Review of Blastomycosis in Dogs and Cats

J.S. Renschler, DVM, PhD, Dipl ACVP and L.J. Wheat, MD

1. Introduction

Blastomycosis is a systemic fungal infection that can be fatal if it is not diagnosed early. Most cases may be diagnosed by identification of the yeast in cytologic or histologic samples. Early diagnosis may also be aided by detection of fungal antigen in urine or serum. This article will review the clinical features of blastomycosis in dogs and cats, and discuss the current diagnostic and treatment recommendations.

2. Epidemiology

While blastomycosis may occur in a wide variety of animals, most diagnosed cases are in dogs. Endemic areas for blastomycosis include the Mississippi, Ohio, and Missouri river valleys, the Eastern Seaboard, Southern Canada, and areas adjacent to the Great Lakes (see Fig. 1). The states with areas of highest endemicity are Wisconsin, Minnesota, Missouri, Illinois, Michigan, Kentucky, West Virginia, Arkansas, Tennessee, North Carolina, South Carolina, Louisiana, and Mississippi. Other endemic states include Indiana, Iowa, Ohio, Virginia, Georgia, Alabama and Vermont.

Figure 1. General endemic range of blastomycosis in North America

Cases, however, may occur outside the endemic area [1]. The annual incidence was 1420 cases per 100,000 dogs in a highly-endemic area [2]. Proximity to waterways and exposure to excavation are significant risk factors but age, sex, and activities such as hunting, swimming and exposure to beavers are not. While most cases occur in dogs with extensive outdoor exposure, cases also may be seen in indoor pets [1]. Cases occur most often in the fall [3, 4], but may occur any time of the year. Blastomycosis occurs mainly in young, large-breed dogs [3], with the highest rates in Coonhounds, Pointers and Weimaraners [4]. Doberman Pinschers and Retrievers also may be at increased risk for blastomycosis, but any breed is susceptible if exposed to the organism. In some reports, the prevalence was higher in males than females [4, 5]. Higher rates in sexually intact male dogs was thought to be caused by roaming behavior or selective use in hunting [4].

The incidence of feline blastomycosis is much lower than that in dogs, with one retrospective study over 11 years at a Canadian veterinary school showing 151 total blastomycosis cases, of which only 6 were feline (4%) [6]. A 5-year survey of the Veterinary Medical Data Program found only 3 infected cats compared to 324 dogs with blastomycosis [7].

3. Pathogenesis and Clinical Findings

Blastomycosis is acquired by inhaling fungal spores, and causes a respiratory and/or disseminated infection. If the inoculum is small and the animal is not immunocompromised, the infection may be limited to the respiratory tract and may have few or no clinical signs. The most

common clinical findings are nonspecific and include loss of appetite, weight loss, and fever. Respiratory abnormalities also are common, and radiographs show nodular or interstitial infiltrates, often referred to as a "snowstorm pattern" [3]. Less frequently thoracic radiographs show tracheal bronchial lymphadenopathy, masses, or cavitary lesions [3]. Draining skin tracts and lymphadenopathy are commonly present. Among fatal cases, the organs most often involved are the lungs, eyes and skin [4]. Ocular lesions occur in about one third of cases [8]. Other less common sites of dissemination include the central nervous system and genitourinary tract [3].

Early detection of the ocular lesions is important for saving vision and for diagnosing the systemic nature of the disease. In a review of cases with ocular involvement, endophthalmitis was most common, followed by posterior segment disease, and anterior segment disease [8]. Lens rupture is a potential complication [9]. In an earlier report, the most common ocular lesion was uveitis, and other manifestations included retinal detachment, panophthalmitis, and glaucoma [10]. The most common ocular findings include photophobia, conjunctival hyperemia, miosis, blepharospasm, and aqueous flare. Most of the patients also exhibited pneumonia and many had skin lesions or enlarged lymph nodes. The presence of ocular disease in patients from areas endemic for blastomycosis should prompt careful evaluation for the condition.

