Thinking Fungus

Systemic Mycoses in Companion Animals

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KEYWORDS

• Fungal • Mycology • Mycosis • Invasive • Infection • Dog • Cat

KEY POINTS

- Systemic mycoses are clinically relevant to cats and dogs throughout the world.
- Clinical findings are variable and overlap with many other diseases.
- Diagnosis often requires routine laboratory work, imaging studies, pathology, and fungal biomarkers.
- Early diagnosis and appropriate treatment are crucial for treatment success.
- Treatment monitoring is multi-modal and considers clinical signs, physical examination, imaging studies, and biomarker testing.

INTRODUCTION

Systemic mycoses (SM) are serious and potentially life-threatening fungal infections that can be multisystemic or localized to any organ-traditionally excluding infections limited to the skin, hair or nails. The most common SM in cats and dogs in North America are discussed in this article. Systemic mycoses can be broadly categorized into dimorphic (blastomycosis, histoplasmosis, coccidioidomycosis), yeast (cryptococcosis), or mold (aspergillosis) infections. Dimorphic pathogens (dimorphs) exist as a mycelium in the environment and yeast in the body. Common dimorphic infections tend to be heavily endemic in specific geographic locations (**Fig. 1**). Systemic yeast and mold infections are less concentrated geographically and occur in all US states and Canadian provinces.

Fungal pathogens are found in the environment, each with a unique niche that best supports growth and sporulation. For pathogens discussed here, inhalation of spore-like structures is the primary mode of infection. Disease of the respiratory tract is common. Dissemination to other organs is possible (**Table 1**). Diagnosing an SM often requires pathology and biomarker testing. Recognizing the clinical pattern is vital for early testing and treatment (**Fig. 2**).

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Abbreviations	
AFST	antifungal susceptibility testing
BALf	broncho-alveolar lavage fluid
EIA	enzyme immunoassay
GM	galactomannan
GXM	glucuronoxylomannan
ID	immunodiffusion
IPA	invasive pulmonary aspergillosis
IV	intravenously
LA	latex agglutination
LCAT	latex cryptococcal agglutination test
SM	systemic mycoses
SQ	subcutaneously
TB	tracheobronchial
TDM	therapeutic drug monitoring
TP	tube precipitin

Pathology

The presence of fungal organisms in pathology (cytopathology or histopathology) supports the diagnosis of SM and warrants antifungal treatment. Fungal organisms are generally accompanied by granulomatous, suppurative, or mixed inflammation. Organisms can be sparse, especially in certain tissues such as bone and synovium. Failure to find organisms does not to rule out SM. Cytopathology is rapid and relatively minimally invasive-with collection techniques including fine needle aspiration, centesis, scrape, swab, or impression. Common samples include cutaneous impression

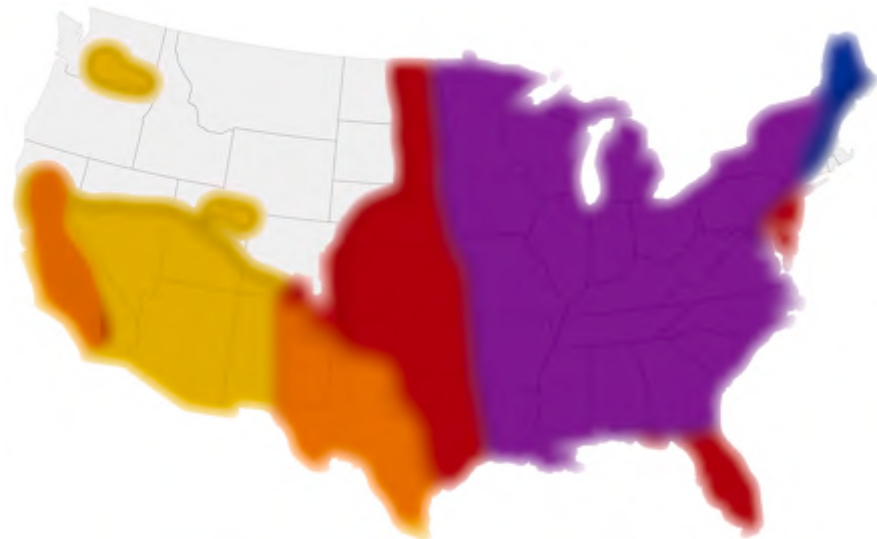


Fig. 1. Map demonstrating endemic regions for blastomycosis, histoplasmosis, and coccidioidomycosis in dogs and cats in the United States. (blue, blastomycosis; red, histoplasmosis; yellow, coccidioidomycosis; orange, coccidioidomycosis and histoplasmosis; purple, blastomycosis and histoplasmosis). Systemic yeast (cryptococcosis) and mold (aspergillosis) are found in all 50 states. Map lines delineate study areas and do not necessarily depict accepted national boundaries.

Table 1
Common pathogens, organs involved, and signs associated with systemic mycoses in dogs and cats

Pathogen	Species Affected (Relative Incidence[a])	Common Organs Involved	Common Organ Specific Signs
Blastomyces	Dog>>>Cat (50 : 1)	Lung	Tachypnea
		Lymph nodes	Cough
		Skin	Lymphadenomegaly
		Eyes & periocular tissues	Vision disturbance
		Bones & joints	Cutaneous Lesions
		Testicles & prostate (dog)	CNS signs (cat)
		CNS (cat)	Lameness
Histoplasma	Cat>Dog (4 : 1)	Lung	Tachypnea
		Lymph node	Lymphadenomegaly
		Spleen & Liver	Abdominal organomegaly
		Eyes & periocular tissues	Mucosal Pallor/Jaundice
		Bone marrow	Lameness (cat)
		Bones & joints (cat)	Vision disturbance
		GI tract (dog)	Cutaneous lesions (cat)
			Diarrhea (dog)
Coccidioides (valley fever)	Dog>>>Cat (50 : 1)	Lung	Cough
		Bones & joints	Tachypnea
		Lymph nodes	Lameness
		Skin	Cutaneous lesions
		CNS	CNS signs
Cryptococcus	Cat>Dog (5 : 1)	Nasal cavity & sinuses	Nasal discharge
		Eyes & periocular tissues	Facial deformity
		Lymph nodes	Cutaneous lesions
		Skin	Vision disturbance
		CNS	CNS signs
		Abdominal viscera (dog)	Vomiting, diarrhea (dog)
Aspergillus (systemic)	Dog>>Cat (25 : 1)	Bones & joints	Lameness
		Vertebral end plates	Paraparesis
		CNS	Pain Paraspinal/Nondescript
		Kidney	Vision disturbance
		Lymph nodes	CNS signs
		Skin	Cutaneous lesions
		Eyes	Polyuria/Polydipsia

[a] Relative incidence is an estimate of host-species predisposition. This will vary by geographic area, patient population, and other factors.

smears, subcutaneous lesion or lymph node aspirates, and rectal mucosal scrapes. Romanowsky-type stains (Diff-Quick) work well. Cytopathology slides should be air-dried and ideally some left unstained, before send-out pathology review. Fungal organisms can be missed on routine histopathology H&E stains, and special fungal stains (GMS, PAS) should be used for suspect cases.

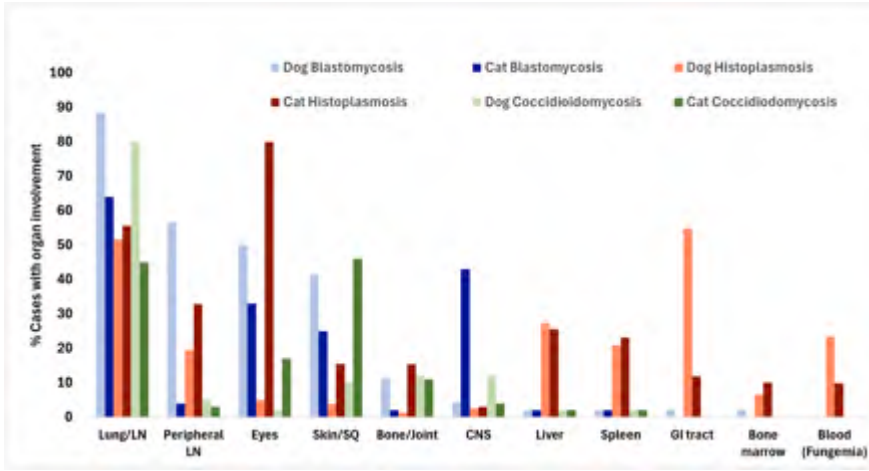


Fig. 2. Prevalence of organ involvement with systemic dimorphic fungal infections in dogs and cats.

