Vet Clin Small Anim
33 (2003) 721–747

THE
VETERINARY
CLINICS
Small Animal Practice

Update on canine and feline fungal diseases

Marie E. Kerl, DVM

Department of Veterinary Medicine and Surgery, University of Missouri–Columbia, 379 East Campus Drive, Columbia, MO 65211, USA

Systemic fungal infections remain a significant cause of disease for dogs and cats in most regions of the United States. Systemic fungal pathogens gain entry through a single portal (commonly the respiratory tract) and disseminate to affect multiple body systems. Antifungal antimicrobials may be effective for treatment; however efficacy is variable among pathogens, treatment periods are prolonged, and drugs are costly. This chapter will focus on clinical signs, diagnosis, and treatment of the most common systemic mycoses of dogs and cats including blastomycosis, histoplasmosis, coccidiomycosis, and cryptococcosis, and will review antifungal drugs currently available for treatment.

Blastomycosis

Blastomycosis is caused by infection with fungal spores of *Blastomyces dermatitidis*, most commonly by way of inhalation and respiratory colonization. Environmental conditions favoring fungal growth include moist, acidic soil with decaying vegetation or animal feces. Environmental moisture is thought to play a major role in dissemination of infective spores [1]. Geographic regions with the greatest prevalence of blastomycosis include the Mississippi, Missouri, and Ohio river valleys. The middle Atlantic and southern states and southern Canadian waterways also have high disease prevalence, but outbreaks have been reported in other regions also [2–4].

Infection occurs most commonly when an animal inhales conidiophores from an appropriate environment, but inoculation by penetration also can cause localized disease (Fig. 1). Dogs and people are affected more commonly than other species [2,3]. Following inhalation, infective conidia

E-mail address: kerlm@missouri.edu

doi:10.1016/S0195-5616(03)00035-4

Fig. 1. Lingual nodular ulceration caused by localized blastomycosis in a dog.

are phagocytized by alveolar macrophages and are transformed from the mycelial to the yeast phase. Normal body temperatures promote formation of yeast. The yeast forms are thick-walled structures 8 to 12 μm in diameter that lack a capsule and bud to form daughter cells with broad-based attachments (Fig. 2). Yeast may produce a localized infection or may disseminate hematogenously or by way of lymphatics to distant sites [5].

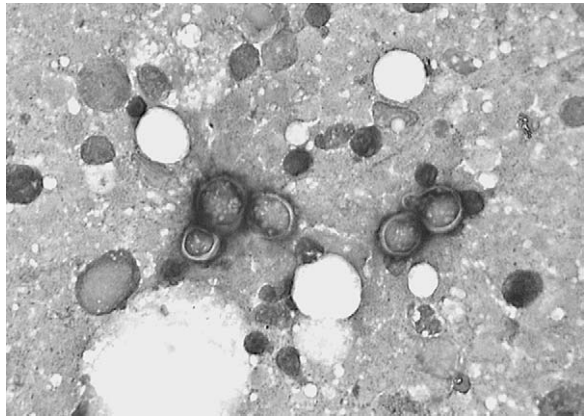

Fig. 2. Cytologic appearance of *Blastomyces dermatitidis* from a lymph node aspirate. (Wright-Giemsa stain, ×100). (*Courtesy of* Linda Berent, DVM, Columbia, MO.)

Clinical signs

Dogs

Typical signalment for dogs with blastomycosis includes young adult, large breeds. Most cases occur in dogs 2 to 4 years of age, with males and females equally represented. Retrievers and Doberman pinschers were overrepresented in one study [6,7].

Clinical signs develop weeks to months after exposure to the organism. Anorexia, depression, lethargy, weight loss, cachexia, and fever are common features of disease. Dissemination occurs by way of lymphatic and hematogenous spread to colonize distant sites including the eye, skeletal system, skin, and lymph nodes. Symptoms often are associated with infection in more than one site at a time. Respiratory signs including tachypnea, dyspnea, cyanosis, or respiratory distress occur in 65% to 85% of dogs in association with pulmonary infection. Lymphadenopathy occurs in 30% to 50% of cases and may be confused with lymphosarcoma if lymph node aspirate or biopsy is not performed [2,6,7]. Ocular involvement, manifesting as chorioretinitis, anterior uveitis, retinal detachment, and secondary glaucoma occurs in 20% to 50% of dogs [8]. Bone involvement is noticed in 10% to 15% of cases, with lesions most commonly occurring over epiphyseal regions below the elbow or stifle [5]. Cutaneous signs are reported in 30% to 50% of cases, including nodules, papules, or plaques of varying sizes that may drain serosanguineous to purulent exudate. Paronychia may occur. Calcinosis cutis may be an unusual manifestation of disease [9]. Central nervous system (CNS) involvement is an uncommon finding in dogs with blastomycosis, occurring in fewer than 5% of cases. Pulmonary thromboembolism may be associated with respiratory blastomycosis [10].

Cats

Blastomycosis is an uncommon fungal disease in cats [3]. It is unclear whether differences in age, breed, or sex contribute to likelihood of infection in cats. Immunosuppression with feline leukemia virus does not seem to increase predisposition [3]. Clinical signs of disease are similar to dogs, except cats more commonly exhibit CNS disease and develop large dermal abscesses [3,5,11].

Diagnosis

Routine screening blood tests of ill patients do not provide definitive diagnoses but may show evidence supporting fungal disease. Complete blood count (CBC) results are often unremarkable but may demonstrate mild nonregenerative anemia, mature neutrophilia, or neutrophilia with left shift. Serum biochemical profile is often within reference ranges.

Hypoalbuminemia is the most commonly identified abnormality, occurring in approximately 75% of cases; 50% develop hyperglobulinemia, and hypercalcemia occurs in 10% of cases [2,7,12].

Thoracic radiographs identify characteristic diffuse or nodular interstitial pattern, alveolar infiltrate, or hilar lymphadenopathy in 70% of cases (Fig. 3). Pleural space abnormalities (fluid or air) are less common. Bone involvement most commonly affects the appendicular skeleton. Osteolysis with periosteal proliferation and soft tissue swelling is demonstrated on radiographic examination. These lesions must be differentiated from primary osteosarcoma, which presents with a similar radiographic appearance [2,5,7].

Definitive diagnosis is made by identifying organisms retrieved from affected sites by aspirate or biopsy. Site of involvement dictates method of sampling. Lymph node aspirate of infected nodes or evaluation of exudates or aspirates from dermal lesions yields organisms reliably. Vitreous aspirate or ocular histopathology following enucleation frequently provides a diagnosis [13]. Respiratory procedures on infected dogs, including lung aspirate, tracheal wash, or bronchoalveolar lavage, are nondiagnostic at least 50% of the time [7]. Low yield of these procedures is explained by interstitial location of the organism. Culture for diagnosis of blastomycosis is not necessary if cytologic or histopathologic examination demonstrates characteristic organisms. Mycelial growth occurs slowly, and cultures may take several weeks to become positive [5]. Blastomycosis has zoonotic potential, and caution should be exercised when handling infected tissues [14,15].

Serologic testing should be considered if multiple attempts to identify the organism by cytologic or histopathologic examination have failed. A variety of serologic tests have been developed, none of which will yield a diagnosis correctly in all cases. Agar gel immunodiffusion (AGID) against the

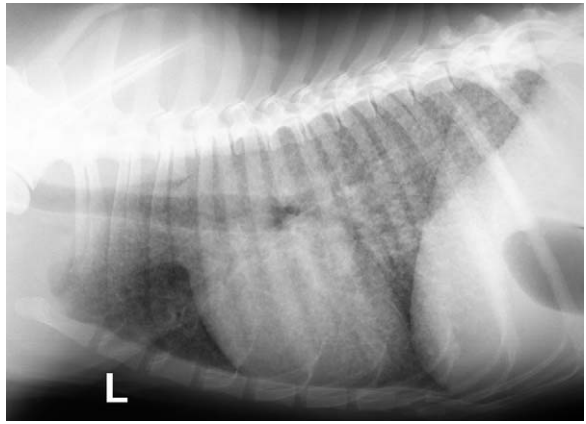

Fig. 3. Lateral thoracic radiograph of a dog with disseminated blastomycosis demonstrating classic military nodular to diffuse pulmonary interstitial infiltrate.