Clinical findings in cats with blastomycosis may be similar to those in dogs; however, large surveys are not available to define the most common clinical manifestations in cats. One case report of 8 cats with naturally occurring blastomycosis described respiratory tract signs and dermal lesions as the most common findings [11]. Chorioretinitis and CNS signs have also been reported in cats with disseminated blastomycosis [12]. Affected cats have usually had negative retroviral status, and immunosuppression is not typically associated with development of clinical blastomycosis [11, 13].

4. Diagnosis

In a review of the Veterinary Medical Database, in over 90% of cases the diagnosis was validated by laboratory tests, while in <5% the diagnosis was based solely on clinical findings [4]. A variety of methods are useful for diagnosis.

Identification of the organism. Cytology and/or histopathology is considered the gold standard method for diagnosis. *Blastomyces* organisms appear in cytologic preparations stained with Romanowsky-type stains as 8-20 µm, blue, spherical, thick-walled yeasts (see Fig. 2). Broad-based budding is commonly observed. Cytology was positive in 71% of cases in one report, including mostly skin and lymph node samples, and occasionally transtracheal washes [3]. In some cases, cytology of subretinal aspirates has been positive [10]. Culture was the basis for diagnosis in only 12% of cases [3], and is not commonly used in veterinary cases due to risk of infection of laboratory personnel when handling the mycelial form of the fungus.
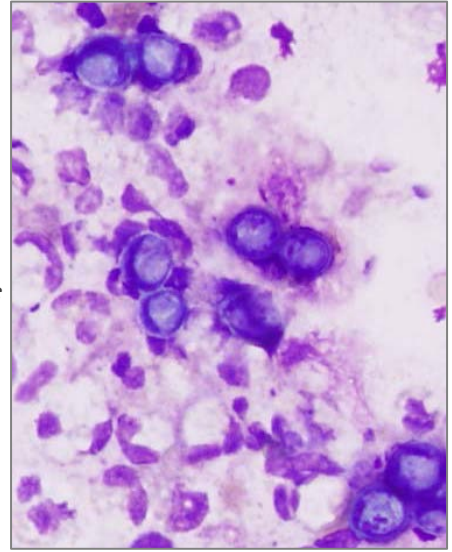

Figure 2. B. dermatitidis yeasts mixed wtih degenerate neutrophils (Diff-Quik stain; 1000X)

Antigen detection. *Blastomyces* surface antigens can be detected by an enzyme immunoassay (EIA) in body fluids including urine, serum, bronchoalveolar lavage fluid, cerebrospinal fluid, etc. (first reported in humans in 2004) [14]. In 2006, Spector *et al*. demonstrated that the antigen test is also useful in dogs, showing 94% sensitivity for urine and 87% sensitivity for serum in dogs with pathology-proven blastomycosis [15]. Antigen concentration correlates with the severity of the infection, and results are almost always positive in moderately-severe or severe blastomycosis. Antigen tests may initially be negative in mild, chronic or localized cases of blastomycosis; therefore, a negative result does not exclude the diagnosis. In addition, nearly complete cross-reactivity occurs between antigen detection in histoplasmosis and blastomycosis, and current antigen tests cannot differentiate the two systemic fungal infections.

Antibody detection. Tests for antibody to *Blastomyces* using immunodiffusion (ID) methods have historically been available but have had limited clinical utility. Sensitivity for ID has been described to be as low as 17% [16]. Enzyme immunoassay (EIA) methods of antibody detection reportedly have higher sensitivity (76%-95%) [16, 17], and a commercial assay for *Blastomyces* canine IgG is currently available (MVista® *Blastomyces* Canine IgG antibody EIA). The specificity of the antibody EIA is high (95% in healthy control dogs from the endemic area, 100% in dogs with nonfungal pulmonary disease), although some cross reactivity is observed in dogs with histoplasmosis [17]. Antibody testing may be useful for diagnosis of cases with suspected false

negative antigen results, or in cases with equivocal low positive antigen results. At the current time, there is no commercially available feline antibody EIA.