Fungal Culture

Culture is uncommonly used to establish the diagnosis of SM. If collected from a non-sterile site (GI, respiratory, urogenital, and skin), isolates can be contaminants, or colonizers (eg, *Cryptococcus* in nasal cavity or *Aspergillus* in respiratory tract). Culture has the disadvantage of a long turnaround (up to 6 weeks for dimorphs). Culture can have a relatively low diagnostic sensitivity, for example, *Histoplasma* can only be isolated in culture from approximately 50% of cats with histoplasmosis.[1] Fungi pose a risk to laboratory personnel and culture should only be done in a microbiology laboratory.

To improve chances of fungal isolation, samples for culture should be collected from as many affected sites and as deep within the lesion(s) as possible. Tissue samples collected via biopsy are highest yield and preferred over swabs or aspirates. Samples should be stored at room temperature and delivered to the microbiology laboratory as soon as possible. Suspicion of a particular pathogen should be reported to the microbiology laboratory as it might affect culture conditions.

Antifungal Susceptibility Testing

Culture isolates can be used for antifungal susceptibility testing (AFST). This is most useful for invasive molds (*Aspergillus*) or yeasts (*Cryptococcus*), where susceptibility is less predictable. Interpretive breakpoints are not available for fungal pathogens in veterinary host-species. However, AFST results in conjunction with available pharmacokinetic data, can guide antifungal selection.

Fungal Biomarkers

Fungal biomarkers include fungal antigens and antifungal antibodies. Common test methods include enzyme-linked immunoassay (EIA or ELISA) for antigen or antibody detection, latex agglutination (LA) for antigen detection, and agar-gel immunodiffusion (ID or AGID) for antibody detection. Diagnostic performances for common biomarker tests are found in **Table 2**. Common antigen biomarkers are polysaccharides continuously shed by the fungus. These include galactomannan (GM) for *Histoplasma*, *Blastomyces*, and *Aspergillus*; and glucuronoxylomannan (GXM) for *Cryptococcus*.

Table 2
Published diagnostic performances of fungal biomarker tests

Pathogen	Test	Host-Species	Sample	Sensitivity[a]	Specificity[a]
Blastomyces	**Antigen EIA**	**K9**	**Urine**	95	97[2–5]
		K9	Serum	91	100[3–5]
		Feline	**Urine**	90	NA[6–8]
	Antibody EIA	K9	Serum	82	97[3,4]
	Antibody ID	Feline	Serum	30	NA[8–10]
		K9	Serum	54	100[3,4,11,12]
Histoplasma	**Antigen EIA**	**K9**	**Urine**	92	99[13,14]
		Feline	**Urine**	94	98[15,16]
		Feline	Serum	73	100[17]
	Antibody EIA	K9	Serum	78	93[18]
		Feline	Serum	83	95[18]
	Antibody ID	K9	Serum	14	98[18]
		Feline	Serum	0	NA[18]
	Real-Time PCR	Feline	Blood	0	NA[19]
Coccidioides (valley fever)	Antigen EIA	K9	Urine	8	100[20,21]
		K9	Serum	27	97[20,21]
	Antibody EIA	**K9**	**Serum**	89	94[20]
	Antibody ID	**K9**	**Serum**	87	92[20,22–24]
		Feline	**Serum**	99	NA[25,26]
Cryptococcus	**Antigen LA**	**K9**	**Serum**	94	100[27–30]
		Feline	**Serum**	97	NA[27,29,31]
Aspergillus (systemic)	**Antigen EIA**	K9	Urine	88	92[32]
		K9	**Serum**	92	84[32]
Aspergillus (sinonasal)	Antigen EIA	K9	Serum	24	82[33]
		Feline	Serum	23	78[34]
	Antibody ID	**K9**	**Serum**	76	100[33]
		Feline	**Serum**	43	100[35]

Bolded tests and samples are the recommended initial test for each pathogen and host-species.
[a] Test performance varies by laboratory. For tests where performance was reported in multiple studies, a pooled-mean sensitivity and specificity was reported.

Antifungal Drugs

Antifungal drugs and dosages used to treat SM can be found in **Table 3**. Itraconazole and fluconazole are the most commonly used antifungals. Hepatotoxicity is possible with all azoles and serum biochemistry should be monitored at 1-month then every few months after starting treatment. Increased alanine transaminase (ALT) activity is the most common abnormality. Much less commonly, toxicity causes decreased liver function (albumin, blood urea nitrogen [BUN], glucose, and cholesterol) with normal liver enzyme activities. Cutaneous vasculitis causing ulcerative skin lesions can occur, most common in dogs with toxic itraconazole blood levels. Drug-to-drug interactions due to decreased metabolism of drugs given concurrently with azoles, is an important consideration. Possible interactions include, but aren't limited to, corticosteroids,

Table 3
Starting antifungal dosages used to treat systemic mycoses in dogs and cats

Drug	Host	Formulation	Dose[a]	Frequency	Route
Itraconazole[b]	Dog	Capsule or Solution	5 mg/kg (max 200 mg/day starting dose)	SID (or split BID)	PO
	Cat	Capsule	10 mg/kg	SID (or split BID)	
		Oral Solution	3–4 mg/kg	SID (or split BID)	
Fluconazole	Dog	Tablet or Oral Solution	20 mg/kg	SID (or split BID)	PO
	Cat	Tablet or Oral Solution	20 mg/kg	SID (or split BID)	
Posaconazole[b]	Dog	Tablet ER	5 mg/kg	EOD	PO
		Solution	5 mg/kg	BID	
	Cat	Oral Solution	15 mg/kg once, then 7.5 mg/kg	SID	
Voriconazole[b]	Dog	Tablet or Oral Solution	3–4 mg/kg	BID	PO
	Cat	Tablet or Oral Solution	12.5 mg (total dose)	Every 3 d	
Terbinafine	Dog	Tablet	20–30 mg/kg	SID	PO
	Cat	Tablet	125 mg (total dose)	SID	
Amphotericin B (lipid/liposomal)	Dog	Solution	1–2 mg/kg	EOD	IV
	Cat	Solution	0.5–1 mg/kg	EOD	
Amphotericin B[c] (deoxycholate)	Dog	Solution	0.5–1 mg/kg	EOD	IV
	Cat	Solution	0.25–0.5 mg/kg	EOD	IV
Caspofungin	Dog	Solution	1 mg/kg	SID	IV
	Cat	Solution	1 mg/kg once, then 0.75 mg/kg	SID	
Micafungin	Dog	Solution	2 mg/kg	SID	IV

Abbreviation: ER, extended release
[a] Starting dosages only. Dosage should be optimized based on clinical response, adverse-effects, and therapeutic drug monitoring as appropriate.
[b] Therapeutic drug monitoring should be considered.
[c] Sub-cutaneous administration protocols are available.

cyclosporine, ivermectin, digoxin, and macrolides. To individualize dosage, itraconazole blood levels should be used for therapeutic drug monitoring (TDM), as absorption and metabolism are variable from animal-to-animal.[36]

Next-generation azoles, voriconazole and posaconazole, have an expanded mold spectrum and maintain activity against dimorphs and yeasts. These should be considered as first-line treatment of systemic mold infections and can be used when first-line treatment of dimorphic or yeast infection fails or is not tolerated (salvage therapy). Voriconazole can cause neurotoxicity, which can manifest as photophobia, mydriasis, decreased menace response, decreased pupillary light reflex, tremors, ataxia, paraplegia, and other signs of central nervous system (CNS) dysfunction. Azoles can occasionally cause polyuria/polydipsia, which is most common with voriconazole in

dogs. Blood levels for TDM should be considered for posaconazole and voriconazole, especially with suspect adverse-effects or inadequate clinical response. Isavuconazole has a promising safety profile in humans, and the pharmacokinetics in cats and dogs has been reported.[37,38]

Amphotericin-b should be considered for life-threatening SM in nonazotemic, euhydrated animals. It is broadly fungicidal and reaches therapeutic concentrations quickly. Lipid or liposomal encapsulated formulations (Ambisome or Abelcet) decrease, but do not eliminate the risk for nephrotoxicity. Kidney values and electrolytes should be checked before each dose. Encapsulated amphotericin-b should be given intravenously (IV). The original deoxycholate formulation can be given IV or subcutaneously (SQ). Subcutaneous administration requires significant dilution (0.45% NaCl/2.5% dextrose) to avoid cellulitis.[39]

Terbinafine has *in vitro* activity against common pathogens and is mostly used in combination with azoles. It should be considered in combination with voriconazole or posaconazole as first-line treatment of systemic mold infections, or as a possible salvage treatment when added to itraconazole or fluconazole for dimorphic or yeast infections. Terbinafine can cause vomiting, diarrhea, anorexia, or hepatotoxicity, and blood biochemistry monitoring should be done.