A-antigen of *Blastomyces dermatitidis* is the most commonly used serologic test, with sensitivity reported to be 60% to 90%, and specificity up to 96% [16–18]. AGID is often negative early in the course of disease and may become negative with treatment or remain positive even with clinical resolution of disease, depending upon the antibody response of the individual animal. AGID in cats is unrewarding [3]. Recent information on radioimmunoassay (RIA) testing for WI-1 antigen of *B dermatitidis* shows a possible advantage in early diagnosis of blastomycosis in dogs. Sensitivity of this test was 91%, and specificity was 100% in dogs from different regions of the United States. The degree of positive titer did not correlate with severity of disease, and titers remained positive for more than 1500 days following successful treatment in some dogs. Therefore, this titer would not predict clinical resolution of disease. This test is not commercially available [18].

Treatment

Although some dogs exposed to blastomycosis clear the organism, dogs and cats that present with clinical disease will not improve spontaneously and require therapeutic intervention [2,5]. Approximately 70% to 75% of dogs that receive treatment with antifungal medications survive. Researchers have found that dogs with severe respiratory infections or multiple body system involvement were more likely to die within the first week of therapy. Brain involvement was significantly associated with treatment failure [19].

Itraconazole (Sporanox) is the treatment of choice for blastomycosis because of its efficacy, relative safety, and convenience of administration. In a study of 112 dogs comparing itraconazole with historical controls treated with amphotericin B (AMB, Fungizone), response and recurrence rates were similar among all groups [19]. Other treatment options include ketoconazole (Nizoral), AMB, and lipid-complexed AMB. Ketoconazole is less effective than itraconazole, with lower response rates, higher relapse rates, and longer treatment periods [5,20]. AMB has been used successfully to treat blastomycosis. Drawbacks of AMB include parenteral administration and risk of nephrotoxicity [21]. Lipid-complexed AMB (AmBisome) is effective for treatment of blastomycosis in dogs, with less risk of nephrotoxicity [22]. Combinations of AMB and itraconazole or ketoconazole may be used in cases of severe respiratory infection [5]. Table 1 contains dose recommendations.

General medical management of dogs and cats with blastomycosis is dictated by the location of fungal infection. Supportive therapy for respiratory involvement includes oxygen therapy in hypoxemic animals, bronchodilators, and possibly antibiotics, if secondary bacterial infection is suspected [23]. Ocular involvement may require specific therapy for anterior uveitis or secondary glaucoma [5,8,13,24]. Animals with orthopedic lesions causing lameness and pain should receive analgesic therapy. Dermal wounds

Table 1
Drug therapy for common systemic mycoses

	Species	Amphotericin B (AMB)[a]	Liposomal AMB	Flucytosine[b]	Ketoconazole[c]	Itraconazole[c]	Fluconazole
Blastomycosis	Canine	0.5 mg/kg IV 3×/wk; cumulative dose: 4–6 mg/kg	1 mg/kg IV 3×/wk; cumulative dose: 12 mg/kg		5–15 mg/kg PO Q 12 h for at least 3 months, with amphotericin B initially	5 mg/kg PO Q 12 h for first 5 days, then Q 24 h for 60–90 days, or 30 days beyond resolution	5 mg/kg PO Q 12 h for at least 60 days, or 30 days beyond resolution
	Feline	0.25 mg/kg IV 3×/wk; cumulative dose: 4 mg/kg			10 mg/kg PO Q 12 h for at least 3 months, with amphotericin B initially	5 mg/kg PO Q 12 h for 60–90 days, or 30 days beyond resolution	
Histoplasmosis	Canine	0.25–0.5 mg/kg IV 3×/wk; cumulative dose: 5–10 mg/kg			10 mg/kg PO Q 12–24 h for at least 3 months, or 30 days beyond resolution	5 mg/kg PO Q 12 h for 4–6 months, or 60 days beyond resolution	2.5–5 mg/kg PO Q 12–24 h for 4–6 months, or 30 days beyond resolution
	Feline	0.25–0.5 mg/kg IV 3×/wk; cumulative dose: 4–8 mg/kg			See canine recommendations	See canine recommendations	See canine recommendations
Cryptococcosis	Canine	0.25–0.5 mg/kg IV 3×/wk; cumulative dose: 4–10 mg/kg	1 mg/kg IV 3×/wk; cumulative dose: 8–12 mg/kg	50 mg/kg PO Q 6–8 h for 1–12 months	10 mg/kg Q 12–24 h following amphotericin B/flucytosine, for 4–6 months		5–15 mg/kg PO Q 12–24 h for 6–10 months, or 30 days beyond resolution

	Feline	0.1–0.5 mg/kg IV, or 0.5–0.8 mg/kg SQ 3×/wk; cumulative dose: 4–10 mg/kg	25–50 mg/kg PO Q 6–12h for 1–9 months	See canine recommendations	5–10 mg/kg PO Q 12 h, or 20 mg/kg Q 24 h for 6–10 months, or 30 days beyond resolution	See canine recommendations
Coccidiomycosis	Canine	0.4–0.5 mg/kg IV 3 ×/wk; cumulative dose: 8–11 mg/kg		5–10 mg/kg PO Q 12 h for 8–12 months	5 mg/kg PO Q 12 h up to 12 months	5 mg/kg PO Q 12 h up to 12 months
	Feline			50 mg per cat PO Q 12–24 h up to 12 months	25–50 mg per cat PO Q 12–24 h up to 12 months	25–50 mg per cat PO Q 12–24 h up to 12 months

[a] Monitor for nephrotoxicity.
[b] Combine with amphotericin B treatment.
[c] Administer with food.
Abbreviations: IV, intravenous; SQ, subcutaneous.
Data from Refs. [2,5,7,19,22,23,27,29,32,40,45,51,53,59].

caused by blastomycosis should be shaved and kept clean and dry. Personnel handling animals with draining wounds should exercise caution to avoid accidental infection [14,15].

Treatment with itraconazole or AMB should be continued for a minimum 60 days or at least 1 month beyond clinical or radiographic resolution of clinical signs. Animals with severe lung involvement should receive therapy for at least 90 days. Recurrence rates of 20% are reported for dogs treated with itraconazole for 60 to 90 days or with AMB [19]. Similar treatment recommendations should be followed for cats, although information about response and long-term follow-up are lacking [3].

Prognosis

Blastomycosis is associated with an overall mortality rate of 25% to 30%. The prognosis is worse when severe pulmonary involvement is present, or more than three body systems are involved [19]. Most animals that die after treatment for blastomycosis do so within the first 5 days after therapy is initiated, likely because of the burden inflicted by the sudden death of many fungal organisms and the subsequent inflammatory response. Pulmonary thromboembolism has been reported as a complication of blastomycosis that causes sudden deterioration or death [10].

Histoplasmosis

Histoplasmosis occurs as a result of infection with the soil-borne, dimorphic fungus *Histoplasma capsulatum*. This organism can survive wide variations of environmental temperature and is most prevalent in moist soil containing bird or bat waste. Regions of the United States with greatest frequency of cases are the Ohio, Missouri, and Mississippi river valleys; however outbreaks may occur in other regions, if environmental conditions favor fungal growth [25–27].

Histoplasma capsulatum has a free-living mycelial stage in soil, with free-living microconidia (2 to 5 μm) or macroconidia (5 to 18 μm) that serve as a source for mammalian infection. Histoplasma organisms are 2 to 4 μm in diameter, with a thin clear halo surrounding a round or crescent-shaped basophilic cytoplasm. Route of entry is thought to be respiratory in most cases. Oral exposure may be possible, since some animals have gastrointestinal [GI] signs only [26,28]. With establishment of active infection, dissemination proceeds to any organ. Lungs, GI tract, lymph nodes, spleen, liver, bone marrow, eyes, and adrenal glands are affected most commonly. The incubation period is 12 to 16 days in dogs and people [5]. Exposure to highly contaminated environments may cause point–source outbreaks in dogs and people. Cats and dogs are equally likely to develop histoplasmosis [27].

