration of multiple doses of activated charcoal should be considered because MAM undergoes enterohepatic circulation.<sup>19</sup>

Potential complications of activated charcoal administration (with or without a cathartic) include emesis, aspiration of charcoal, hypernatremia, dehydration, constipation, or diarrhea.<sup>31</sup> Administration of oral activated charcoal to weak, neurologically impaired patients can worsen the risk of aspiration and is contraindicated.<sup>34</sup> The risk of aspiration can be reduced by the use of a nasogastric or orogastric tube with concurrent endotracheal intubation.<sup>29</sup> Of note is that commercially available activated charcoal can cause black stools (thus masking melena) and can cause hyperlactatemia despite adequate tissue perfusion.<sup>35</sup>

The administration of enemas, although not well studied, might be beneficial in light of the unique metabolism and absorption of cycad toxins. For example, the localization of MAM-induced intestinal neoplasms in the large intestine suggests that the active carcinogen is concentrated in the large bowel.<sup>8</sup> This localization perhaps occurs as a result of the crucial role of intestinal bacteria in the release of MAM. As with oral activated charcoal, administration of multiple enemas to irrigate the large bowel can be justified because MAM undergoes enterohepatic circulation.

### Supportive Care

For symptomatic patients, therapy should include supportive care for gastrointestinal, neurologic, and hepatic signs. In general, intravenous fluid therapy, antiemetics, and gastroprotectants are recommended.<sup>2</sup> Gastroprotectants can include proton pump inhibitors and H<sub>2</sub> blockers, which can be administered parenterally in patients that are vomiting or not eating. Administration of oral medications such as sucralfate in neurologically impaired and vomiting patients is not recommended. Therapy for coagulopathy and DIC can include vitamin K<sub>1</sub> and fresh frozen plasma transfusions. Vitamin K<sub>1</sub> therapy is not indicated for coagulopathy that results from decreased hepatic production of vitamin K<sub>1</sub>-dependent factors but is appropriate for decreased gastrointestinal absorption of vitamin K<sub>1</sub> due to severe cholestasis.<sup>31</sup> Symptomatic therapy should address known complications of cycad toxicosis, which are multisystemic and can include hepatic encephalopathy, hypoglycemia, anemia, sepsis, and, in some cases, acute renal injury.

### Monitoring

Short-term monitoring of patients with cycad toxicosis should include monitoring of biochemistry values at presentation, within 24 to 48 hours of ingestion,<sup>5</sup> and during the course of treatment. Attention should be paid to renal values and urine sediment findings to detect acute renal injury. Clotting times and bile acids

should also be monitored initially and throughout the course of illness, depending on the severity of clinical signs. Potential long-term consequences of cycad ingestion include hepatic fibrosis, acquired portosystemic shunts,<sup>6</sup> and carcinogenicity. Although it is not known how common these conditions are in dogs, survivors should be monitored long-term for the development of liver dysfunction and neoplasms (**FIGURE 3**).

### Prognosis

It is difficult to draw conclusions regarding the overall prognosis in dogs based on the available veterinary literature. Survival as reported by the NAPCC was 67.9%, which was more favorable than the survival rate of about 50% reported among dogs presenting to the LSU VTH.<sup>5,6</sup> However, of patients reported to the NAPCC, only 27% had documented ingestion. The more favorable prognosis seen in this first study may have been due to inclusion of patients that had not truly ingested cycad.<sup>6</sup> On the other hand, the patients presenting to the LSU VTH, a tertiary care referral facility, may have been more severely affected.<sup>6</sup>

In the report from South Africa, all three dogs that ingested *C. revoluta* made an uneventful recovery within several days after receiving outpatient therapy that included subcutaneous fluids and antibiotics.<sup>4</sup> In the other two case reports, two of three dogs were euthanized despite treatment, and another died during the course of treatment.<sup>9,26</sup>

Of the two retrospective studies of cycad toxicosis in dogs, only one evaluated prognostic indicators for survival. Due to the limited number of cases, risk factors for death could not be determined.<sup>6</sup> However, significant differences were found between survivors and nonsurvivors.<sup>6</sup> Initial ALT activity, initial serum albumin concentration, lowest recorded albumin concentration, and total bilirubin were found to be significantly different between survivors and nonsurvivors. Nonsurvivors had significantly higher ALT, higher total bilirubin, lower initial albumin, and lower trough albumin levels than survivors. More nonsurvivors than survivors had initial elevations in PT and PTT. The history, time of presentation after ingestion, and presence or absence of neurologic signs were not significantly different between survivors and nonsurvivors. No significant differences were found between the two groups in platelet count or in BUN, cholesterol, glucose, and initial lactate levels. In multivariate analysis, charcoal administration was found to be significantly associated with survival.<sup>6</sup>

