Blastomycosis in Mammals

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Abstract

Blastomycosis is a serious fungal disease of dogs, humans, and occasionally other mammals caused by geographically restricted, thermally dimorphic *Blastomyces* species. Blastomycosis is primarily a canine disease, with approximately ten dogs diagnosed for every human case. Dogs also develop disease more rapidly, thus becoming sentinels for possible human disease. Human and canine blastomycosis may differ according to epidemiology/epizoology, clinical features, performance and use of diagnostics, and management.

8.1 Introduction

Blastomycosis is a disease of mammals caused by the geographically restricted, thermally dimorphic fungi *Blastomyces* species. Human blastomycosis was first reported by Gilchrist in 1894 in a case of cutaneous disease first mistakenly attributed to protozoan disease (Gilchrist 1894). Four years later, Gilchrist and Stokes isolated the causative agent, a fungus they called *Blastomyces dermatitidis* (Gilchrist and Stokes 1898). The first case of canine blastomycosis was reported by Meyer in 1912 (Meyer 1912). Since then, blastomycosis has been recognized as a common and serious disease of people and animals in endemic/enzootic areas.

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8.2 Ecology and Distribution

Our understanding of the ecology of *Blastomyces* species is incomplete due to the difficulty in isolating the fungus from the environment (Restrepo et al. 2000). Blastomycosis is acquired primarily through inhalation of airborne conidia of *Blastomyces* species. These are liberated from the mold phase, which is associated with moist, acidic, sandy soils enriched with decaying organic matter and animal droppings (Restrepo et al. 2000). Aerosolization of conidia is promoted by disturbances to soil that may be caused by natural phenomena or due to human or animal activities such as excavation (Bradsher 2014b). Upon inhalation, conidia undergo a temperature-dependent transformation to yeast-like cells, capable of causing local and disseminated disease (Bradsher 2014b).

The geographic range of endemicity for canine and human blastomycosis includes North America, where it primarily occurs in states and provinces along the Great Lakes, and Ohio, Mississippi, Missouri, and St. Lawrence rivers (Bradsher 2014b). Autochthonous blastomycosis has also been reported from most of Africa (Broc and Haddad 1952; Carman et al. 1989), parts of India (Randhawa et al. 1983), and the Middle East (Kuttin et al. 1978; Kingston et al. 1980). However, the etiological agent may not always be the same species between and within geographical regions. Genetic studies of large collections of *B. dermatitidis* isolates have identified the presence of two distinct genetic populations (Meece et al. 2011; Brown et al. 2013), leading Brown et al. (2013) to conclude the presence of a cryptic species which they called *B. gilchristii*. These species are indistinguishable in morphology, physiology, and in most currently applied molecular bar codes (Dukik et al. 2017). Although clinical and demographic phenotypic differences have been suggested (Meece et al. 2013), the clinical significance of distinguishing *B. dermatitidis* from *B. gilchristii* is not yet established. Geographic differences exist, and epidemiological differences (such as outbreak potential) are surmised by the fact that isolates identified as *B. gilchristii* predominate in northern Ontario and Wisconsin, areas with the highest reported incidence of blastomycosis (Brown et al. 2013).

On the other hand, differences have long been noted in isolates from Africa compared to those implicated in disease in North America. In fact, isolates from Africa have been observed to be slightly smaller (Kaufman et al. 1983), more difficult to convert to yeast phase (Lombardi et al. 1988), and have different antigenic expression (Kaufman et al. 1983) than isolates from North America. Moreover, clinical differences in human disease have been suggested (Vandepitte and Gatti 1972). Strikingly, no cases of animal blastomycosis have been reported from Africa (Carman et al. 1989). Recently, a new species of *Blastomyces*, *B. percursus*, was described from Israel and South Africa (Dukik et al. 2017); *B. dermatitidis* and *B. gilchristii* have also been confirmed in isolates from sub-Saharan Africa (Brown et al. 2013), and so the extent that disease is attributable to each species there and elsewhere outside of North America has not yet been defined.