BLASTOMYCOSIS

Blastomycosis is caused by cryptic species *Blastomyces dermatitidis* and *B gilchristii*. Other species including *B helicus*, which causes pneumonia in animals in the western United States and Canada, are not discussed. Fungal growth, sporulation, and aerosolization occur in areas with wet/dry cycles, and living within one-fourth mile of fresh water (lake, river, stream, and canal) is a significant risk.[40] Inhalation of conidia (spores) from the environment is the primary mode of infection. Blastomycosis is found throughout the United States and Canada east of the Rockies, with the highest incidence being in states/provinces that border the Great Lakes and St. Lawrence, Ohio, Missouri, and Mississippi Rivers. Outdoor activities that increase exposure to aerosolized spores increases chance of infection, but indoor only cats are still at risk.

Blastomycosis is the most common SM in dogs in the eastern United States and Canada. Dogs are significantly more likely to be diagnosed as compared to cats. Dogs and cats of any age, breed, or sex are at risk. It is most common in young-middle aged animals. Coonhounds, pointers, Doberman pinschers, retrievers, and weimaraners are potentially predisposed.[11,41] In some reports, prevalence is higher in male dogs.[41,42]

Clinical Findings

Nonspecific signs are common and include loss of appetite, lethargy, weight loss, and intermittent fever. The most common organs involved include lung, eye, skin, lymph node, and bone/joints (see **Fig. 1**). Respiratory findings can include cough, tachypnea/dyspnea, exercise intolerance and adventitial lung sounds. CNS involvement is more common in cats and can include any neurolocalization. Reported findings have included seizures, hyperesthesia, proprioceptive ataxia, extensor rigidity, paraparesis, head tilt, and circling.[8,10] Nodular and/or ulcerative skin lesions with draining tracts and lymphadenopathy are common. Osteoarticular involvement can include one or multiple bone/joints. A single or multiple swollen digits is a relatively common presenting complaint. It is due to cellulitis with or without underlying osteomyelitis. Animals with maxillary or mandibular osteomyelitis can present for oral pain and losing teeth.

Early detection of ocular disease is important for salvaging vision. Disease can be unilateral or bilateral. In dogs, involvement of both segments (endophthalmitis, panophthalmitis, panuveitis) is most common, followed by disease limited to the posterior segment (chorioretinitis, retinal detachment) then anterior segment (anterior uveitis).[43] Secondary glaucoma is common with anterior uveitis. Disease of the posterior or anterior segment is more common than involvement of both segments in cats.[8,44] Many, but not all, animals with ocular involvement have disease in other organs.

Imaging

On chest radiographs, a structured interstitial pattern (nodular and miliary) is most common, but is only found in approximately 50% of cases.[11] Other findings can include an alveolar pattern, large solitary or multiple masses (cannon ball pattern), cavitary lesions, or tracheobronchial lymphadenopathy.[11] With osteoarticular disease, radiographic findings include bone lesions that are primarily lytic and joint effusion with overlying soft tissue swelling.

Diagnosis

The diagnosis of blastomycosis is often made based on clinical findings, pathology, and antigen testing (**Table 2**). In pathology samples, *Blastomyces* yeasts are 8 to 20 μm spherical structures with double-contoured walls. Broad-based budding is common (**Fig. 3**). Organisms were found in cytopathology in 71% of dogs with blastomycosis in one report, including mostly skin, lymph node, and lower respiratory samples.[11]

Blastomyces antigen, GM, is consistently shed by the fungus and can be detected by enzyme immunoassay (EIA) in many body fluids.[45] Antigen testing is the biomarker of choice for cats and dogs. Urine is preferred over serum for initial testing, due to higher GM concentration (see **Table 1**). There is high cross-reactivity between *Blastomyces* and *Histoplasma* antigens. Testing for both antigens in the same animal at the same time, is generally not recommended. Anti-*Blastomyces* antibody tests are recommended in specific clinical scenarios. Immunodiffusion (ID) is commercially available and is not recommended due to low diagnostic performance. An EIA is commercially available for dogs and is recommended in the following scenarios.

1. Negative antigen test and moderate-high suspicion of blastomycosis
2. Low positive ($\leq$1 ng/mL) antigen test and low suspicion of blastomycosis
3. Localized disease (skin, bone, eye, etc.)

Treatment

Itraconazole is considered the first-line treatment of choice for mild-moderate disease. Fluconazole is an alternative, although *Blastomyces* is relatively more susceptible to itraconazole. Anecdotally, intravitreal voriconazole has been used for severe ocular disease, and additional research is needed to optimize the protocol. Amphotericin-B is the treatment of choice for nonazotemic, euhydrated animals with life-threatening disease, which generally includes severe respiratory disease or CNS involvement. Amphotericin-b should be followed by azole treatment. Concurrent anti-inflammatory corticosteroids, for as short a duration as possible (<4 weeks), should be considered with CNS, ocular, or severe pulmonary disease. All of the criteria described in **Table 4** should be met before stopping treatment.

Prognosis

For dogs, survival rate to discharge, and 2 and 6 months after diagnosis was 87%, 74%, and 69%, respectively, in one study.[2] In the same study, all dogs with urine

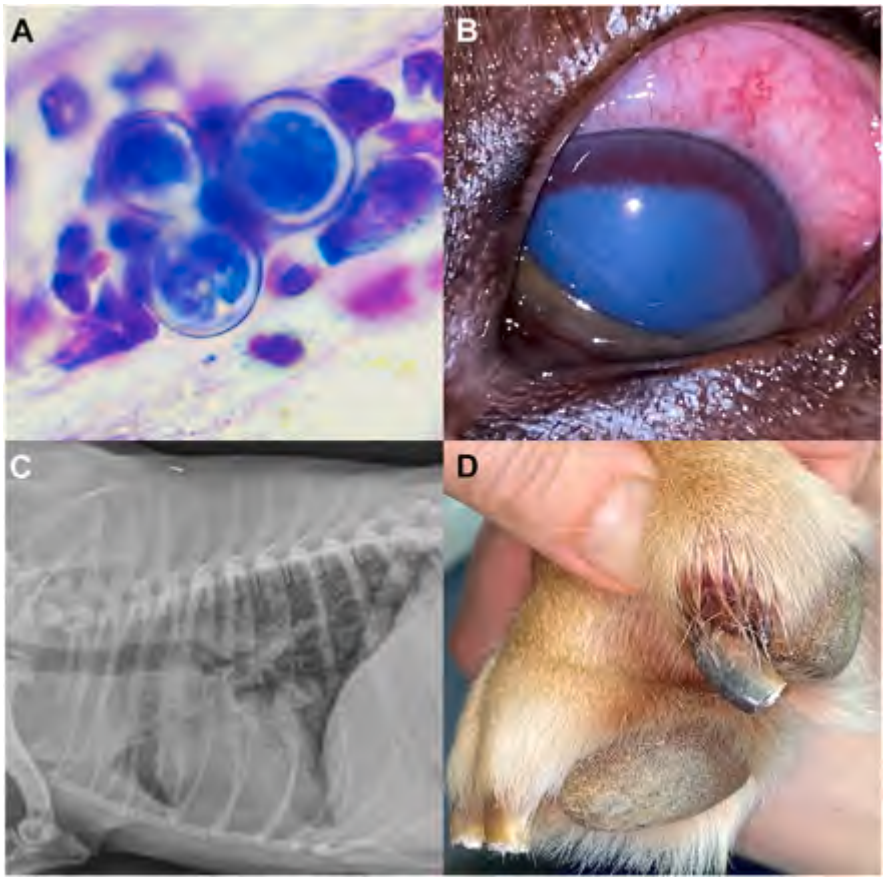


Fig. 3. (*A-D*) (*A*) *Blastomyces*, note the double contoured wall, dark staining nucleus and broad-based budding yeasts; (*B*) Anterior uveitis, note the conjunctival hyperemia, episcleral injection, chemosis, and corneal edema with perilimbal corneal vascularization in a dog; (*C*) Thoracic radiograph showing a diffuse structure interstitial pattern and small volume pleural effusion in a dog; (*D*) Cellulitis and draining tract on the toe in a dog. (*Image courtesy* Image A is courtesy of Dr. Jeff Powers, Images B and D are courtesy of Dr. Helga Kecova.)

antigen concentration less than 5 ng/mL were alive at the end of the study. Negative prognostic indicators include more severe pulmonary disease (more radiographic lung disease) and CNS involvement.[2]

HISTOPLASMOSIS

Histoplasmosis is primarily caused by the cryptic species *Histoplasma mississippense* and *H ohioense*, formerly known as strains (NAM1 and NAM2) of *Histoplasma capsulatum*. *Histoplasma* has an environmental niche for nitrogen rich soil contaminated with bird or bat feces. Activities that disturb dirt and aerosolize microconidia (spores) in the environment, increase the risk of infection. Cats with access to poultry are at increased risk. Indoor-only cats are commonly diagnosed with histoplasmosis, suggesting it is in the home.