Molecular techniques. Polymerase chain reaction (PCR) assays were demonstrated to detect *Blastomyces* DNA in 8/13 paraffin-embedded canine tissue samples in which yeast cells were seen microscopically, as well as in soil samples from a dog kennel housing dogs with blastomycosis [18, 19]. Real-time PCR assays for the *B. dermatitidis BAD1* gene promotor are available from several diagnostic laboratories, and human studies have shown that *Blastomyces* can be detected by RT-PCR in culture specimens, paraffin-embedded tissue specimens and clinical samples (respiratory specimens, blood, bone marrow, peritoneal fluid, etc.) [20, 21]. The sensitivity for RT-PCR was 86% (10/12 clinical specimens) and 83% (5/6 tissue specimens) in two human studies [20, 21]; therefore, the number of samples was quite low to make any conclusions regarding the clinical utility of RT-PCR. Additionally, no peer-reviewed publications are apparently available at this time to assess the utility of molecular testing for the diagnosis of canine or feline blastomycosis. The acquisition of respiratory or tissue specimens may be challenging or invasive in some cases; therefore, testing urine or serum for the presence of antigen or antibodies is often advantageous. Due to the low incidence of fungemia, whole blood is unlikely to be a desirable specimen for RT-PCR testing. When more invasive procedures are performed to obtain respiratory or tissue specimens, a diagnosis may often be obtained by cytology or histopathology.

5. Treatment

Although effective therapy is available, up to one quarter of dogs with blastomycosis die, usually during the first week of treatment, and most often due to respiratory failure (12). There is a strong correlation between the extent of lung involvement and survival time. Outcome was especially poor in cases with brain, spinal cord (1) or ocular involvement (6). In another report over half of patients with ocular blastomycosis were euthanized or died, while some dogs did respond to amphotericin B (8). A high concentration of antigen in the urine or blood correlates with clinical severity in dogs. In an unpublished study, 75% of dogs with antigen concentrations > 14.7 ng/mL required oxygen treatment and 86% were euthanized, compared with 8% and 15% of dogs, respectively, that had antigen concentrations <14.7 ng/mL (A. Mourning, presented at 2010 ACVIM forum, Anaheim, CA).

There is limited information in the literature regarding treatment and prognosis for feline blastomycosis. Affected cats have been successfully treated with itraconazole at 5 mg/kg BID [7]. Treatment and monitoring of feline blastomycosis is presumed to be similar to that for histoplasmosis (much more commonly observed in cats).

Itraconazole. Itraconazole is currently the treatment of choice for blastomycosis in dogs. The typical dosage to achieve therapeutic blood concentration is 5 mg/kg/d, although therapeutic drug monitoring is highly

recommended to attain the optimum dosage. A loading dose of 5 mg/kg q12h or 10mg/kg q24h is sometimes used for the first 3-4 days of treatment to achieve a more rapid steady state of drug concentration [22]. Legendre *et al.* showed that response to a two month course of itraconazole at 10 mg/kg/d was 74%, while a lower dose of 5 mg/kg/d given with food was nearly as effective [23]. Dogs receiving the higher dosage had significantly more adverse effects including anorexia and increased activity of alanine aminotransferase and alkaline phosphatase.

When possible, brand-name itraconazole capsules (Sporanox®, Janssen Pharmaceuticals), FDA approved oral suspension (Sporanox® or Itrafungol®, Elanco Animal Health) or generic capsules containing pelletized itraconazole should be used, as compounded preparations may have poor bioavailability [24, 25]. In a study performed at MiraVista Diagnostics, it was demonstrated that 98% of dogs and cats receiving compounded itraconazole (from a variety of compounding pharmacies) had subtherapeutic itraconazole blood levels [26]. There was no statistical difference in mean itraconazole blood concentration of patients receiving generic capsules or Sporanox capsules, although subtherapeutic and potentially toxic levels were observed in some patients from both groups (demonstrating the importance of therapeutic drug monitoring). Itraconazole capsules require an acid pH for maximum absorption, and should be taken with food. Concurrent use of antacids (H2 receptor antagonists or proton pump blockers) will decrease bioavailability. The Sporanox® suspension does not require an acidic environment, and should be taken on an empty stomach.