Clinical signs

Dogs

Similar to dogs with blastomycosis, most dogs with histoplasmosis are large breed, young adults. Males are slightly predisposed, and hunting breeds including Brittanys, Pointers, and Weimaraners, may be over-represented [5,26]. Clinical signs are dictated by the organ systems involved; dogs manifest signs of GI or respiratory disease, but seldom both. Disseminated histoplasmosis with GI involvement accounts for most clinical presentations of histoplasmosis [5,27,28]. GI signs are usually consistent with small and large intestinal diarrhea, and include weight loss, hypoalbuminemia, intestinal blood loss (melena or hematochezia), and tenesmus. Hepatosplenomegaly occurs in up to 50% of cases (Fig. 4) [28]. Coughing, tachypnea, dyspnea, or pleural effusion occurs with pulmonary involvement. Less specific findings include fever, anorexia, depression, and severe weight loss. Unlike blastomycosis, however, histoplasmosis seldom is associated with bone, ocular, or dermal lesions [27].

Cats

Unlike blastomycosis, histoplasmosis is as likely to occur in cats as in dogs. Histoplasmosis occurs most commonly in cats younger than 4 years of

Fig. 4. Dorsoventral abdominal radiograph of a dog with disseminated histoplasmosis causing diffuse hepatomegaly.

age, with no breed or sex predilection [25,27]. Infection with feline leukemia virus is not associated with increased occurrence of infection [25]. Clinical signs are those of nonspecific disease, including weight loss, depression, fever, anorexia, and anemia. Weight loss and emaciation are common findings. Unlike dogs, specific GI signs are identified less commonly. Pulmonary involvement results in clinical signs of dyspnea, tachypnea, or abnormal lung sounds. Lymphadenopathy and hepatosplenomegaly occur with dissemination. In the author's experience, bone marrow involvement can occur frequently, and can be associated with various cytopathies. Dermal, ocular, orthopedic, and oral lesions occur uncommonly. Bone involvement may cause osteolytic lesions of the distal appendicular skeleton and result in lameness [5,27].

Diagnosis

As with other fungal infections, there are no pathognomonic findings on routine laboratory evaluation for histoplasmosis. Nonregenerative anemia is the most common finding on CBC. Causes include chronic inflammation, GI blood loss, and bone marrow infection [5]. *Histoplasma* organisms are seen rarely on CBC. Thrombocytopenia may occur. Abnormalities on serum biochemical profile include hypoalbuminemia, elevated hepatic enzymes, total bilirubin, and hypercalcemia [5]. Thoracic radiographs reveal diffuse or nodular interstitial pattern, or hilar lymphadenopathy in animals with pulmonary involvement [27]. Abdominal ultrasound is helpful to evaluate organomegaly (Fig. 5).

Definitive diagnosis is established by identification of *H capsulatum* on cytologic or histopathologic evaluation. Organisms typically are found within cells of the mononuclear phagocyte system. Cytologic differentiation from other fungal pathogens is facilitated by the fact that *Histoplasma capsulatum* organisms are much smaller and typically are clustered within cells (Fig. 6). Diagnostic samples may be obtained from a variety of locations. Rectal mucosal scraping in dogs with GI involvement is frequently diagnostic for histoplasmosis. For disseminated disease, aspiration of lymph nodes, dermal nodules, bone marrow, liver, spleen, or endotracheal wash should be considered. Tissue biopsy and histopathology may demonstrate organisms if cytology is unrewarding.

Serologic tests to diagnose histoplasmosis are unreliable, with false-negatives occurring in active disease and false-positives occurring in animals without active disease. No reliable immunodiagnostic test is available for identification of histoplasmosis in companion animals [27].

Treatment

Although pulmonary histoplasmosis may resolve spontaneously, treatment is recommended to prevent dissemination from occurring early in the

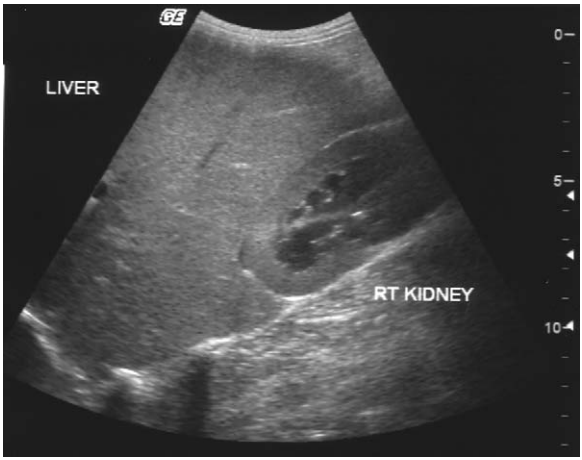

Fig. 5. Ultrasonographic image demonstrating bright hepatic parenchyma and hepatomegaly as evidenced by liver contacting dorsal and lateral surfaces of the right kidney.

course of disease. Similar to treatment for blastomycosis, itraconazole is the treatment of choice for histoplasmosis [27,29]. In a case series of cats with histoplasmosis, itraconazole was more effective than ketoconazole, with fewer adverse effects [29]. In dogs, itraconazole is also likely the treatment of choice; however it has not been studied extensively. GI drug absorption has not been predicted accurately in animals with GI or disseminated histoplasmosis. Fluconazole (Diflucan) has better penetration into the eye

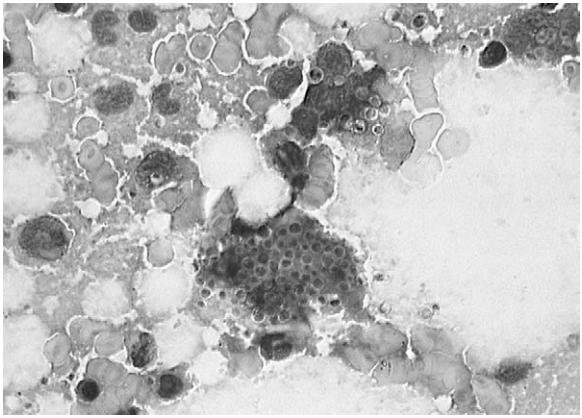

Fig. 6. Cytologic appearance of *Histoplasma capsulatum* from hepatic aspirate (Wright-Giemsa stain, ×100). (*Courtesy of* Linda Berent, DVM, Columbia, MO.)

and CNS than itraconazole, but in people with histoplasmosis, fluconazole is less effective than itraconazole [27]. This drug has not been studied extensively for treatment of histoplasmosis in dogs and cats [27]. Fluconazole should be considered with CNS involvement, or in individuals refractory to treatment with AMB and itraconazole. With severe GI or disseminated disease, treatment with parenteral AMB combined with itraconazole or high-dose itraconazole has been recommended for more rapid control of the fungal disease [27].

Treatment should be continued for at least 60 days, or until 1 month following resolution of clinical signs. Complete resolution of GI or disseminated histoplasmosis is difficult to determine, and serologic testing cannot help identify response to therapy. Animals that experience relapse with discontinuation of therapy should resume antifungal drug treatment. Table 1 contains dosing recommendations.

Ancillary therapy for GI histoplasmosis includes dietary modification for small or large bowel disease (highly digestible diet for small intestinal disease, increased fiber diet for large intestinal disease) and antibiotic therapy to control concurrent small intestinal bacterial overgrowth. Antidiarrheal therapy may be helpful in conjunction with antifungal therapy for symptomatic relief [5,27]. If malabsorption is causing malnutrition in severe GI histoplasmosis, nutritional support with partial or total parenteral nutrition should be considered until normal GI function resumes. Concurrent respiratory therapy for animals with pulmonary involvement includes oxygen and bronchodilator therapy for hypoxemic patients, minimizing handling that exacerbates respiratory distress, and possibly short-term anti-inflammatory corticosteroids [23,30].

Prognosis

Statistics on mortality with histoplasmosis have not been reported for dogs since the advent of itraconazole therapy. In one report, eight cats that had failed initial treatment with ketoconazole were cured with itraconazole [29]. In the author's experience, prognosis is guarded to good depending upon the nature of systemic involvement of organ systems.