### Future Research

Although the toxicity of MAM has been extensively evaluated in cattle and laboratory animals, prospective clinical research in the companion animal population is lacking. Future areas of research can include prospective evaluation of prognosis and risk factors for mortality. The potential benefits of activated charcoal (given orally or rectally) in these patients warrant further investigation. Furthermore, the role of intestinal bacteria in cycad toxicosis provides opportunities to investigate more specific therapies and methods of decontamination. Inhibition of bacterial metabolism of the parent azoxyglycoside with antibiotics, prebiotics, or probiotics



merits consideration. These modalities have not been studied in companion animals, but studies in the human literature have shown that diet and antibiotics can alter the activities of enzymes involved in carcinogen and toxic metabolite formation.<sup>19</sup> Furthermore, prebiotic nondigestible oligosaccharides (such as lactulose) have been shown to alter and potentially suppress bacterial metabolic enzymes.<sup>19</sup> Lastly, given the documented teratogenic, mutagenic, neurotoxic, and hepatotoxic effects of cycad toxins, the long-term consequences of cycad ingestion should be investigated in the veterinary population.

## Conclusion

In dogs, cycad plant ingestion results in an array of severe systemic clinical signs. In the short term, these signs can lead to fulminant hepatic failure, severe gastrointestinal signs, coagulopathy, and DIC. Potential long-term consequences of cycad ingestion include hepatic fibrosis, cirrhosis, acquired portosystemic shunts, systemic neoplastic conditions, and teratogenesis. Because of the vague and nonspecific presenting signs of dogs experiencing toxicosis, and because laboratory changes are not apparent for 24 to 48 hours after ingestion, this toxicosis might be underdiagnosed. Given the increasing popularity of cycads as ornamental plants and the potential for life-threatening consequences of ingestion, clinicians faced with an acutely vomiting patient should keep this toxicosis on their list of differentials. Owners should be thoroughly questioned regarding environmental and plant toxin exposure. Treatment should include aggressive decontamination (and, when possible, activated charcoal administration) as well as supportive care. Education of clients about the potential toxicity of this plant can help decrease exposure to, and prevent ingestion of, this toxin.

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**1. Which three toxins are thought to be present in cycad species?**

- a.  $\beta$ -methylamino-L-alanine (BMAA),  $\beta$ -glucosidase, methylazoxymethanol
- b. BMAA,  $\beta$ -glucuronidase, azoxyglycoside
- c. azoxyglycoside, unidentified high-molecular-weight compound, BMAA
- d. azoxyglycoside, unidentified high-molecular-weight compound, methylazoxymethanol

**2. Azoxyglycoside is metabolized by intestinal flora to**

- a. BMAA.
- b. azoxyglycoside.
- c. methylazoxymethanol (MAM).
- d. cyanide.

**3. MAM is known to be**

- a. carcinogenic, cardiotoxic, and hepatotoxic.
- b. neurotoxic, hepatotoxic, and carcinogenic.
- c. teratogenic, nephrotoxic, and hepatotoxic.
- d. hepatotoxic, carcinogenic, and teratogenic.

**4. A diagnosis of cycad toxicosis relies on**

- a. identification of MAM in the blood.
- b. a history of known or suspected exposure with associated clinical signs.
- c. identification of BMAA in the blood.
- d. all of the above

**5. The most commonly reported clinical sign in dogs with cycad toxicosis is**

- a. lethargy.
- b. vomiting.
- c. diarrhea.
- d. seizures.

**6. Which statement regarding decontamination measures for dogs with cycad toxicosis is true?**

- a. Induction of emesis is contraindicated in all patients.

- b. Activated charcoal administration has not been found to have a protective effect.
- c. Gastric lavage should not be performed in a patient that has already vomited.
- d. Administration of multiple enemas to irrigate the large bowel cannot be justified.

**7. The toxic effects of MAM include**

- a. decreases in mitochondrial and adenosine triphosphatase activity as well as in glucose-6-phosphatase activity in the liver.
- b. hepatocellular necrosis, hepatic mitochondrial injury, and breakdown of the hepatocyte endoplasmic reticulum.
- c. in vitro methylation of nucleic acids (RNA and DNA) within the hepatic cells of rats.
- d. all of the above

**8. Which of the following histopathologic changes is pathognomonic for cycad toxicosis?**

- a. pigmentary bile duct distention
- b. hydropic degeneration of hepatocytes
- c. centrilobular pattern of necrosis and destruction of hepatic veins
- d. none of the above

**9. Which statement regarding clinical signs of cycad toxicosis in dogs is true?**

- a. Clinical signs may develop before laboratory tests show abnormal results.
- b. The onset of clinical signs is always within 12 hours of cycad ingestion.
- c. The duration of clinical signs is limited to less than 1 week.
- d. Most dogs present with neurologic signs.

**10. Monitoring of dogs with cycad toxicosis should include**

- a. serial assessment of biochemistry values.
- b. urinalysis.
- c. long-term follow-up.
- d. all of the above