Itraconazole is eliminated by hepatic metabolism through cytochrome P450 3A4, and blood levels may be affected by medications that interact with that enzyme. Itraconazole blood level measurement is recommended at steady state for all patients (day 14 of treatment for dogs, day 21 for cats) and any time treatment failure or drug toxicity is suspected. Trough blood levels of at least 1µg/ml by high performance liquid chromatography (HPLC), and 3 µg/ml by bioassay, are recommended. Itraconazole is currently assessed by bioassay at MiraVista, as this procedure adequately estimates the drug concentration by inhibition of growth of a plated *Candida* yeast around the patient serum. This minimal technology assay may be performed at a low cost to encourage more testing in the veterinary community. Other antifungal agents will cause interference in the assay (overestimation of itraconazole concentration). If specific itraconazole assessment is required, one source of HPLC testing is Fungus Testing Laboratory (University of Texas Health Science Center at San Antonio).

Itraconazole may cause a variety of adverse effects, most commonly loss of appetite, anorexia, vomiting, or diarrhea, which may be related to high blood levels [27]. Serum liver enzymes should be monitored during therapy. Activity of serum alanine aminotransferase (ALT) greater than 200 U/L may warrant discontinuation of itraconazole until appetite returns and ALT activity returns to <100 U/L [7]. Itraconazole may be restarted at

half of the former dose. Ulcerative dermatitis was also observed in 7.5% of dogs receiving itraconazole at 10 mg/kg/d [23].

Fluconazole. Fluconazole is often used for treatment of blastomycosis because of its lower cost, and in some cases because of its central nervous system penetration. Response to itraconazole and fluconazole was compared in a retrospective study [28]. Of note is that severity of disease, namely respiratory difficulty, was greater in dogs treated with itraconazole. Ninety percent of dogs treated with itraconazole at an average dose of 5 mg/kg/d for a median time of 4 months achieved clinical remission, but 18% relapsed. Seventy-five percent of dogs treated with fluconazole 10 mg/kg/d for six months responded to therapy, but 22% relapsed. There was a 10% mortality rate with itraconazole and a 25% rate with fluconazole. While the differences in survival rate and treatment response between itraconazole and fluconazole were not statistically significant, they suggest that itraconazole may be slightly more efficacious than fluconazole, which is the case in humans [29]. In cases where itraconazole cannot be used (due to high cost or intolerance of the medication), fluconazole is another treatment option. Fluconazole blood level monitoring is usually unnecessary because levels are generally predictable if the recommended dosage is administered as prescribed.

Other azoles. Other treatment options include newer azoles such as posaconazole and voriconazole. Both are active in vitro [30] and effective in animal models of blastomycosis [31, 32]. However, neither has been adequately studied for treatment of blastomycosis in dogs or cats. There are case reports of patients with CNS blastomycosis treated successfully with voriconazole [33, 34]. These newer azoles are more expensive than itraconazole, and require monitoring to assure adequate blood levels. Ketoconazole is less effective than other azoles, but may be used if the cost of itraconazole or fluconazole is prohibitive [35].

Amphotericin B. Amphotericin B was historically recommended for treatment of blastomycosis in dogs and cats [1, 36, 37], as in humans; however, the risk of nephrotoxicity has limited its use at the current time. Itraconazole has largely replaced amphotericin B as the recommended therapy. In severe or refractory cases of disseminated blastomycosis, the use of liposomal or lipid-complexed forms of amphotericin B should be considered initially, before transitioning to itraconazole. Lipid-complexed amphotericin B (Abelcet®, Enzon Pharmaceuticals; Bridgewater, NJ) may be used at a dosage of 1-2.5 mg/kg, every 48 hours or three times a week, until a cumulative dose of 12-15 mg/kg is reached [22]. Despite a lower incidence of nephrotoxicity as compared to unaltered amphotericin B, renal function and serum electrolytes should be monitored during treatment.

Terbinafine. This allylamine antifungal agent has been anecdotally used for the treatment of blastomycosis in dogs, sometimes in combination with itraconazole or other azoles. Studies to evaluate the efficacy of terbinafine in the treatment of canine or feline blastomycosis are lacking, although one pharmacokinetic study

in dogs provided evidence that oral terbinafine (30-35 mg/kg) could potentially be effective against *Blastomyces* [38].