In the United States, histoplasmosis is most commonly found east of the Rockies and in California (see **Fig. 1**).[46–48] Cats are more likely than dogs to be infected. In

Table 4
Recommended criteria for determining when to discontinue antifungal treatment (meet all criteria) in dogs and cats with blastomycosis

Monitoring Tool	Criteria	Notes
Minimum Duration	Minimum of 6 mo of treatment	• Required duration is often much longer.
History	Past resolution of clinical signs	• Mild exercise intolerance might persist, most notable in working or performance animals. • Persistent tracheobronchial lymphadenopathy can cause cough, requiring concurrent corticosteroid treatment.
Physical Examination	Past resolution of physical examination abnormalities	• Differentiating active ocular disease from permanent inactive change is important.
Imaging Studies	Past resolution of imaging abnormalities	• Pulmonary scarring can be permanent and can cause static focal unstructured interstitial lung disease. • Radiographic bone lesions should improve but might never return to normal.
Blastomyces Antigen EIA	No detectable antigen OR Antigen $\leq$0.5 ng/mL on 2 consecutive rechecks at least 3 mo apart	• Urine is the ideal sample • Most dogs, and essentially all cats, have no detectable antigen at the time of remission. • Submit antigen test at diagnosis, every 3 mo during treatment, and at 6 mo then every 12 mo after treatment.

many areas of the eastern United States, histoplasmosis is the most common SM in cats.[9,42] Any age, breed, or sex can be affected. The median age for dogs and cats is 3-year and 7-year, respectively.[9,42,49–51] The Brittany, weimaraner, and pointer in addition to dogs in the American Kennel Club working, sporting, and terrier groups might be predisposed.[42] There is no clear sex predilection in either dogs or cats.

Clinical Findings

Disseminated multisystemic disease is found in approximately 60% and 75% of dogs and cats, respectively. This is followed disease localized to the lung (20%) in cats and the GI tract (33%) in dogs.[50,52–54] *Histoplasma* is an intracellular pathogen and involvement of hemolymphatic organs (bone marrow, spleen, liver, lymph node) is relatively more common as compared with other common fungal pathogens (see **Fig. 2**). Nonregenerative anemia, thrombocytopenia, or pancytopenia can be seen with bone marrow involvement, most common in cats.

Signs are often nonspecific and include lethargy, weight loss, anorexia, and intermittent fever. With pulmonary involvement, dyspnea or tachypnea without a cough is common. Greater than 80% of cats have ocular involvement most commonly chorioretinitis and retinal detachment.[55] Blindness can be the first or only sign. Findings can also include optic neuritis, anterior uveitis, conjunctivitis, and blepharitis. Over 50% of dogs with histoplasmosis have GI involvement. Mixed or large bowel diarrhea with mucous, blood, and tenesmus is common. Abdominal distension might be

present, which is caused by ascites and/or organomegaly. With liver involvement, jaundice might be evident. Osteoarticular disease causes lameness and joint effusion, more common in cats.[56] Peripheral lymphadenopathy is common. Nodular and/or ulcerative oral, cutaneous, or mucocutaneous lesions can be found. CNS involvement is uncommon (<5%).

Imaging

Chest radiographs can reveal any lung pattern, lymphadenopathy, and/or pleural effusion. A diffuse structured interstitial pattern (nodular or miliary) is found in approximately 50% of cases with lung involvement. Large fungal granulomas can cause pulmonary masses, which can be calcified. Radiographic bone lesions are often primarily lytic. Multiple bones in the carpi and tarsi are often affected in cats, accompanied by joint effusion and overlying soft tissue swelling (**Fig. 4**).

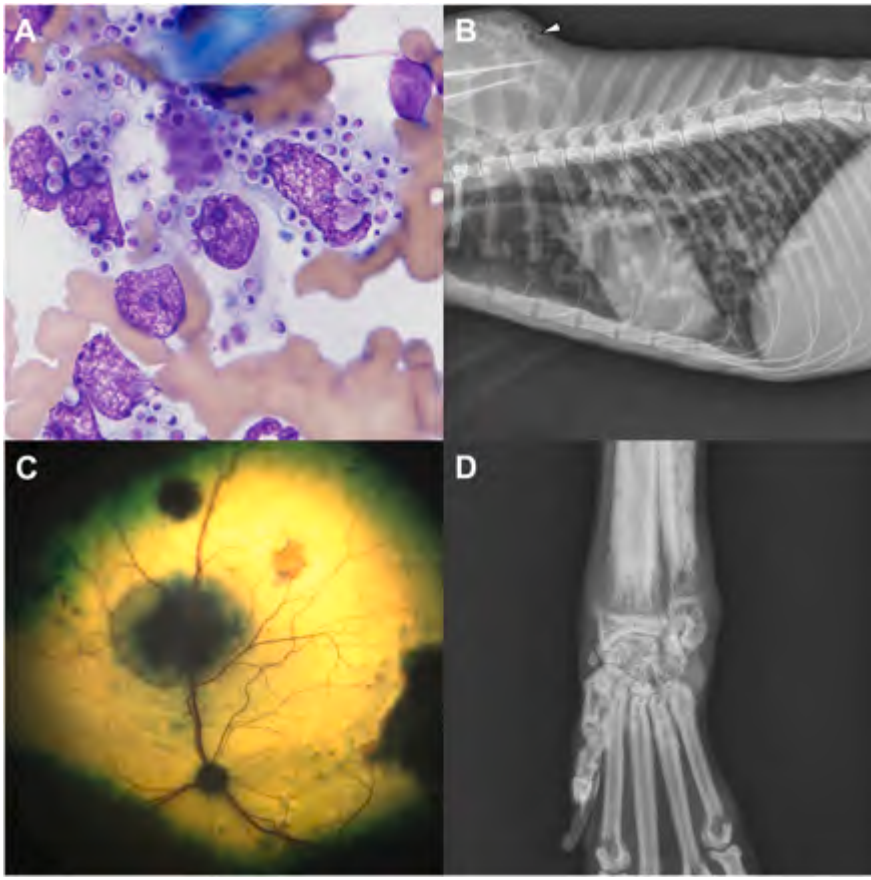


Fig. 4. (*A-D*) (*A*) *Histoplasma*, note the small intracellular yeasts with a dark staining eccentrically placed nuclei and small clear pseudocapsule; (*B*) Thoracic radiograph showing a mixed lung pattern and osteomyelitis of the scapulas (*arrowhead*) in a cat; (*C*) Chorioretinitis in a cat; (*D*) Osteomyelitis of the carpus with primarily osteolysis of multiple bones, joint effusion and overlying soft tissue swelling in a cat. (*Image courtesy* Image A is the courtesy of Dr. Jim Meinkoth and Image C is the courtesy of Dr. Emily McCool.)

On abdominal ultrasonography splenic changes include splenomegaly and hypoechogenicity.[51] Other findings can include free abdominal fluid; hepatomegaly with or without hyperechogenicity; lymphadenopathy; and GI wall thickening with or without a loss of normal layering. The distal colon and rectum are most often affected in dogs.

Diagnosis

Diagnosis is made based on clinical findings, pathology, and antigen testing. Small oval-round yeasts, 2 to 5 μm in diameter (see **Fig. 4**), are found within macrophages on pathology of lung, liver, spleen, lymph node, skin, and bone marrow samples. With GI involvement, organisms can be found on rectal scrape cytology. In 10% to 20% of animals, organisms can be found on blood smear in white blood cells (fungemia). Organisms can also be found in pleural or abdominal fluid, lower respiratory specimens, and synovial fluid.

The *Histoplasma* antigen EIA is the biomarker of choice in cats and dogs.[13–16] Urine is preferred over serum for initial testing. There is cross-reactivity with other dimorphic pathogens, especially *Blastomyces*. False negative antigen testing is more likely with localized disease (eyes, GI tract, or bone/joint). There are two methods for anti-*Histoplasma* antibody detection. Immunodiffusion (ID), offered by many laboratories, has a low diagnostics sensitivity (0%–14%) and is not recommended for dogs or cats.[18] An IgG EIA has a higher diagnostic sensitivity (78%–81%), and is positive in dogs and cats with histoplasmosis that have false negative antigen testing (see **Table 2**).[18] Anti-*Histoplasma* antibody testing is recommended in the following scenarios.