Coccidiomycosis

Coccidiomycosis is a systemic fungal infection caused by *Coccidioides immitis*, a soil saprophyte that grows in areas with sandy, alkaline soils and semiarid conditions. In the environment, *C immitis* grows as a mycelium with thick-walled, barrel shaped arthroconidia, 2 to 4 μm wide and 3 to 10 μm long. Following exposure by inhalation, the arthroconidia enlarge to form a spherule 20 to 200 μm in diameter. (Fig. 7). The disease has been reported in most mammals. In companion animals, dogs are more frequently infected than cats [31,32].

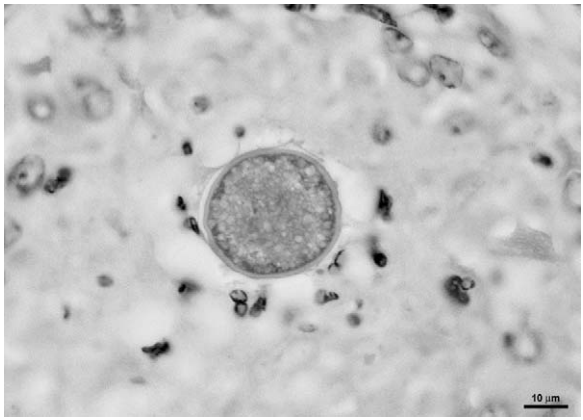

Fig. 7. Histopathologic appearance of *Coccidioides immitis* (Hematoxylin & eosin stain). (*Courtesy of* Susan Turnquist, DVM, Columbia, MO.)

Growth of *C immitis* is localized to regions in the lower Sonoran life zone. This includes the southwestern United States, Mexico, and Central and South America. A pattern of increased rainfall followed by drought conditions can cause epidemics. Dust storms or earthquakes facilitate spread. Coccidiomycosis also is known as valley fever or San Joaquin valley fever, so named for regions in which the disease is reported frequently [5,32].

Exposure and infection occur by way of the respiratory route; however, direct inoculation of infective spores can cause localized subcutaneous infection [31,32]. Inhaled arthrospores migrate through the pleural tissue to the subpleural space. Incubation period ranges from 1 to 3 weeks in dogs. An intense inflammatory response develops, resulting in clinical respiratory signs. The disease most commonly involves the respiratory tract. If dissemination occurs, involvement of other organ systems may be found in bones, eyes, heart, pericardium, testicles, brain, spinal cord, and visceral organs. People are considered immune following resolution of infection; however the same is not known for dogs and cats [31,32].

Clinical signs

Dogs

Similar to other systemic mycoses, young adult large breed dogs that are housed outdoors seem to be predisposed. Breeds that may be at increased risk for infection include the boxer, pointer, Australian shepherd, beagle, Scottish terrier, Doberman pinscher, and cocker spaniel [5]. Symptoms in the dog are primarily respiratory and may be inapparent or manifest only as mild respiratory signs following exposure. In a small subset of animals, immune response is ineffective, and clinical signs become more severe. Chronic cough is the most common presenting complaint. The cough may

be dry if it occurs as a result of hilar lymphadenopathy secondary to fungal infection, or it may be moist and productive with alveolar involvement. Respiratory lesions may progress to severe pneumonia. Fever, weight loss, and anorexia are common findings with clinical disease [5,32].

In addition to respiratory involvement, coccidiomycosis may become disseminated. Osseous lesions occur in 65% of dogs and may be associated with draining skin nodules over the lesions [5]. Regional lymphadenopathy associated with appendicular skeletal lesions may be seen, but peripheral lymphadenopathy is considered rare. Renal or GI systems may become involved. Myocardial or pericardial infection may occur, causing cardiac arrhythmias or restrictive pericarditis, resulting in right or left-sided heart failure [32,33]. CNS infection may cause seizures, behavior change, or coma. Granulomatous meningoencephalitis has been associated with coccidiomycosis [34]. Ocular lesions involving the anterior and posterior segments occur; however ocular involvement is less common with coccidiomycosis than with other systemic fungal infections [8].

Cats

Cats are relatively immune to coccidiomycosis compared with dogs. There is no obvious age, breed, or sex predilection for coccidiomycosis in cats. Skin lesions from dermal inoculation with fungus are the most common presentation. Lesions may form masses or be associated with abscessation or drainage [35]. Localized lymphadenopathy associated with draining lesions may occur. Fever, inappetence, and weight loss commonly occur in affected cats. Respiratory symptoms similar to those seen in dogs occur in about 25% of affected cats [35]. Ocular involvement including retinal detachment and uveitis or iritis occurs in approximately 12% of cats [11,35]. CNS localization is uncommon.

Diagnosis

Characteristics of CBC and serum biochemical profile are suggestive of chronic inflammatory disease. Mild, normocytic, normochromic, nonregenerative anemia, neutrophilia, left shift, and monocytosis may be identified on evaluation of CBC. Serum biochemical profile results vary depending upon organ systems involved; hypoalbuminemia and hyperglobulinemia are common; hepatic transaminase elevation occurs with hepatic involvement, and azotemia occurs with renal involvement. Hypercalcemia has been reported, but is less common than with other fungal diseases [5].

Thoracic radiographs often reveal diffuse interstitial or peribronchilar pattern, frequently with hilar lymphadenopathy. Alveolar infiltrate sometimes occurs (Fig. 8). Pleural involvement occurs in 65% of cases, either as pleural effusion or fibrosis and thickening. Hypertrophic osteopathy of long bones may occur with pulmonary involvement [32].

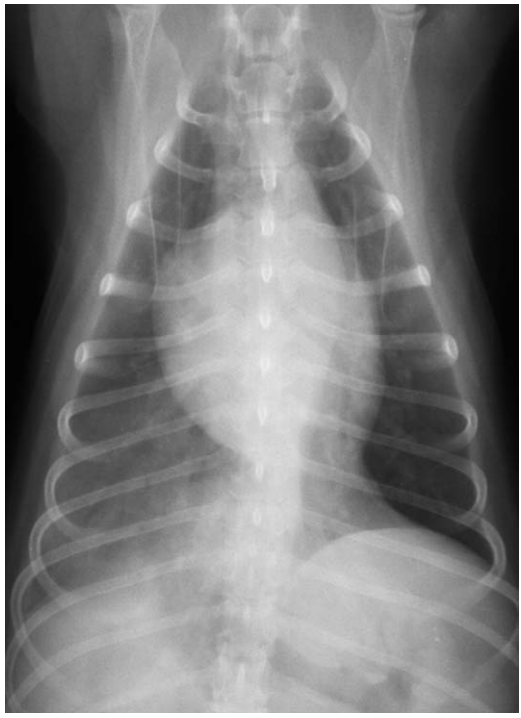

Fig. 8. Ventrodorsal thoracic radiograph of a dog with coccidiomycosis causing focal alveolar infiltrate of the right caudal lung lobe.

Demonstration of the offending organism by cytologic or histopathologic examination provides a conclusive diagnosis for coccidiomycosis. Because of the relatively low numbers of organisms, location of lesions, or invasiveness of procedures necessary for obtaining samples, organism identification is often difficult, however. Evaluation of pleural fluid or pus from draining skin nodules affords the greatest frequency of organism identification. Tracheal wash, bronchoalveolar lavage, lung aspirate, or lymph node aspirate yield organisms less commonly, and bone aspirate is largely unrewarding. Lung biopsy and histopathology may reveal organisms in pulmonary microabscesses; obtaining samples from more than one site is recommended [5,32].

Fungal culture is not a clinically useful tool for diagnosis of coccidiomycosis. *C immitis* grows readily on commercial agars at room temperature; however definitive identification requires inoculation into animals to induce spherule formation. Laboratory personnel must exercise precautions to prevent accidental exposure and infection [36].

Serologic diagnosis of coccidiomycosis is more rewarding than for blastomycosis or histoplasmosis. If symptoms are consistent with coccidiomycosis,

and organisms cannot be identified, a variety of serologic tests may be used to detect IgM and IgG antibodies. Compliment fixation (CF) testing represents IgG antibodies and should become positive within 4 to 6 weeks after exposure in clinical infection. Tube precipitin (TP) testing represents IgM antibody response. The TP test will become positive earlier in the course of infection (2 weeks after exposure) and becomes negative within 4 to 6 weeks [32]. CF titers generally increase with severe or disseminated disease. Low titers (less than 1:16) are suggestive of early or past infection, while titers of 1:32 or greater are consistent with active infection. Other methods of serologic testing have been reported for people, with varying rates of success [37]. In cats, CF and TP testing can become positive, and can remain positive for long periods of time even with treatment of disease. [35] Serologic testing should be interpreted in light of clinical signs consistent with active infection to confirm diagnosis when attempted visualization of fungal organisms is unrewarding. Repeat CF testing in 2 to 4 weeks to demonstrate increasing titer is warranted in questionable cases [32].