Duration of antifungal therapy. The optimal duration of therapy is somewhat unclear, and variable based on disease presentation.   Plumb recommends two months for fluconazole but two to three months for itraconazole [39]. Mazepa treated for a median of six months if fluconazole was used and 4.5 months if itraconazole was used, and relapse occurred in 21% of dogs that survived initial therapy [28].   Legendre, using itraconazole, treated for two months in about 90% of cases, but relapse occurred in 28% of dogs that responded to the initial therapy, supporting a statement that longer treatment may reduce relapse [23]. Bromel recommends that at least four to six months of itraconazole should be given to reduce the likelihood of relapse [1]. Urine antigen monitoring after clinical remission is achieved is beneficial in determining the endpoint for antifungal therapy.

Adjunctive therapy. Lung infiltrates in 23% of dogs worsened in the initial week of therapy with antifungals, likely attributed to an inflammatory response to dying organisms [40]. Fifty percent of dogs with severe lung disease die during the first week of therapy. Dexamethasone (0.25-0.5 mg/kg IV for 2-3 days) may be given to dogs that develop life-threatening respiratory signs [7].   Concurrent antifungal therapy is recommended in order to reduce the risk for progressive dissemination caused by corticosteroid-induced immunosuppression.

Monitoring therapy. Antigen concentration declines with effective therapy [15], and it may be used as a marker to determine endpoint of antifungal therapy. In one study, among 27 dogs treated for blastomycosis with fluconazole for an average of six months, antigen was detectable in the urine in 8 (30%) at discontinuation of treatment, but all at low levels (<1 ng/mL in 7 and 1.4 ng/mL in the 8th dog) [41]. Relapse occurred in 7 dogs (26%), 2 of which had a positive urine antigen at treatment discontinuation, including the dog with a result of 1.4 ng/mL. Relapse was associated with a rise in antigenuria in 5 of 7 dogs (71%), one of which occurred a month before the relapse. The authors recommended continuing therapy until clinical signs and radiographic lesions resolved (or were stable) and urine antigen result was negative. The significance of low level antigenuria at the time of clinical remission remains unclear, as the number of cases in the study was low. A conservative approach to therapy would indicate that treatment should be continued until the urine antigen is negative. If antifungal therapy is discontinued in a patient with low positive urine antigen result, the antigen test should be reassessed every 1-3 months off therapy.

Failure of the antigen concentration to decline may also raise concern about the effectiveness of treatment, which may be caused by inadequate itraconazole blood levels or development of resistance to fluconazole [42, 43]. If itraconazole levels are subtherapeutic, the dosage should be increased and blood levels should be rechecked 14-21 days later. Increase in antigen concentration after stopping treatment suggests relapse,

which occurs in about 15-20% of cases treated with either itraconazole [23, 28] or fluconazole [28]. Testing for antigenuria about every three months during and for six months after stopping therapy, and any time that clinical signs suggest recurrence, is recommended.

References

1. Bromel, C. and J.E. Sykes, *Epidemiology, diagnosis, and treatment of blastomycosis in dogs and cats.* Clin. Tech. Small Anim Pract, 2005. **20**(4): p. 233-239.

2. Baumgardner, D.J., D.P. Paretsky, and A.C. Yopp, *The epidemiology of blastomycosis in dogs: north central Wisconsin, USA.* J Med Vet. Mycol, 1995. **33**(3): p. 171-176.

3. Arceneaux, K.A., J. Taboada, and G. Hosgood, *Blastomycosis in dogs: 115 cases (1980-1995).* J. Am. Vet. Med. Assoc, 1998. **213**(5): p. 658-664.

4. Rudmann, D.G., et al., *Evaluation of risk factors for blastomycosis in dogs: 857 cases (1980-1990).* J. Am. Vet. Med. Assoc, 1992. **201**(11): p. 1754-1759.