Most human and animal cases of blastomycosis are sporadic or endemic/enzootic (Bradsher 2014b), although occasionally outbreaks have occurred which have

informed our understanding of the ecology, attack rate, and natural history of outbreak-related *B. dermatitidis* infection (Klein et al. 1986; Armstrong et al. 1987; Baumgardner and Burdick 1991; Smith and Gauthier 2015). Outbreaks have involved both rural and urban exposures (Smith and Gauthier 2015). Recreational outdoor activities and especially water activities as well as exposure to excavation and construction are frequently implicated in human and canine blastomycosis (Baumgardner et al. 1995; Smith and Gauthier 2015). Proximity to waterways has been identified as a risk factor for sporadic blastomycosis in people (Baumgardner et al. 1992) and in dogs (Archer et al. 1987; Baumgardner et al. 1995; Arceneaux et al. 1998). For instance, case-control studies of canine blastomycosis in Louisiana and Wisconsin have identified residence within 400 m of a body of water to be a significant risk factor for the disease in dogs (Baumgardner et al. 1995; Arceneaux et al. 1998). In Louisiana, Arceneaux et al. found the odds of living near water was tenfold higher for dogs with blastomycosis than controls (Arceneaux et al. 1998).

Most people who develop blastomycosis are immunocompetent. Persons with immunodeficiencies who develop blastomycosis are reported to have more severe forms of the disease (Pappas et al. 1993), but the numbers of cases reported to date have been small. Persons treated with tumor necrosis factor (TNF)-α inhibitors may represent a growing cohort at risk of blastomycosis (Smith and Kauffman 2009). Individuals with diabetes mellitus appear to be at higher risk of blastomycosis (Lemos et al. 2002) and of requiring management in an intensive care unit (Kralt et al. 2009). Most animals with blastomycosis were previously healthy, although Davies and Troy reported 10% of infected cats in a small series had feline leukemia virus (Davies and Troy 1996).

Anderson et al. (2016) recently showed that people can become reinfected with *Blastomyces* spp.; previously, whether a second episode of blastomycosis represented reinfection and not relapse was inconclusive. These authors reported on two persons in whom blastomycosis was diagnosed and treated, only to later develop the disease again (Anderson et al. 2016). By genotyping isolates from the initial and subsequent episodes in each respective patient using 27 polymorphic microsatellite markers, they demonstrated that relapse occurred in one case (concordance between the two isolates at 27/27 loci) and reinfection occurred in the other (concordance at just 15/27 loci) (Anderson et al. 2016).

Blastomycosis is most common in dogs residing in or visiting enzootic areas (Baumgardner et al. 1995). The incidence of blastomycosis in dogs is eight to ten times that of humans (Baumgardner et al. 1995; Herrmann et al. 2011), presumably related to time spent outdoors, proximity to soil, and activities, such as digging, that may result in soil disturbances and conidial exposure. Most affected dogs are immunocompetent (Sykes and Merkel 2014). The incidence appears to be highest in young, large sporting dogs and hounds, including coonhounds, pointers, Weimaraners (Rudmann et al. 1992), golden retrievers, Labrador retrievers, and Doberman pinschers (Arceneaux et al. 1998). Sporting dogs may be more likely to be exposed due to selective use in hunting (Rudmann et al. 1992). Some but not all studies have found the disease is more common in intact males (Rudmann et al. 1992; Arceneaux et al. 1998). Blastomycosis has also been described in wild canids.

For example, Nemeth et al. (2016) reviewed the database of wild animals sent to the Canadian Wildlife Health Cooperative from 1991 to 2014. Blastomycosis was diagnosed in 14 wild canids, including 11 of 149 (7.6%) red foxes (*Vulpes vulpes*) and 3 of 185 (1.6%) gray wolves (*Canis lupus*).

Feline blastomycosis is encountered 28–100 times less frequently than canine blastomycosis (Legendre 2012; Davies et al. 2013) and has been reported even among indoor-only cats (Blondin et al. 2007; Houseright et al. 2015). Blastomycosis has also been reported in captive wild felids, including lions (*Panthera leo*), Siberian tiger (*Panthera tigris*), cheetah (*Acinonyx jubatus*), and snow leopard (*Panthera uncia*) (Storms et al. 2003).