Treatment

Coccidiomycosis is difficult to cure compared with other fungal infections, and lifelong therapy may be necessary. Commonly recommended treatments for dogs and cats include azole antibiotics (ketoconazole, itraconazole, and fluconazole), and AMB; however, controlled therapeutic trials with these agents are lacking. Respiratory infection can be cleared spontaneously by the host immune response; therefore debate exists over the criteria indicated to initiate prolonged therapy with expensive and potentially toxic medication [5,32]. Early initiation of therapy in primary respiratory coccidiomycosis may be appropriate, since dissemination is possible. The decision to discontinue therapy is based upon resolution of clinical signs and resolution of elevated titers; CF titers may become negative, or may remain positive at 1:2 to 1:4.

Ketoconazole traditionally has been the drug of choice in dogs and cats for treatment of coccidiomycosis. Table 1 contains dose recommendations. Serologic testing should be repeated in 4 to 6 weeks of initiation of therapy. If the titer is increasing, or clinical signs deteriorating, alternative therapy should be chosen. Treatment may need to be continued for 8 to 12 months [5,32].

Itraconazole may be an alternative to ketoconazole with fewer adverse effects; however efficacy remains undetermined for dogs and cats. Some animals seem to have a more favorable response, while others require change in therapy to ketoconazole following unsuccessful itraconazole treatment [32]. AMB is indicated in animals that cannot tolerate the adverse effects of azole drugs. Liposome-encapsulated AMB formulations may have fewer adverse effects while retaining efficacy; however, they have not been studied for this disease [32].

Relapse is common after discontinuation of therapy, particularly in cats [35]. Therapy duration generally is recommended for months. Decisions to discontinue therapy should be based upon resolution of clinical signs and serologic testing. Positive CF test results are not unusual even with treatment; however increasing titer can be interpreted as treatment failure or relapse following discontinuation of therapy [32].

Chitin synthesis inhibitors interfere with fungal cell wall formation. In addition, they are cidal and may require relatively low doses for shorter periods of time than azole antibiotics. This class of drug is under investigation in people as antifungal therapy [38]. Lufenuron (Program) is a chitin synthesis inhibitor approved for veterinary use to control ectoparasites. A case series of dogs with coccidiomycosis treated with daily doses of lufenuron showed clinical improvement in 1 week, and resolution of radiographic lesions occurred in 8 weeks [32,39]. The main drawback to lufenuron therapy is drug cost; however, this might be offset if the treatment duration is shorter than with traditional antifungal therapy. Lufenuron is not approved for this use [39].

Prognosis

Coccidiomycosis remains a challenge to treat and is difficult to cure compared with other systemic mycoses. Localized respiratory infections may resolve spontaneously and generally carry a good prognosis. Disseminated infections will result in death if not treated. An overall recovery rate of 60% has been noted with ketoconazole therapy; however, multiple bone or CNS involvement carries a worse prognosis [32].

Cryptococcosis

Cryptococcosis is caused by a variety of species of *Cryptococcus*. *Cryptococcus neoformans*, which thrives at normal body temperature, is the most clinically significant agent. Unlike other fungal infections, cryptococcosis does not occur in a defined geographic region [40]. *C neoformans* is a saprophytic, round, yeast-like fungus 3.5 to 7 μm in diameter, with a large heteropolysaccharide capsule of 1 to 30 μm that does not uptake common cytologic stains (Fig. 9) [41]. *Cryptococcus* reproduces by budding from the parent cell. Buds can break off at different stages of growth, resulting in size variation of organisms in the tissues. Most likely environmental sources are locations near avian habitats or in leaf and bark litter of eucalyptus trees. The pigeon is thought to be the most important vector; the elevated body temperature of the pigeon is thought to protect it from disease. Cryptococcosis has become an important health problem in people with HIV and AIDS [42].

Unlike other fungal infections, cryptococcosis occurs with equal or greater frequency in cats compared with dogs [43]. The most likely route for

Fig. 9. Cytologic appearance of *Cryptococcus neoformans*. (Wright-Giemsa stain, ×100). (*Courtesy of* Linda Berent, DVM, Columbia, MO.)

infection is the respiratory tract. *Cryptococcus* is unencapsulated in the environment and may be as small as 1 μm, enhancing respiratory colonization. Following deposition in tissues, organisms colonize the upper or lower respiratory tract, where they regenerate their capsules. The capsule interferes with the normal host immune response and organism elimination. CNS involvement is common in cats and dogs and may occur as a result of hematogenous spread or extension from nasal cavity disease [44–47].

In people, natural disease resistance is strong, and infection is a sign of immunosuppression [42]. In dogs and cats, corticosteroid therapy has exacerbated infection [41]. In cats, concurrent feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) infections decrease the likelihood of favorable response to treatment [48]. It is unknown whether cats with FeLV or FIV are predisposed to cryptococcosis. Immunosuppression in dogs has not shown to increase risk for cryptococcosis.

Clinical signs

Cats

Cryptococcosis is the most common systemic fungal infection of cats [43]. There is no obvious age or sex predilection. Siamese cats are overrepresented in some studies [49]. Upper respiratory infection is evident in 50% to 60% of cases [41,48,50]. Symptoms may include nasal or facial deformity, mass protruding from nares, nasal discharge, sneezing, respiratory noise, or change of voice (Fig. 10). Skin lesions occur in 40% to 50% of cases, and ocular and CNS signs occur in approximately 15% of cases [43]. Ocular signs consist of blindness caused by retinal detachment and granulomatous chorioretinitis [11]. Neurologic symptoms include depression, temperament changes, ataxia, vestibular signs, and blindness [40,46].

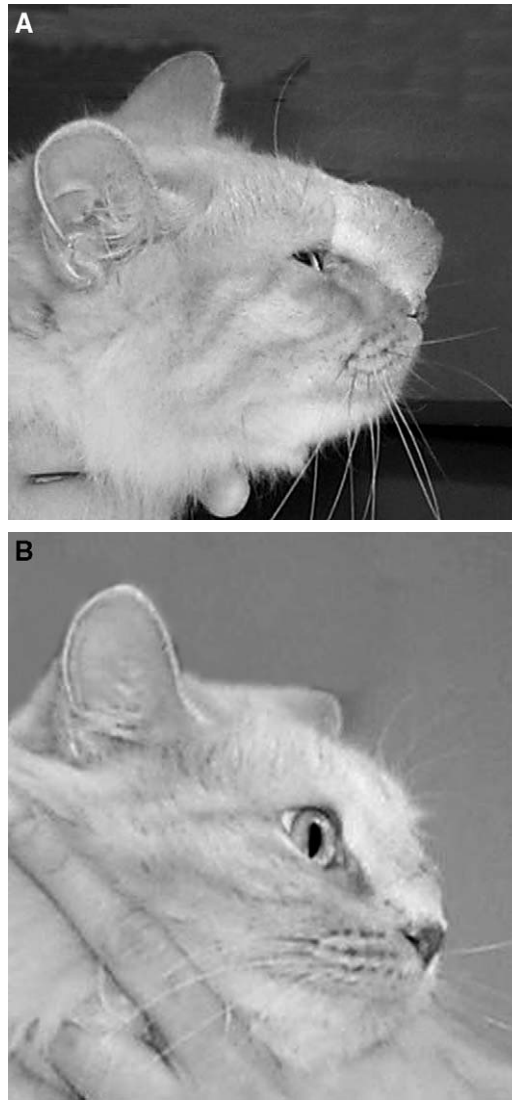

Fig. 10. (*A*) Nasal swelling caused by cryptococcosis in a cat. (*B*) Same cat following successful therapy with itraconazole.

Lungs are affected less commonly, and cats typically do not show signs of lower respiratory tract disease. Nonspecific findings of weight loss, listlessness and anorexia are common with chronic disease.