1. Negative antigen test and moderate-high suspicion of histoplasmosis
2. Low positive (<1 ng/mL) antigen test and low suspicion of histoplasmosis
3. Localized disease (skin, bone, eye, GI etc.)

Real-time PCR (RT-PCR or qPCR) assays that target *Histoplasma* DNA are commercially available but perform poorly when blood is tested in cats and are not recommended.[19]

Treatment

Itraconazole has traditionally been considered the oral antifungal of choice.[57] Fluconazole is a reasonable alternative. Retrospective studies have failed to detect a difference in survival or relapsed rates when comparing itraconazole and fluconazole in cats.[49,54] Amphotericin-b should be considered for life-threatening disease – severe lung (need for O2 supplementation), liver (hyperbilirubinemia), CNS, or bone marrow disease (pancytopenia).[54,58] Amphotericin-b should be followed with azole therapy. Posaconazole or voriconazole are options for salvage therapy. The addition of terbinafine to itraconazole could also be considered. Corticosteroid therapy, administered concurrently with antifungal drug, should be considered when signs of severe respiratory disease, CNS involvement, ocular involvement, or when amphotericin-b is administered. In general, an anti-inflammatory dose is tapered over 7 to 14 days. Prolonged or high dose corticosteroid therapy should be avoided. Reported disease relapse rates are 25% to 40% in cats.[49,53] Similar data is not available for dogs. **Table 5** shows criteria to meet before stopping antifungal treatment.

Survival with treatment is similar for cats and dogs—90% to hospital discharge, 75% at 1 to 2 months, and 65% at 6 months after diagnosis.[54,58] The best prognosticator is the initial response to treatment. Negative prognosticators include severe respiratory (tachypnea, dyspnea, need for O2 supplementation), liver (hyperbilirubinemia), or CNS disease.[54,58] Bone marrow involvement causing pancytopenia or fungemia is a negative prognosticator in cats.[58]

Table 5
Recommended criteria for determining when to discontinue antifungal treatment (meet all criteria) in dogs and cats with histoplasmosis

Monitoring Tool	Criteria	Notes
Minimum Duration	Minimum of 6 mo of treatment	• Required duration is often longer.
History	Past resolution of clinical signs	• Mild exercise intolerance might persist, most notable in working or performance animals. • Persistent tracheobronchial lymphadenopathy can cause cough, requiring concurrent corticosteroid treatment.
Physical Examination	Past resolution of physical examination abnormalities	• Differentiating active ocular disease from permanent inactive change is important.
Imaging Studies	Past resolution of imaging abnormalities	• Pulmonary scarring can be permanent and can cause static focal unstructured interstitial lung disease. • Radiographic bone lesions should improve but might never return to normal.
Histoplasma Antigen EIA	No detectable antigen OR Antigen $\leq$0.5 ng/mL on 2 consecutive rechecks at least 3 mo apart	• Urine is the ideal sample. • Most dogs, and essentially all cats, have no detectable antigen at the time of remission. • Submit antigen test at diagnosis, every 3 mo during treatment, and at 6 mo then every 12 mo after treatment.

COCCIDIOIDOMYCOSIS (VALLEY FEVER)

Valley fever (VF) is caused by *Coccidioides immitis* and *C posadasii*. VF is found most abundantly in the semiarid Southwestern US - but can be found anywhere west of the Rockies and in Oklahoma and Texas. The endemic region is expanding with warmer, drier weather patterns. Small mammals might also contribute to perpetuation and geographic spread (endozoan hypothesis).[59] Travel or relocation with pets is common and animals can be diagnosed years after traveling to the endemic region. The primary mode of infection is inhalation of arthroconidia (spores) that are aerosolized in the environment.

Valley fever is the most common SM in dogs in the Western United States, which are significantly more likely to be diagnosed as compared to cats although the disease is an important consideration in both species. Large breed, young adult dogs with more outdoor access and freedom to roam, are most often infected, but any age and breed in endemic areas is at risk.[60] Indoor only cats are at risk, accounting for 75% of cases in one study.[25]

Clinical Findings

Disease localized to the lung and associated lymph nodes (pulmonary VF) occurs in approximately 75% of dogs, with disseminated disease making up the remainder of cases.[61] Disseminated disease is most common in cats, accounting for 60% of

cases.[25] In dogs, dissemination to a single organ is common primarily of the bone/joint, CNS, skin/SQ, pericardium, and eyes. In cats, lung involvement is less common and ocular and skin/SQ involvement is more common (see **Fig. 2**).[25,26]

Signs can be nonspecific or associated with the body systems involved. Fever, anorexia, weight loss, and lethargy are common. Respiratory signs include cough, tachypnea, dyspnea, and exercise intolerance. Skin lesions are nodular or ulcerative with draining tracts. Large subcutaneous masses can be seen. Osteoarticular involvement often causes lameness, joint effusion, and surrounding soft tissue swelling. Restrictive pericarditis, right sided congestive heart failure, and arrhythmias can cause cavitary effusions, exercise intolerance, or collapse. Seizures are the most common sign of CNS involvement, but neurolocalization can be multifocal and include ataxia, cranial nerve deficits, behavioral changes, paraspinal hyperesthesia, and tetraparesis or paraparesis.[62,63] Ocular involvement can cause anterior uveitis, chorioretinitis, or involve both segments. Periocular swelling can also be present.

Imaging

Tracheobronchial (TB) lymphadenopathy is the most common finding on thoracic radiographs being found in 50% to 80% of dogs and approximately 30% of cats with respiratory involvement (**Fig. 5**).[22,25,64,65] Approximately 50% of dogs and most cats with large TB lymph nodes also have pulmonary parenchymal changes.[25,64] Any lung pattern including mixed patterns and mass-like lesions can be found.[22,25,64,65] Pleural effusion is present in approximately 3% to 5% of dogs and 20% of cats, and should raise suspicion of pericarditis.[64,65] Bone radiographs reveal mostly proliferative changes with lesser bony lysis (see **Fig. 5**). With CNS involvement, MRI can be normal or show solitary or multiple intra-axial or extra-axial mass lesions indicative of granulomas or less well-defined lesions of meningoencephalomyelitis.[62 62]

Diagnosis

Diagnosis includes finding organisms (spherules and endospores) in pathology samples and/or antibody testing. A GM antigen test is available but lacks diagnostic sensitivity, likely because *Coccidioides* sheds less GM as compared with other dimorphs.[21] Two types of antibody assays are available—Immunodiffusion (ID) and EIA. ID detects antibodies against 2 antigen preparations, tube precipitin ([TP], often called IgM) and complement fixation ([CF], often called IgG). Most laboratories perform dilution titers, when antibodies to CF antigen (IgG) are detected. Only 22% to 46% of dogs at diagnosis are TP (IgM) positive.[64,65] The available EIA detects IgG antibodies to a mix of *Coccidioides* antigens. False negative results are possible with either antibody test (see **Table 2**). In dogs, the combined sensitivity of ID and EIA was greater than 98% in one study.[20] Immunodiffusion is recommended for treatment monitoring (**Table 6**).[66] One limitation of antibody testing is the overlap between current and past infection. For example, CF (IgG) titers up to 1:16 can be been found in apparently healthy dogs in an endemic area.[67] With disease localized to the CNS, serum antibody testing can be false negative, and antibody EIA and antigen EIA testing of CSF should be considered.[63]

Treatment

Fluconazole is the most commonly used antifungal and is the first oral option for CNS involvement. *Coccidioides* is relatively more sensitive to itraconazole, which concentrates in the bone and synovium and could be considered with osteoarticular involvement.[68] Itraconazole is superior to fluconazole in humans with osteoarticular disease.[69] Amphotericin-b should be considered for life-threatening valley fever