Blastomycosis has been reported in a range of domestic and captive animals including kinkajou (*Potos flavus*) (Harris et al. 2011), ferret (Nemeth et al. 2016), red ruffed lemur (*Varecia rubra*) (Rosser et al. 2016), and rhesus monkey (*Macaca mulatta*) (Wilkinson et al. 1999). Marine mammals reported with blastomycosis include sea lion (*Zalophus californianus*) (Zwick et al. 2000) and Atlantic bottlenose dolphin (*Tursiops truncatus*) (Cates et al. 1986). Wild, free-roaming animals (other than canids) that have developed blastomycosis include an American black bear (*Ursus americanus*) (Dykstra et al. 2012).

Among livestock, some cases of blastomycosis have been described in horses living in endemic areas (Wilson et al. 2006; Stewart and Cuming 2015). Blastomycosis has also been reported in an alpaca (Imai et al. 2014).

Animals do not play a role in transmission of *Blastomyces* spp., aside from rare cases of inoculation blastomycosis reported due to a bite (Gray and Baddour 2002; Harris et al. 2011) or percutaneous injury during autopsy of an infected animal (Gray and Baddour 2002). The concurrent or sequential infection of a person and his or her dog is common (Baumgardner et al. 1992) and likely due to a common exposure (Sarosi et al. 1979; Armstrong et al. 1987; Baumgardner et al. 1992). Even so, dogs appear to develop disease earlier (Sarosi et al. 1979). In experimental murine blastomycosis, larger inocula lead to earlier disease (Williams and Moser 1987), and it has been inferred that the shorter prepatent period in dogs reflects increased inocula from being closer to the ground (Legendre 2012). In any case, a history of blastomycosis in one's dog should raise suspicion for the disease in a person with a compatible syndrome (Sarosi et al. 1979).

8.3 Clinical Signs

8.3.1 In Humans

Clinical signs encountered in persons with blastomycosis will depend on the organ systems involved, but clinicians should be aware of the protean nature of the disease (Bradsher 2014a). Pulmonary infection can be subclinical or can result in an acute or chronic pneumonia (Sarosi et al. 1974). Acute pulmonary blastomycosis can present with fevers, sepsis, and hypoxia, with clinical examination and radiographs consistent with focal airspace disease (Sarosi et al. 1974; Lemos et al. 2002). In other

words, the disease can be indistinguishable from community-acquired (bacterial) pneumonia (Lemos et al. 2002; Bradsher 2014a; Alpern et al. 2016), and it is common for patients to receive multiple courses of antibiotics before the correct diagnosis is established (Alpern et al. 2016). Acute respiratory distress syndrome (ARDS) occurs in 8–15% of cases of symptomatic blastomycosis (Meyer et al. 1993; Vasquez et al. 1998; Lemos et al. 2001; Azar et al. 2015) and is associated with mortality rates of at least 40% (Meyer et al. 1993; Vasquez et al. 1998; Lemos et al. 2001; Azar et al. 2015; Schwartz et al. 2016). Patients with chronic pulmonary involvement may present with chronic dyspnea, cough and hemoptysis, often accompanied by constitutional symptoms. The radiographic appearance is like acute disease but with a third of patients having mass-like lesions (Patel et al. 1999). Not surprisingly, chronic blastomycosis is frequently mistaken for pulmonary malignancies or tuberculosis (Lemos et al. 2002; Bradsher 2014a).

Extrapulmonary disease occurs in ~25–40% of cases (Baumgardner et al. 1992; Lemos et al. 2002). The most common extrapulmonary site of blastomycosis is the skin, usually manifesting as ulcerative or verrucous lesions (Bradsher 2014b). Osteoarticular disease is the next most common form (Kralt et al. 2009). In a series of persons with osteoarticular blastomycosis, disease of the axial skeleton was most common, followed by long bones of the lower limb (Oppenheimer et al. 2007). Vertebral disease may rarely present with spinal cord compression syndromes (Saccente et al. 1998). As with bacterial osteomyelitis, disease of long bones most often localizes to the metaphyses (Oppenheimer et al. 2007). Arthritis is less common than osteomyelitis. It is generally monoarticular and mimics pyogenic bacterial septic arthritis (Oppenheimer et al. 2007). In males, the third most common site of extrapulmonary blastomycosis is the prostate and genitourinary system (Saccente and Woods 2010). Central nervous system disease is less common, occurring in approximately 5% of cases with extrapulmonary dissemination (Bariola et al. 2010). Patients may present with meningitis, encephalitis, or signs of a space-occupying lesion (Bush et al. 2013). Cerebrospinal fluid pleocytosis occurs and can have either lymphocytic or neutrophilic predominance (Bariola et al. 2010). Ocular involvement has been reported but it is uncommon (Lopez et al. 1994).