Dogs

Affected dogs are generally younger than 4 years of age, although an occasional older dog may become affected. Great Danes, Doberman

pinschers, Labrador retrievers and American cocker spaniels are overrepresented [5,40]. Clinical signs most often are localized to the CNS, with presentations of seizure, ataxia, central vestibular disease, papilledema, cervical pain, tetraparesis, or multifocal cranial nerve involvement [45]. Dogs also may have ocular lesions to include granulomatous chorioretinitis, retinal hemorrhage, and optic neuritis [8]. Skin lesions, fever, and peripheral lymphadenopathy may be seen in occasional cases [40]. Weight loss and lethargy are common but nonspecific findings.

Diagnosis

Results of CBC and serum biochemical profile are usually unremarkable with cryptococcosis. Nonregenerative anemia, neutrophilia, or left shift may be identified. Thoracic radiographs occasionally reveal nodular interstitial infiltrates, hilar lymphadenopathy, or pleural effusion. Skull radiographs or CT can demonstrate nasal bone destruction and soft tissue swelling [5]. With CNS involvement, cerebrospinal fluid (CSF) evaluation commonly exhibits increased protein and mixed mononuclear and neutrophilic pleocytosis [45].

The most reliable method to establish diagnosis of cryptococcosis is direct visualization of the causative organism on cytologic or histopathologic evaluation of specimens from an affected area. Cytologic examination may be performed on nasal discharge, skin exudates, CSF, tissue aspirate, or samples obtained by ocular paracentesis. Dogs may have subclinical renal infection; therefore microscopic evaluation of urine sediment is warranted. Wright's stain may cause some distortion of *Cryptococcus* species, while Gram's stain may facilitate visualization [40].

Serologic testing is available and useful to compliment other diagnostic procedures. Recommended serologic testing consists of latex agglutination (LA) testing to identify cryptococcal capsular antigen. This is an important distinction from serologic testing for other fungal infections, which relies on evaluation of antibody response of the infected individual. Antigen testing is considered positive at a titer of 1:16 or greater. Response to treatment is correlated with declining titer results [40,50]. Testing for cryptococcal antigen in CSF can confirm diagnosis of dogs with CNS involvement when the organism cannot be demonstrated in CSF [44].

Histopathology of affected tissue is indicated if cytology is negative; however, impression smears always should be made of biopsy samples because of the comparative ease of cytologic diagnosis. Histopathologically, the large capsule differentiates *Cryptococcus* from *Blastomyces*, while budding and lack of endospores differentiate it from *C immitis*.

Fungal isolation is available if definitive diagnosis cannot be achieved by other means, but it is not clinically useful because of prolonged growing time (up to 6 weeks may be required for positive cultures). Interpretation

demands caution, since results from nasal swabs may be positive in dogs and cats without any clinical evidence of disease [5]. CSF culture may be appropriate if CNS cryptococcosis is suspected, and cytology is negative. Culturing large volumes (10 to 15 mL) of CSF may enhance diagnosis, but this is prohibitive in small animal species. [40,45].

Treatment

Several dosing protocols and regimens have been developed for treatment of cryptococcosis in dogs and cats; choice of therapy depends upon available drugs, location of infection, and adverse effects in an individual [5]. Itraconazole therapy has been shown to be curative in 57% of cats [51]. Ketoconazole also has been shown to cure infection; however, deleterious adverse effects occurred more frequently with ketoconazole than with itraconazole [52]. Subcutaneous AMB has been used with flucytosine or ketoconazole in feline and canine cryptococcosis [53].

Therapy duration is generally prolonged. Azole antifungals typically are administered for 6 to 10 months [40]. The decision to discontinue therapy should be based on resolution of clinical signs. Recommendations to discontinue therapy 1 month after resolution of clinical signs, and decrease in antigen titer by two orders of magnitude or until negative have been proposed for cats [40]. Table 1 contains dose recommendations.

Prognosis

Cats have a good prognosis when disease occurs outside of the CNS [43]. Progressive decrease of antigen titer by tenfold over 2 months has been associated with favorable prognosis in cats. Dogs with any form of disease, and cats with CNS disease, have a guarded prognosis [5,44].

Drug therapy for systemic mycoses

A limited number of drugs are available to treat fungal infections. Antifungal drugs are expensive; treatment protocols dictate long-term therapy for cure or control of systemic mycoses, and rate of drug toxicities is relatively high. Cell-mediated immunity is crucial for host defense against systemic mycoses. Without a functional immune system, fungal infections occur more commonly, and definitive cure with any therapy is difficult or impossible [42,48].

Mainstays of antifungal therapy include polyene antibiotics and azole derivatives. Supportive care for dogs and cats with fungal disease dictates administration of a variety of therapeutics in addition to antifungal drugs. Medications with known nephrotoxicity should be avoided with concurrent AMB administration. Drugs that are metabolized by the hepatic p450

enzyme system (especially histamine-2 receptor antagonists) may delay metabolism of azole antifungals, especially ketoconazole, thereby resulting in higher plasma drug concentrations [54]. Some clinicians have used this drug interaction to delay metabolism of ketoconazole in an effort to administer a lower, and therefore less costly, dose of ketoconazole in large breed dogs.

The use of corticosteroids to treat animals with fungal disease is controversial. There is no question that administering corticosteroid drugs can lead to dissemination and worsening of fungal infection. Corticosteroids profoundly impair the cell-mediated immunity that is crucial for protection from fungal infection, and even to facilitate clearance of infection in animals treated with antifungal drugs [55]. Corticosteroids are also potent anti-inflammatory medications, however [56]. Much of the morbidity and mortality that accompanies treatment of fungal disease results from massive inflammation as a response to the death of fungal organisms within the first week of treatment. For animals with respiratory compromise resulting from pulmonary fungal infection, many clinicians administer anti-inflammatory dosages of corticosteroids either simultaneously with the instigation of antifungal medication, or if respiratory signs worsen within the first few days of antifungal therapy. In either case, steroids are used in conjunction with antifungal medications and are continued for only a brief time, typically 1 to 2 weeks [30].

Polyene antibiotics useful for treating systemic mycoses include AMB and lipid-complexed AMB. AMB is a polyene macrolide antibiotic produced by the microorganism *Streptomyces nodosus*, and it is considered the standard by which other antifungal therapies are judged [5,57]. GI absorption is poor; therefore AMB must be administered parenterally. Following intravenous (IV) administration, AMB is highly protein-bound. It then redistributes from the blood to the tissues. Metabolic pathways of AMB are unknown. Biphasic elimination occurs, with an initial half-life of 2 to 4 days, and a terminal half-life of 15 days [54]. Only a small amount undergoes renal and biliary elimination. CNS penetration is poor. AMB binds to sterols, including ergosterol in fungal cell membranes, to increase permeability and eventually cause cell death. Affinity is greater for ergosterol in fungal cell membranes than for cholesterol found in mammalian cell membranes; however, affinity for cholesterol explains AMB toxic effects. Subcutaneous administration at higher doses has been used in an attempt to delay absorption and reduce toxicity [57]. In animals with severe GI fungal disease and poor drug absorption, polyene antifungals administered parenterally may be preferred to oral therapies.

Typical dosing protocols for AMB include intermittent administration until a cumulative dose has been achieved, with interruption of therapy in the event of azotemia. Cats typically receive lower intermittent and cumulative doses than dogs (Table 1). Bolus IV administration is possible, but occurrences of nephrotoxicity can be reduced if AMB is infused in 5%

dextrose and administered over 1 to 5 hours. Serum urea nitrogen (BUN) and urine sediment evaluation should be measured before administration of each dose. Identification of tubular casts in urine sediment is an earlier indicator of ongoing renal tubular damage than serum biochemical tests, and the treatment regimen should be altered. With BUN greater than 50 mg/dL, the drug should be discontinued until azotemia resolves [5]. Administration of 0.9% IV saline before AMB administration decreases the incidence of nephrotoxicity in people [58].