5. Selby, L.A., S.V. Becker, and H.W. Hayes, Jr., *Epidemiologic risk factors associated with canine systemic mycoses.* Am. J Epidemiol, 1981. **113**(2): p. 133-139.

6. Davies, J.L., T. Epp, and H.J. Burgess, *Prevalence and geographic distribution of canine and feline blastomycosis in the Canadian prairies.* Can Vet J, 2013. **54**(8): p. 753-60.

7. Legendre, A.M., *Blastomycosis*, in *Infectious Diseases of the Dog and Cat*, C.E. Greene, Editor. 2012, Elsevier: St. Louis. p. 606-614.

8. Bloom, J.D., R.E. Hamor, and P.A. Gerding, Jr., *Ocular blastomycosis in dogs: 73 cases, 108 eyes (1985-1993).* J. Am. Vet. Med. Assoc, 1996. **209**(7): p. 1271-1274.

9. Hendrix, D.V., et al., *Comparison of histologic lesions of endophthalmitis induced by Blastomyces dermatitidis in untreated and treated dogs: 36 cases (1986-2001).* J. Am. Vet. Med. Assoc, 2004. **224**(8): p. 1317-1322.

10. Buyukmihci, N., *Ocular lesions of blastomycosis in the dog.* J. Am. Vet. Med. Assoc, 1982. **180**(4): p. 426-431.

11. Gilor, C., et al., *Clinical aspects of natural infection with Blastomyces dermatitidis in cats: 8 cases (1991-2005).* J. Am. Vet. Med. Assoc, 2006. **229**(1): p. 96-99.

12. Breider, M.A., et al., *Blastomycosis in cats: five cases (1979-1986).* J Am Vet Med Assoc, 1988. **193**: p. 570-72.

13. Davies, C. and G.C. Troy, *Deep mycotic infections in cats.* J Am Anim Hosp Assoc, 1996. **32**(5): p. 380-391.

14. Durkin, M., et al., *Antigen assay with the potential to aid in diagnosis of blastomycosis.* J. Clin Microbiol, 2004. **42**(10): p. 4873-4875.

15. Spector, D., et al., *Antigen Testing for the Diagnosis of Blastomycosis.* Journal of Veterinary Internal Medicine, 2006. **20**(3): p. 711-712.

16. Klein, B.S., et al., *Canine antibody response to Blastomyces dermatitidis WI-1 antigen.* Am. J. Vet. Res, 2000. **61**(5): p. 554-558.

17. Mourning, A.C., et al., *Evaluation of an enzyme immunoassay for antibodies to a recombinant Blastomyces adhesin-1 repeat antigen as an aid in the diagnosis of blastomycosis in dogs.* J. Am. Vet. Med. Assoc, 2015. **247**(10): p. 1133-1138.

18. Bialek, R., et al., *Nested PCR assays for detection of Blastomyces dermatitidis DNA in paraffin-embedded canine tissue.* J Clin Microbiol, 2003. **41**(1): p. 205-208.

19. Burgess, J.W., W.R. Schwan, and T.J. Volk, *PCR-based detection of DNA from the human pathogen Blastomyces dermatitidis from natural soil samples.* Med. Mycol, 2006. **44**(8): p. 741-748.

20. Babady, N.E., et al., *Detection of Blastomyces dermatitidis and Histoplasma capsulatum from culture isolates and clinical specimens by use of real-time PCR.* J Clin Microbiol, 2011. **49**(9): p. 3204-3208.

21. Sidamonidze, K., et al., *Real-time PCR assay for identification of Blastomyces dermatitidis in culture and in tissue.* J. Clin. Microbiol, 2012. **50**(5): p. 1783-1786.

22. Greene, C.E. and J. Calpin, *Antimicrobial Drug Formulary*, in *Infectious Diseases of the Dog and Cat*, C.E. Greene, Editor. 2012, Elsevier: St. Louis. p. 1207-1230.

23. Legendre, A.M., et al., *Treatment of blastomycosis with itraconazole in 112 dogs.* J. Vet. Intern. Med, 1996. **10**(6): p. 365-371.