8.3.2 In Animals

Canine disease is more commonly disseminated beyond the lungs at the time of diagnosis (Legendre 2012). Chest radiographs may show focal airspace disease or a "snowstorm" pattern of reticulonodular disease (Crews et al. 2008b) (Fig. 8.1). Ocular disease is much more common in dogs than in humans, occurring in up to half of all cases (Bloom et al. 1996; Arceneaux et al. 1998). Among these, bilateral disease occurs in half (Bloom et al. 1996). Ocular disease can be localized to anterior segments, posterior segments, or, most commonly, both (i.e., endophthalmitis) (Bloom et al. 1996). Like in human disease, cutaneous involvement is common in canine blastomycosis, occurring in approximately half of infected dogs (Arceneaux et al. 1998). An example of a dog with bilateral ocular and cutaneous disease is shown in Fig. 8.2. Other common sites of extrapulmonary disease include lymphatic

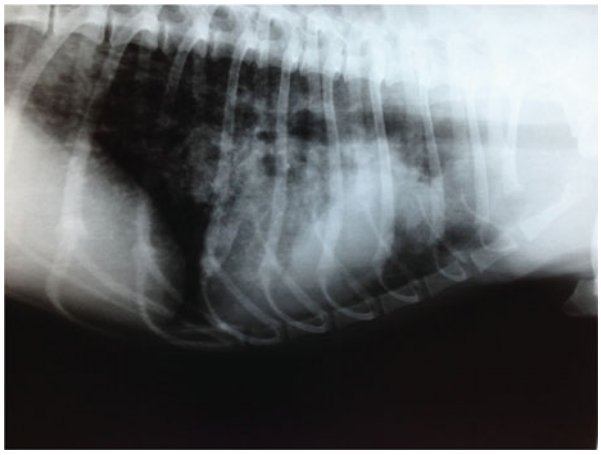

Fig. 8.1 Lateral thoracic X-ray of a dog with pulmonary blastomycosis demonstrating diffuse reticulonodular disease (Courtesy of Dr. Peter Schwartz, DVM, Assiniboine Animal Hospital, Winnipeg, Manitoba)

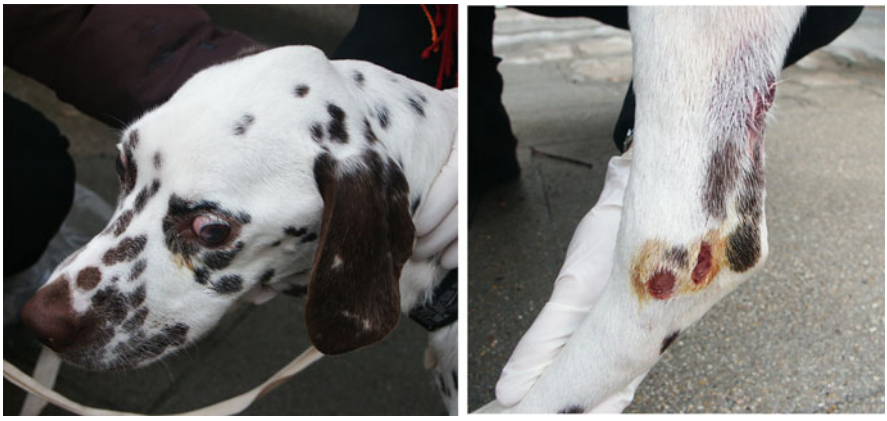

Fig. 8.2 Ocular involvement and ulcerative cutaneous lesions in a dog infected in Quebec, Canada (Courtesy of Dr. René Chermette, DVM, dipl. EVPC, Parasitology-Mycology, EnvA, Maisons-Alfort, France)

and osteoarticular structures (Arceneaux et al. 1998). Central nervous system disease is less common, occurring in 6% of dogs in a series (Arceneaux et al. 1998). Cardiovascular blastomycosis has been reported in nine dogs (Langlois et al. 2013; Schmiedt et al. 2015); it is extraordinarily uncommon in people.