Lipid-complexed AMB drugs are available, and these are significantly less nephrotoxic than AMB. Three formulations are approved for use in people: AMB lipid complex (ABLC, Abelcet), AMB colloidal dispersion (Amphotec), and liposome-encapsulated AMB (AmBisome) [59]. The advantage of these preparations is the ability to administer higher intermittent and cumulative doses with less nephrotoxicity. There are relatively few head-to-head comparisons of these drugs, so comparisons of efficacy are difficult [60]. Abelcet has been used successfully to treat blastomycosis in dogs [22]. The disadvantage of these drugs is increased cost compared with AMB.

Flucytosine (Ancobon) is a pyrimidine originally developed as an antineoplastic agent for people [57,60]. Although this drug was ineffective for that use, antifungal activity was discovered in 1973. The drug is taken up by the fungal cell and converted to 5-fluorouracil, which then interferes with DNA and protein synthesis. Drug resistance develops rapidly. It has been used in combination with AMB as a treatment for cryptococcosis before the availability of newer azole antifungals [53]. Toxicities include dermal eruptions in dogs, and hematologic changes at high doses in people [57,60].

The azole antifungals include ketoconazole, itraconazole, and fluconazole. Azole antifungals act by inhibiting the fungal P450 enzyme necessary for development of ergosterol [60]. Itraconazole and fluconazole were approved by the US Food and Drug Administration (FDA) in the early 1990s, and they have become mainstays of therapy for veterinary systemic mycoses. All are administered orally, and peak plasma concentrations do not occur for 6 to 14 days after initiating treatment with azole antifungals. Ketoconazole and itraconazole are weak bases, lipophilic, and protein-bound. Absorption is improved in an acid environment, and uptake may be impaired with concurrent use of antacids or H2 receptor antagonists. Distribution occurs through most tissues except the CNS and urine. Fluconazole is minimally protein-bound and highly water soluble. It crosses the blood-brain, blood-ocular, and blood-prostate barriers well [5,57]. Dosing of fluconazole should be adjusted in animals with reduced glomerular filtration rate (GFR) [57].

Ketoconazole has been effective as a sole agent for treatment of systemic mycoses, but in general it is less efficacious than AMB. In serious systemic fungal infections, combination therapy with AMB and ketoconazole may

allow reduced dosage and toxicity of AMB while still maintaining efficacy. Adverse effects of ketoconazole therapy include GI upset, which may be reduced by administering it with meals and dividing the dose into multiple smaller doses daily. Hepatic transaminases and alkaline phosphatase elevations may occur, as well as a clinical hepatitis that may be fatal [54,57]. Ketoconazole also can suppress testosterone and cortisol synthesis, and it has been used as a treatment for pituitary-dependent hyperadrenocorticism [61].

Itraconazole has been effective as a sole treatment agent in blastomycosis, histoplasmosis, and cryptococcosis. It can be used to treat coccidiomycosis; however, some dogs with this infection fail to respond to this drug and have a more favorable response to ketoconazole. Absorption is most consistent with administration following a full meal. Itraconazole selectively inhibits fungal P450 enzymes and not mammalian enzymes; therefore toxicities occur less frequently. Mild elevations of hepatic transaminase activity can occur [29,57]. Cutaneous reactions consisting of localized ulcerative dermatitis and vasculitis occur in a small percentage of dogs receiving itraconazole treatment; dermal lesions resolve following discontinuation of therapy [5].

Fluconazole crosses the blood–brain barrier better than the other azole antifungals, and it has more consistent oral absorption on an empty stomach. Therefore, it would be indicated for CNS involvement in systemic mycoses and for anorexic animals. Because of excellent CNS penetration, fluconazole is the treatment of choice for people with meningeal coccidiomycosis, and it should be considered in canine and feline meningeal coccidiomycosis. Fluconazole has been used to treat cryptococcosis successfully in cats [49]. Fluconazole crosses the blood–ocular barrier better than itraconazole, but itraconazole has been used successfully to treat ocular histoplasmosis in cats [29].

Summary

Systemic fungal diseases cause significant morbidity and mortality in dogs and cats. Blastomycosis, histoplasmosis, coccidiomycosis, and cryptococcosis represent the four most common systemic fungal diseases. Young adult, large breed dogs generally are predisposed; cats usually do not have predictable predispositions. Intact cell-mediated immunity is essential to initial resistance to infection and response to treatment in animals. Several body systems can be affected. Diagnosis can be confirmed on the basis of clinical signs and demonstration of the causative organism. Serology is helpful with coccidiomycosis and cryptococcosis. Treatment is complicated by limited availability of fungicidal antimicrobials and the necessity of long-term treatment with expensive drugs.

References

[1] Klein BS, Vergeront JM, Weeks RJ, Kumar UN, Mathai G, Varkey B, et al. Isolation of *Blastomyces dermatitidis* in soil associated with a large outbreak of blastomycosis in Wisconsin. N Engl J Med 1986;314(9):529–34.

[2] Legendre A. Blastomycosis. In: Greene C, editor. Infectious diseases of the dog and cat. 2nd edition. Philadelphia: WB Saunders; 1998. p. 371–7.

[3] Miller PE, Miller LM, Schoster JV. Feline blastomycosis; a report of three cases and literature review (1961–1988). J Am Anim Hosp Assoc 1990;26(4):417–24.

[4] Cote E, Barr SC, Allen C, Eaglefeather E. Blastomycosis in six dogs in New York state. J Am Vet Med Assoc 1997;210(4):502–4.

[5] Taboda J. Systemic mycoses. In: Ettinger SJ, Feldman EC, editors. Textbook of veterinary internal medicine. 5th edition, volume 1. Philadelphia: WB Saunders; 2000. p. 453–76.

[6] Baumgardner DJ, Buggy BP, Mattson BJ, Burdick JS, Ludwig D. Epidemiology of blastomycosis in a region of high endemicity in north central Wisconsin. Clin Infect Dis 1992;15(4):629–35.

[7] Arceneaux KA, Taboada J, Hosgood G. Blastomycosis in dogs: 115 cases (1980–1995). J Am Vet Med Assoc 1998;213(5):658–64.

[8] Krohne SG. Canine systemic fungal infections. Vet Clin North Am Small Anim Pract 2000;30(5):1063–90.

[9] Gortel K, McKiernan BC, Johnson JK, Campbell KL. Calcinosis cutis associated with systemic blastomycosis in three dogs. J Am Anim Hosp Assoc 1999;35(5):368–74.

[10] McGuire NC, Vitsky A, Daly CM, Behr MJ. Pulmonary thromboembolism associated with *Blastomyces dermatitidis* in a dog. J Am Anim Hosp Assoc 2002;38(5):425–30.

[11] Gionfriddo JR. Feline systemic fungal infections. Vet Clin North Am Small Anim Pract 2000;30(5):1029–50.

[12] Dow SW, Legendre AM, Stiff M, Greene C. Hypercalcemia associated with blastomycosis in dogs. J Am Vet Med Assoc 1986;188(7):706–9.

[13] Bloom JD, Hamor RE, Gerding PA Jr. Ocular blastomycosis in dogs: 73 cases, 108 eyes (1985–1993). J Am Vet Med Assoc 1996;209(7):1271–4.

[14] Cote E, Barr SC, Allen C. Possible transmission of *Blastomycosis dermatitidis* via culture specimen. J Am Vet Med Assoc 1997;210(4):479–80.

[15] Ramsey DT. Blastomycosis in a veterinarian. J Am Vet Med Assoc 1994;205(7):968.

[16] Phillips WE, Kaufman L. Cultural and histopathologic confirmation of canine blastomycosis diagnosed by an agar-gel immunodiffusion test. Am J Vet Res 1980;41(8):1263–5.

[17] Legendre AM, Becker PU. Evaluation of the agar-gel immunodiffusion test in the diagnosis of canine blastomycosis. Am J Vet Res 1980;41(12):2109–11.

[18] Klein BS, Squires RA, Lloyd JK, Ruge DR, Legendre AM. Canine antibody response to *Blastomyces dermatitidis* WI-1 antigen. Am J Vet Res 2000;61(5):554–8.

[19] Legendre AM, Rohrbach BW, Toal RL, Rinaldi MG, Grace LL, Jones JB. Treatment of blastomycosis with itraconazole in 112 dogs. J Vet Intern Med 1996;10(6):365–71.

[20] Dunbar M Jr., Pyle RL, Boring JG, McCoy CP. Treatment of canine blastomycosis with ketoconazole. J Am Vet Med Assoc 1983;182(2):156–7.