24. Mawby, D.I., et al., *Bioequivalence of orally administered generic, compounded, and innovator-formulated itraconazole in healthy dogs.* J. Vet. Intern. Med, 2014. **28**(1): p. 72-77.

25. Christensen, K.J., et al., *Relative bioavailability of itraconazole from an extemporaneously prepared suspension and from the marketed capsules.* American Journal of Health-System Pharmacy, 1998. **55**(3): p. 261-265.

26. Renschler, J.S., et al., *Comparison of compounded, generic and innovator-formulated itraconazole in dogs and cats.* J Am Anim Hosp Assoc, (in press).

27. Lestner, J.M., et al., *Toxicodynamics of itraconazole: implications for therapeutic drug monitoring.* Clin Infect. Dis, 2009. **49**(6): p. 928-930.

28. Mazepa, A.S., L.A. Trepanier, and D.S. Foy, *Retrospective comparison of the efficacy of fluconazole or itraconazole for the treatment of systemic blastomycosis in dogs.* J Vet. Intern Med, 2011. **25**(3): p. 440-445.

29. Chapman, S.W., et al., *Clinical Practice Guidelines for the Management of Blastomycosis: 2008 Update by the Infectious Diseases Society of America.* Clin. Infect. Dis, 2008. **460**: p. 1801-1812.

30. Gonzalez, G.M., et al., *In vitro activities of new and established triazoles against opportunistic filamentous and dimorphic fungi.* Med Mycol, 2005. **43**(3): p. 281-284.

31. Sugar, A.M. and X.P. Liu, *In vitro and in vivo activities of SCH 56592 against Blastomyces dermatitidis.* Antimicrob. Agents Chemother, 1996. **40**(5): p. 1314-1316.

32. Sugar, A.M. and X.P. Liu, *Efficacy of Voriconazole in Treatment of Murine Pulmonary Blastomycosis.* Antimicrobial Agents and Chemotherapy, 2001. **45**(2): p. 601-604.

33. Bakleh, M., et al., *Successful treatment of cerebral blastomycosis with voriconazole.* Clin Infect Dis, 2005. **40**(9): p. e69-e71.

34. Borgia, S.M., et al., *Cerebral blastomycosis: a case series incorporating voriconazole in the treatment regimen.* Med. Mycol, 2006. **44**(7): p. 659-664.

35. Legendre, A.M., et al., *Treatment of canine blastomycosis with amphotericin B and ketoconazole.* J. Am. Vet. Med. Assoc, 1984. **184**(10): p. 1249-1254.

36. Krohne, S.G., *Canine systemic fungal infections.* Vet. Clin. North Am. Small Anim Pract, 2000. **30**(5): p. 1063-1090.

37. Kerl, M.E., *Update on canine and feline fungal diseases.* Vet. Clin. North Am. Small Anim Pract, 2003. **33**(4): p. 721-747.

38. Sakai, M.R., et al., *Terbinafine pharmacokinetics after single dose oral administration in the dog.* Vet. Dermatol, 2011. **22**(6): p. 528-534.

39. Plumb, D.C., *Plumb's Veterinary Drug Handbook.* Fifth ed. 2005, Stockholm, WI: PharmaVet, Inc.

40. Crews, L.J., et al., *Radiographic findings in dogs with pulmonary blastomycosis: 125 cases (1989-2006).* J. Am. Vet. Med. Assoc, 2008. **232**(2): p. 215-221.

41. Foy, D.S., et al., *Serum and urine blastomyces antigen concentrations as markers of clinical remission in dogs treated for systemic blastomycosis.* J. Vet. Intern. Med, 2014. **28**(2): p. 305-310.

Updated: 11/2017

42. Wheat, L.J., et al., *Emergence of resistance to fluconazole as a cause of failure during treatment of histoplasmosis in patients with acquired immunodeficiency disease syndrome.* Clin. Infect. Dis, 2001. **33**(11): p. 1910-1913.

43. Renschler, J.S., et al., *Reduced susceptibility to fluconazole in a cat with histoplasmosis.* J Fel Med Surg Open Reports, (in press).

Updated: 11/2017