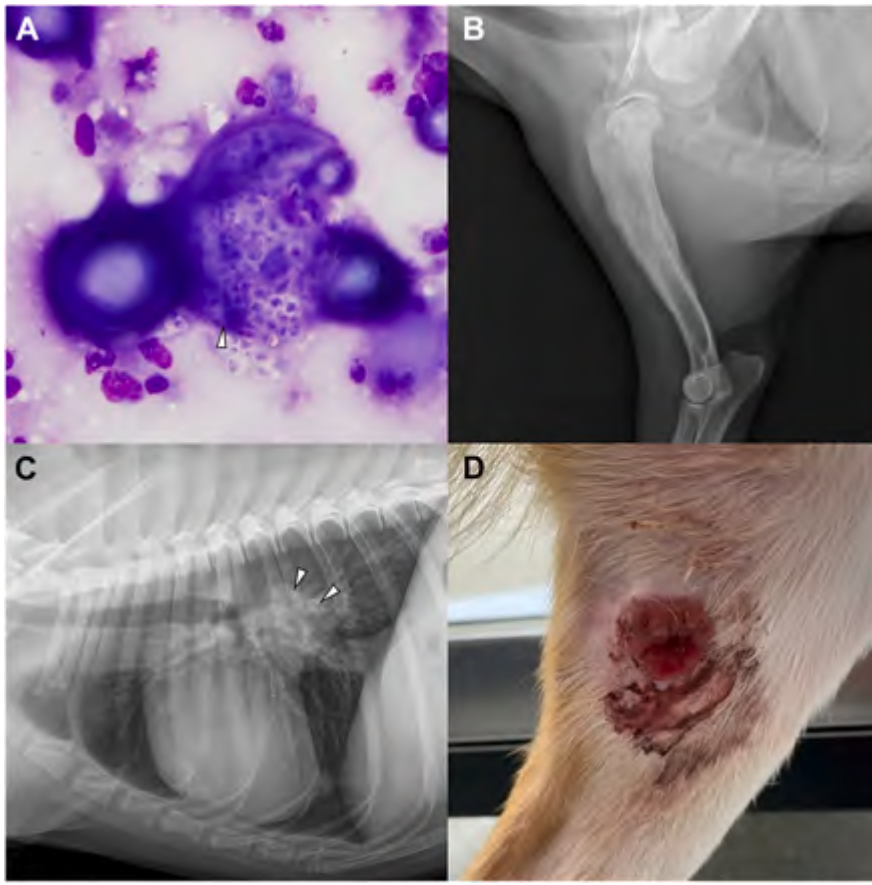


Fig. 5. (*A-D*) (*A*) *Coccidioides*, note the variably sized spherules with a mature spherule (*arrowhead*) rupturing and releasing endospores; (*B*) Osteomyelitis of the humerus in a dog, note the bony proliferation; (*C*) Thoracic radiographic showing large tracheobronchial lymph nodes (*arrowheads*) in a dog; (*D*) Chronic cutaneous lesion with a draining tract and granulation tissue in a dog. (*Image courtesy* Image A is the courtesy of Dr. Jim Meinkoth, Image B and C is the courtesy of Dr. Jared Jaffey and Image D is the courtesy of Dr. Rebecca Gerevics.)

(VF). This is usually with CNS or severe respiratory disease. It needs to be followed by azole therapy. Voriconazole or posaconazole could be considered for salvage therapy. In a study of 8 dogs that required salvage therapy, 6 dogs achieved remission with posaconazole.[70] Terbinafine in combination with fluconazole or itraconazole could also be considered. Concurrent anti-inflammatory corticosteroids, for as short a duration as possible (<4 weeks), should be considered with CNS, ocular, pericardial, or severe pulmonary disease.

Most dogs with pulmonary VF achieve remission within 6 to 9 months and antifungal treatment can be discontinued.[66] Animals with disseminated VF often require prolonged treatment (≥12 months). Indefinite fluconazole treatment should be considered with CNS involvement. Antifungal treatment should be continued until all criteria are met in **Table 6**. In dogs with pulmonary VF, 15% relapsed after discontinuation of

Table 6
Recommended criteria for determining when to discontinue antifungal treatment (meet all criteria) in dogs and cats with coccidioidomycosis

Monitoring Tool	Criteria	Notes
Minimum Duration	Minimum of 6 mo (pulmonary) or 12 mo (disseminated)	• Required duration can be significantly longer for disseminated disease.
History	Past resolution of clinical signs	• Mild exercise intolerance might persist, most notable in working or performance animals.
Physical Examination	Past resolution of physical examination abnormalities	• Differentiating active ocular disease from permanent inactive change is important.
Imaging Studies	Past resolution of imaging abnormalities	• Pulmonary scarring can be permanent and can cause static focal unstructured interstitial lung disease. • Large TB lymph nodes decrease in size most significantly in first 3 mo • Radiographic bone lesions should improve but might never return to normal.
Coccidioides Antibody Immunodiffusion	CF (IgG) $\leq$1:4 OR CF (IgG) $\leq$1:8 after $\geq$1-y of treatment	• Submit antibody test at diagnosis and every 3 mo during treatment.

Abbreviation: CF, complement fixing.

primarily fluconazole treatment, in one study.[66] In cats, most with disseminated VF, 35% relapsed after discontinuation of fluconazole.[25]

ASPERGILLOSIS

There are many molds that can cause SM in cats and dogs. Most mold infections fit into one of a few categories-hyalohyphomycosis (hyaline molds; *Penicillium*, *Sedosporium*, *Lomentospora*), phaeohyphomycosis (pigmented molds; *Alternaria*, *Bipolaris*, *Curvularia*), genus Entomophthorales (*Basidiobolus*, *Conidiobolus*), and genus Mucorales (*Mucor*, *Rhizopus*). *Aspergillus* spp. is a hyaline mold but placed in a separate category as the most common mold pathogen.

Many species of *Aspergillus* can cause disease in dogs and cats. *Aspergillus fumigatus* is the most common cause of sino-nasal aspergillosis, while nonfumigatus species (*A. terreus* complex, *A deflectus*) are more common causes of systemic aspergillosis. *Aspergillus* spp. are ubiquitous, found abundantly in soil and decaying vegetation, and even within the home. The primary mode of infection is inhalation of aerosolized conidia (spores). As an example of its abundance, the average human inhales up to 200 conidia per day.[71] Likewise, healthy animals are commonly exposed without clinical infection. Without an adequate immune response, *Aspergillus* can survive in the respiratory tract causing localized disease or disseminate to other organs.

Dogs are significantly more often diagnosed with systemic aspergillosis as compared with cats —but it is relevant in both species. German shepherd dogs are heavily predisposed, accounting for approximately 65% of cases. This is possibly due to a hereditary IgA deficiency leading to defective mucosal immunity. Anecdotally,

Rhodesian ridgebacks, vizslas, and weimaraners might also be predisposed (internal data). The median age at diagnosis is 3.5 to 4.5 years.[72] There is a female predilection accounting for 60% to 77% of cases.[72,73]

Clinical Findings

Aspergillosis occurs as localized sino-nasal (or sino-orbital) or disseminated infection (systemic aspergillosis). This article will focus on systemic aspergillosis, which often involves the bones/joints, lymph nodes, lung, eyes, CNS, and kidneys (**Fig. 6**). Kidney involvement can lead to PU/PD, azotemia, and active urine sediment. Aspergillus has the unique propensity for vertebral endplates and is the causative agent in approximately 20% of dogs with discospondylitis (see **Fig. 6**).[74] Lung involvement is less common as compared with dimorphic infections, but a bronchopulmonary form, similar to invasive pulmonary aspergillosis (IPA) in humans, does occur.[32]