[21] Legendre AM, Selcer BA, Edwards DF, Stevens R. Treatment of canine blastomycosis with amphotericin B and ketoconazole. J Am Vet Med Assoc 1984;184(10):1249–54.

[22] Krawiec DR, McKiernan BC, Twardock AR, Swenson CE, Itkin RJ, Johnson LR, et al. Use of an amphotericin B lipid complex for treatment of blastomycosis in dogs. J Am Vet Med Assoc 1996;209(12):2073–5.

[23] Legendre AM, Toal RL. Diagnosis and treatment of fungal diseases of the respiratory system. In: Bonagura JD, editor. Kirk's current veterinary XIII small animal practice. Philadelphia: WB Saunders; 2000. p. 815–9.

[24] Gionfriddo JR, Powell CC. Disseminated blastomycosis with ocular involvement in a dog. Vet Med 2002;97(6):423–31.

[25] Clinkenbeard KD, Cowell RL, Tyler RD. Disseminated histoplasmosis in cats: 12 cases (1981–1986). J Am Vet Med Assoc 1987;190(11):1445–8.
[26] Clinkenbeard KD, Cowell RL, Tyler RD. Disseminated histoplasmosis in dogs: 12 cases (1981–1986). J Am Vet Med Assoc 1988;193(11):1443–7.
[27] Wolf AM. Histoplasmosis. In: Greene CE, editor. Infectious diseases of the dog and cat, Volume 1. Philadelphia: WB Saunders; 1998. p. 378–83.
[28] Clinkenbeard KD, Wolf AM, Cowell RL, Tyler RD. Canine disseminated histoplasmosis. Compendium of Continuing Education for the Practicing Veterinarian 1989;11(11): 1347–60.
[29] Hodges RD, Legendre AM, Adams LG, Willard MD, Pitts RP, Monce K, et al. Itraconazole for the treatment of histoplasmosis in cats. J Vet Intern Med 1994;8(6):409–13.
[30] Schulman RL, McKiernan BC, Schaeffer DJ. Use of corticosteroids for treating dogs with airway obstruction secondary to hilar lymphadenopathy caused by chronic histoplasmosis: 16 cases (1979–1997). J Am Vet Med Assoc 1999;214(9):1345–8.
[31] Stevens DA. Coccidioidomycosis. N Engl J Med 1995;332(16):1077–82.
[32] Greene RT. Coccidiomycosis. In: Greene CE, editor. Infectious diseases of the dog and cat, Vol. 1. Philadelphia: WB Saunders; 1998. p. 391–8.
[33] Shubitz LF, Matz ME, Noon TH, Reggiardo CC, Bradley GA. Constrictive pericarditis secondary to *Coccidioides immitis* infection in a dog. J Am Vet Med Assoc 2001;218(4):537–40.
[34] Burtch M. Granulomatous meningitis caused by *Coccidioides immitis* in a dog. J Am Vet Med Assoc 1998;212(6):827–9.
[35] Greene RT, Troy GC. Coccidioidomycosis in 48 cats: a retrospective study (1984–1993). J Vet Intern Med 1995;9(2):86–91.
[36] Kohn GJ, Linne SR, Smith CM, Hoeprich PD. Acquisition of coccidioidomycosis at necropsy by inhalation of coccidioidal endospores. Diagn Microbiol Infect Dis 1992;15(6):527–30.
[37] Martins TB, Jaskowski TD, Mouritsen CL, Hill HR. Comparison of commercially available enzyme immunoassay with traditional serological tests for detection of antibodies to *Coccidioides immitis*. J Clin Microbiol 1995;33(4):940–3.
[38] Gupte M, Kulkarni P, Ganguli BN. Antifungal antibiotics. Appl Microbiol Biotechnol 2002;58(1):46–57.
[39] Bartsch R, Greene R. New treatment of coccidiomycosis. Veterinary Forum 1997; 14:50–2.
[40] Jacobs GJ, Medleau L. Cryptococcosis. In: Greene CE, editor. Infectious diseases of the dog and cat, Vol. 1. Philadelphia: WB Saunders; 1998. p. 383–90.
[41] Gerds-Grogan S, Dayrell-Hart B. Feline cryptococcosis: a retrospective evaluation. J Am Anim Hosp Assoc 1997;33(2):118–22.
[42] Chuck SL, Sande MA. Infections with *Cryptococcus neoformans* in the acquired immunodeficiency syndrome. N Engl J Med 1989;321(12):794–9.
[43] Buergelt CD. Cryptococcosis in cats. Vet Med 2001;96(3):187–94.
[44] Berthelin CF, Bailey CS, Kass PH, Legendre AM, Wolf AM. Cryptococcosis of the nervous system in dogs. 1. Epidemiologic, clinical, and neuropathologic features. Progress in Veterinary Neurology 1994;5(3):88–97.
[45] Berthelin CF, Legendre AM, Bailey CS, Kass PH, Wolf AM. Cryptococcosis of the nervous system in dogs, 2. Diagnosis, treatment, monitoring, and prognosis. Progress in Veterinary Neurology 1994;5(4):136–46.
[46] Beatty JA, Barrs VR, Swinney GR, Martin PA, Malik R. Peripheral vestibular disease associated with cryptococcosis in three cats. J Feline Med Surg 2000;2(1): 29–34.
[47] Tiches D, Vite CH, Dayrell-Hart B, Steinberg SA, Gross S, Lexa F. A case of canine central nervous system cryptococcosis: management with fluconazole. J Am Anim Hosp Assoc 1998;34(2):145–51.

[48] Jacobs GJ, Medleau L, Calvert C, Brown J. Cryptococcal infection in cats: factors influencing treatment outcome, and results of sequential serum antigen titers in 35 cats. J Vet Intern Med 1997;11(1):1–4.
[49] Malik R, Wigney DI, Muir DB, Gregory DJ, Love DN. Cryptococcosis in cats: clinical and mycological assessment of 29 cases and evaluation of treatment using orally administered fluconazole. J Med Vet Mycol 1992;30(2):133–44.
[50] Flatland B, Greene RT, Lappin MR. Clinical and serologic evaluation of cats with cryptococcosis. J Am Vet Med Assoc 1996;209(6):1110–3.
[51] Medleau L, Jacobs GJ, Marks MA. Itraconazole for the treatment of cryptococcosis in cats. J Vet Intern Med 1995;9(1):39–42.
[52] Medleau L, Greene CE, Rakich PM. Evaluation of ketoconazole and itraconazole for treatment of disseminated cryptococcosis in cats. Am J Vet Res 1990;51(9):1454–8.
[53] Mikiciuk MG, Fales WH, Schmidt DA. Successful treatment of feline cryptococcosis with ketoconazole and flucytosine. J Am Anim Hosp Assoc 1990;26(2):199–201.
[54] Boothe D. Treatment of fungal infections. In: Boothe DM, editor. Small animal clinical pharmacology and therapeutics. Philadelphia: WB Saunders; 2001. p. 222–36.
[55] Bondy PJ, Cohn LA. Physiological effects and pharmacologic considerations of glucocorticoids. Vet Med 2002;97(11):836–40.
[56] Bondy PJ, Cohn LA. Choosing an appropriate glucocorticoid treatment plan. Vet Med 2002;97(11):841–9.
[57] Greene CE, Watson ADJ. Antifungal chemotherapy. In: Greene CE, editor. Infectious diseases of the dog and cat. 2nd edition. Philadelphia: WB Saunders; 1998. p. 357–62.
[58] Branch RA. Prevention of amphotericin B-induced renal impairment. A review on the use of sodium supplementation. Arch Intern Med 1988;148(11):2389–94.
[59] Plotnick AN. Lipid-based formulations of amphotericin B. J Am Vet Med Assoc 2000;216(6):838–41.
[60] Lu I, Dodds E, Perfect J. New antifungal agents. Semin Respir Infect 2002;17(2):140–50.
[61] Feldman EC, Nelson RW. Hyperadrenocorticism. In: Feldman EC, Nelson RW, editors. Canine and feline endocrinology and reproduction. 2nd edition. Philadelphia: WB Saunders; 1996. p. 187–265.