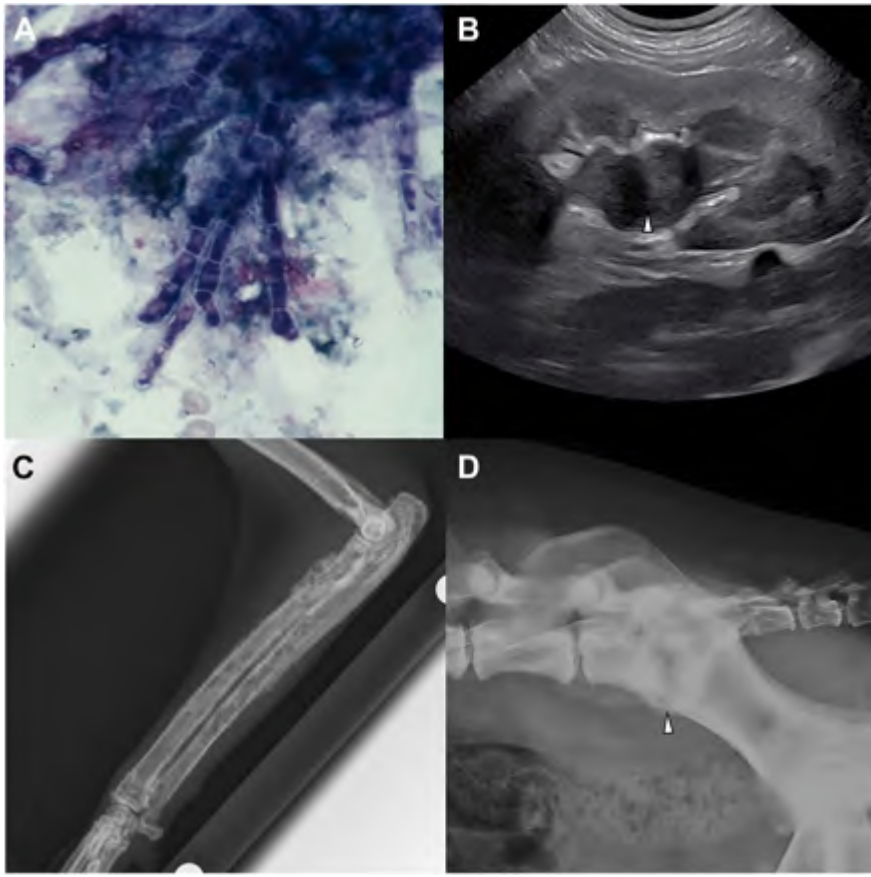


Fig. 6. (*A-D*) (*A*) *Aspergillus*, note the narrow, septate hyphae with acute angle branching and globuse ends; (*B*) Ultrasonographic image of a kidney with dilated renal pelvis and echogenic debris (*arrowhead*) due to pyelonephritis in a dog; (*C*) Osteomyelitis of the radius and ulna in a cat; (*D*) Spinal radiograph showing discospondylitis (*arrowhead*) at L7-S1 in a dog. (*Image courtesy* Image A is the courtesy of Dr. Jim Meinkoth and Image B is the courtesy of Dr. Laura Nafe.)

Clinical signs commonly include nonspecific findings such as lethargy, anorexia, and weight loss. Other findings can include limb pain and lameness due to long bone involvement and nonlocalized or paraspinal pain with possible paraparesis/paraplegia due to discospondylitis or myelitis. With CNS involvement, seizures, obtundation/mental dullness, or other intracranial signs can be found. With fungal pyelonephritis, polyuria and polydipsia might be present. Ocular disease can cause visual disturbance and other signs related to uveitis or chorioretinitis. Cutaneous lesions with ulceration or draining tracts can be found. Lung involvement causes cough, tachypnea or dyspnea.

Imaging

Radiographic abnormalities can include evidence of discospondylitis, osteomyelitis and intrathoracic lymphadenopathy.[32,73] Abdominal ultrasonographic changes are most often detected in the kidneys, spleen, liver and lymph nodes. Kidney changes can include an irregular serosal margin, parenchymal changes, and a dilated pelvis with echogenic debris. In dogs with CNS disease, brain MRI can be normal or have multifocal intra-axial or extra-axial lesions with variable T2 hyperintensity and contrast enhancement.[73,75]

Diagnosis

Diagnosis includes clinical findings along with identifying hyphae in pathology and antigen testing. *Aspergillus* morphology can vary but generally appear as narrow (3–8 μm), septate, hyaline hyphae with parallel walls and acute angle branching (see **Fig. 6**). Pyogranulomatous inflammation is also present. *Aspergillus* morphology is not unique enough from many other molds to allow for identification to the genus level, and speciation requires gene sequencing of a culture isolate. Panfungal PCR and sequencing of tissue sample (fresh or formalin fixed) or cytology slide might be an alternative. With kidney involvement, hyphae might be found in urine sediment. Samples from other affected sites might reveal hyphae such as lymph nodes, liver, spleen, kidneys, bone, joint fluid, and lower respiratory specimens. In dogs with neurologic signs, CSF cytology often reveals neutrophilic pleocytosis.[73]

The *Aspergillus* antigen EIA (Platelia, Bio-Rad Laboratories) is FDA-cleared for the detection of antigen (galactomannan) in serum and broncho-alveolar lavage fluid (BALf) in humans. The assay has been validated for cat and dog serum, urine, CSF, and BALf. In dogs with systemic aspergillosis, the performance was similar when urine or serum was tested.[32] All false negative results were from dogs with localized pulmonary aspergillosis; therefore, the sensitivity was 100% (in either serum or urine) for disease outside of the lung. Increasing the cutoff to $\geq$1.5 IU (manufacturer recommended is $\geq$0.5 IU), increases specificity without significantly decreasing sensitivity.[32] Most dogs with systemic aspergillosis have high antigen levels in both serum and urine (>4.0 IU). Lower antigen levels (0.5 - 4 IU) can be found with localized disease (discospondylitis, bone, eye, and lung). False positives can be attributed to other hyaline mold infections, recent administration of *Penicillium*-derived antibiotics (amoxicillin-clavulanate, other beta lactams), or recent administration of IV fluids (Vetivex pHLyte, Dechra; or Isolyte, Braun).[32] Plasmalyte (Baxter) no longer causes false positive results. A second *Aspergillus* antigen (galactofuranose) assay (MycoMEIA, Pearl Diagnostics) has received FDA-clearance to test human urine. Performance in dogs and cats is currently unknown. Anti-*Aspergillus* antibody testing is not recommended for systemic aspergillosis but is the biomarker of choice for sinonasal or sinoorbital disease.

Treatment

Culture and AFST should be considered. Fully clearing an invasive mold infection is challenging and many animals need long-term, or indefinite, antifungal treatment. Ability to discontinue antifungal treatment is more likely if a source of immunosuppression can be removed (eg, cyclosporine). Published survival rates underestimate treatment success with the more recent available mold-active azoles, voriconazole, and posaconazole. Multiple in vitro studies have demonstrated synergism between azoles and terbinafine, and the combination should be considered for first-line treatment. In one study, dogs that received a combination of antifungals had a median survival significantly longer than sole itraconazole treatment (830 v 63 days).[72] Amphotericin-b should be considered for life-threatening infection as it reaches therapeutic concentrations very quickly and is active against most *Aspergillus*, and many other mold species. The aspergillus antigen test can be used to monitor treatment (**Table 7**). If there is no significant drop in antigen level at 1-year but clinical improvement, antigen testing can be discontinued as indefinite antifungal treatment is likely needed.

CRYPTOCOCCOSIS

Cryptococcosis is caused by the *Cryptococcus neoformans* and *C gattii* comprised of 8 genotypes (VNI—VNIV and VGI—VGIV). Cryptococcosis occurs worldwide and is most common in the western United States and Canada. *Cryptococcus* is found in soil and decaying matter. Soil contaminated with bird droppings creates an ideal ecological niche for growth and sporulation.[76] Birds rarely develop disease, but can shed *Cryptococcus* in feces, which can survive for years in the environment.[76] The

Table 7
Recommended criteria for determining when to discontinue antifungal treatment (meet all criteria) in dogs and cats with systemic aspergillosis

Monitoring Tool	Criteria	Notes
Minimum Treatment Duration	Minimum of 12 mo	• Required duration can be indefinite unless a source of immunosuppression can be removed.
History	Past resolution of clinical signs	• Mild exercise intolerance or neurologic deficits might persist, most notable in working or performance animals.
Physical Examination	Past resolution of physical exam abnormalities	• Differentiating active ocular disease from permanent inactive change is important. • Neurologic deficits might be permanent.
Imaging Studies	Past resolution of imaging abnormalities	• Pulmonary scarring can be permanent and can cause static focal unstructured interstitial lung disease. • Radiographic bone lesions should improve but might never return to normal.
Aspergillus Antigen EIA	Antigen <1.5 IU	• Serum is the ideal sample. • Submit antigen test at diagnosis, every 3 mo during treatment, and if there is no significant decrease at 1-y, antigen monitoring can be discontinued as indefinite treatment is likely.

Abbreviation: IU, index units.

primary mode of infection occurs by inhalation of basidiospores. Living within 10 km of significant soil disturbance or logging, or partaking in outdoor activities such as hiking and visiting botanic gardens, have all been shown to increase the risk of cryptococcosis in cats and dogs.[77] Indoor-only cats are at risk, suggesting *Cryptococcus* can be found in the home.[29,78]

Clinical Findings

Cryptococcosis is more likely in cats than dogs.[29] Any aged animal can be affected, and average age is 6 to 8 years for cats and 2 to 3 years for dogs.[29,39,78,79] Breed and sex predilections have been inconsistent between studies. Some have shown a predisposition for pure bred cats such as the Abyssinian, Birman, Siamese, and ragdoll.[9,79,80] Some studies have shown a slight male predilection.[9,29,39,78,80] Staffordshire bull terriers, English bulldogs, Dalmatians, Irish setters, and cocker spaniels are overrepresented in certain studies.[29,79] Cats with feline immunodeficiency virus (FIV) or feline leukemia virus (FeLV) are not predisposed to cryptococcosis, and coinfection likely does not affect prognosis, but response to treatment might be slower.[39,78,79,81] Cats with concurrent FIV are more likely to be asymptomatic carriers.

Disease can be localized to the nasal cavity and sinuses, eyes, skin, or CNS. It can also be multi-systemic. The nasal cavity and sinuses are most common site of infection in cats. Disease localized to the nasal cavity is relatively less common in dogs.[29,79] Facial deformity, most common over the bridge of the nose, occurs due to subcutaneous or cutaneous infiltration (**Fig. 7**). These lesions might be ulcerated or have draining tracts. In some cases, a mass can be visualized extending through the nares. Nasal signs include nasal discharge (bilateral or unilateral), stertor, sneezing, and open mouth breathing. Nasopharyngeal lesions can cause stridor, stertor, dysphagia, and dyspnea.[82] Local lymph nodes can be involved. Disease can spread into the brain and orbit. Ocular disease is relatively common and includes chorioretinitis, anterior uveitis, retinal detachment, and optic neuritis.[29]

Skin lesions, most common on the head and neck, might be found anywhere on the body. Disease can be localized to the skin. CNS signs can be multifocal and localize to anywhere in the nervous system. Blindness, seizures, muscle tremors and twitching, mentation changes, ataxia, circling, cranial nerve deficits, hyperesthesia and pain are the most common signs of neurologic disease.[83,84] Dogs tend to have cervical pain in contrast to cats that more commonly have generalized or hind limb pain.[83]

Cryptococcosis less commonly affects the lungs as compared with dimorphic SM.[29,79] Abdominal visceral organ involvement is relatively more common in dogs than cats.[29,39] Dogs can have disease localized to the gastrointestinal (GI) tract, which might to be due to ingestion of *Cryptococcus*.[85,86] In general, dogs are less likely to have sinonasal and skin involvement and more likely to have CNS or distant organ involvement.[29,39,79] Other less common manifestations of cryptococcosis can include bone and joint disease, otitis media, and pyothorax.[87–90]

Diagnosis

Diagnosis is often made by combination of clinical findings, pathology, and antigen testing. Finding narrow-based budding yeasts, with a large capsule in pathology samples can confirm the diagnosis (see **Fig. 7**). Uncommonly *Cryptococcus* can be capsule deficient (rough), which can be morphologically similar to other pathogens such as *Histoplasma* or *Candida*. Yeasts might be found in tissue aspirates, CSF, cavitary effusions, skin impressions, and nasal swabs. *Cryptococcus* is relatively easy to culture (requiring 1+ weeks) from clinical specimens, and most studies report a high recovery rates.[29,80]

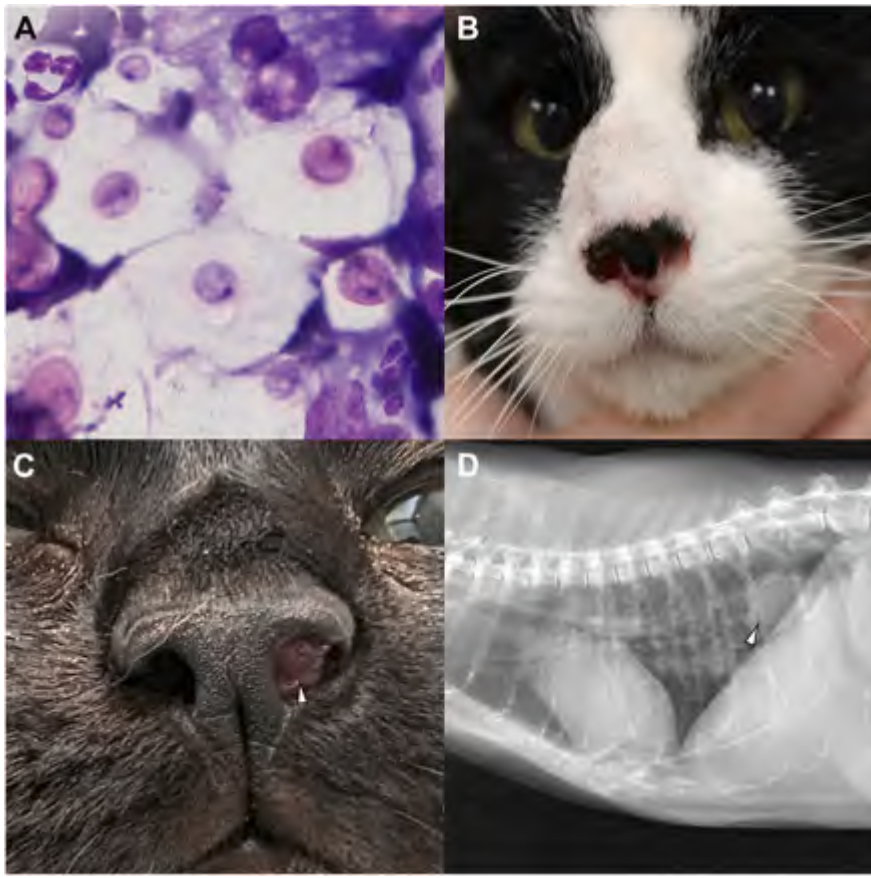


Fig. 7. (*A-D*) (*A*) *Cryptococcus*, note the variable cell and nuclear size with a large clear capsule and centrally placed nucleus; (*B*) Facial deformity due to subcutaneous infiltration; (*C*) Soft tissue mass (*arrowhead*) protruding from the nares; (*D*) Thoracic radiograph showing a mixed lung pattern and large granuloma (*arrowhead*) in the caudal lung fields. (*Image Courtesy* Image A is the courtesy of Dr. Jim Meinkoth and Image B and D is the courtesy of Dr. Laura Nafe.)

The cryptococcal antigen latex agglutination test (LCAT) is highly sensitive and specific (see **Table 2**).[27,31] It detects glucuronoxylomannan (GXM) in serum and CSF. Animals with cryptococcosis often have very high dilution titers, but even a titer of 1:2 can be significant. For lower titers (<1:200), it is recommended to confirm the diagnosis by other means, if possible.[29] Titers are highly variable between laboratories and the same laboratory should be used when using LCAT over time to monitor treatment.

Treatment

Fungal culture and AFST should be considered. The treatment of choice for life-threatening infection, mostly CNS disease, is amphotericin-b. Fluconazole is the treatment of choice for mild to moderate disease and following amphotericin-b. Itraconazole, voriconazole, and posaconazole can be considered for salvage therapy.

Table 8
Recommended criteria for determining when to discontinue antifungal treatment (meet all criteria) in dogs and cats with cryptococcosis

Monitoring Tool	Criteria	Notes
Minimum Duration	Minimum of 6 mo of treatment	• Required duration is often much longer.
History	Past resolution of clinical signs	• Nasal discharge and stertor should resolve.
Physical Examination	Past resolution of physical exam abnormalities	• Differentiating active ocular disease from permanent inactive change is important. • Facial deformity should resolve.
Imaging Studies	Past resolution of imaging abnormalities	• Nasal or nasopharyngeal lesions should resolve but turbinate destruction might be permanent.
Cryptococcus Antigen LA	No detectable antigen OR ≤1:8 after 12-mo of treatment[a]	• Serum is the ideal sample. • Submit antigen test at diagnosis, every 3 mo during treatment, and at 6 mo then every 12 mo after treatment.

[a] Titers are highly variable between laboratories.

Serum antigen titers decrease with successful treatment and should be measured every 3 months during treatment to monitor response.[80] All criteria in **Table 8** should be met before stopping treatment. After discontinuation of antifungal treatment, relapse has been reported in 16% to 17% of cases.[39,80]

Prognosis

Reported survival rates are 45% to 76% in cats and 27% to 71% in dogs.[39,79,84] Animals with CNS involvement have a mortality rate four times higher than those without.[39,79,84] Altered mentation appears to be an especially important prognostic indicator.[83] Disease outside of nasal cavity and sinuses was a negative prognostic indicator in one study.[79]

CLINICS CARE POINTS

- Systemic mycoses are clinically relevant to cats and dogs throughout the world.
- Clinical findings are variable and overlap with many other diseases.
- Diagnosis often requires routine lab work, imaging studies, pathology, and fungal biomarkers.
- Early diagnosis and appropriate treatment are crucial for treatment success.
- Treatment monitoring is multi-faceted and considers clinical signs, physical examination, imaging studies, and biomarker testing.

DISCLOSURE

Andrew Hanzlicek is employed by MiraVista Diagnostics which offers commercially some of the fungal biomarker tests described in this article.

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