Like the disease in humans, clinical signs commonly encountered in canine blastomycosis are nonspecific. In decreasing frequency of occurrence reported by a large study, these include fever, lymphadenopathy, harsh lung sounds, cutaneous lesions, chorioretinitis, anterior uveitis, cough, emaciation, and retinal detachment (Arceneaux et al. 1998).

Cats are often diagnosed only upon autopsy and with widespread disease (Davies and Troy 1996). In one series, clinical signs of respiratory, neurologic, and cutaneous disease were present in 59, 41, and 18% of cats, respectively (Davies and Troy 1996).

In horses, clinical signs generally include pneumonia and with reports of respiratory infection or cutaneous and subcutaneous lesions (Wilson et al. 2006; Stewart and Cuming 2015).

8.4 Diagnosis

8.4.1 Culture

Culture of *Blastomyces* spp. from a clinical specimen is the gold standard diagnostic for blastomycosis. *Blastomyces dermatitidis/gilchristii* grow on general fungal media such as Sabouraud's dextrose agar or potato dextrose agar, incubated at 25–30 °C (Bradsher 2014b). Growth of white to buff colonies usually appears within 10–14 days but may require up to 6 weeks incubation (Bradsher 2014b). Microscopically, *B. dermatitidis/gilchristii* characteristically have conidiophores of varying lengths that run perpendicular to hyphae and terminate with single conidia that resemble "lollipops" (Bradsher 2014b). In contradistinction, the conidia of *B. percursus* appear in clusters at the end of conidiophores (Dukik et al. 2017). Traditionally, conversion of the mold to a yeast phase at 37°C was performed for confirmation of the identification, but this is rarely done today (Saccente and Woods 2010). Most microbiology laboratories confirm identification of *B. dermatitidis/gilchristii* with a DNA probe (AccuProbe; GenProbe Inc., San Diego, CA), but cross-reactions can occur, including with other dimorphic fungi (Saccente and Woods 2010).

The diagnostic yield of culture is surmised from a retrospective review of cases of human pulmonary blastomycosis (Martynowicz and Prakash 2002). *Blastomyces dermatitidis* was isolated from the first sputum sample in 75% of cases, which increased to 81% after a mean of 2.3 samples (Martynowicz and Prakash 2002); the diagnostic yield of bronchial washings was even higher. Nonetheless, the true sensitivities are likely lower since only diagnosed cases (i.e., those with at least one positive test) are included in this type of study.

Despite favorable operating characteristics, culture has important limitations. Slow turnaround times limit reliance on this test for management decision (Bradsher 2014b). In addition, occupational exposure of laboratory workers to highly infectious mycelia is a real concern (Denton et al. 1967). While culture is a standard investigation of humans suspected of blastomycosis (Bradsher 2014b), it is rarely used in veterinary practice (Legendre 2012; Sykes and Merkel 2014). In a survey of small-animal veterinary practices in Wisconsin, 80% of respondents reported that they never used culture for the diagnosis of blastomycosis (Anderson et al. 2014). Similarly, large retrospective case series of dogs with pulmonary blastomycosis from

Louisiana (Arceneaux et al. 1998) and Minnesota (Crews et al. 2008a) found that fungal cultures were sent for only 17 of 115 dogs (12%) and 6 of 125 dogs (5%), respectively.

8.4.2 Microscopy, Cytology, and Histopathology

Microscopic examination of clinical specimens using wet smears, cytopathology, and histopathology are cornerstone diagnostic tools for blastomycosis in humans and animals (Saccente and Woods 2010). The classic appearance is of large (8–15 μm), round, multinucleate yeast-like cells with thick, double refractile walls that may have a single bud with broad bases (Guarner and Brandt 2011) (Fig. 8.3). Small yeast forms are also known to occur and may be difficult to distinguish histologically from the yeast-like cells of other dimorphic fungi (Guarner and Brandt 2011).

The most expedient test is a wet preparation using potassium hydroxide (KOH) solution, with or without staining with calcofluor white or lactophenol blue (Saccente and Woods 2010). The sensitivity of this test is poor: a study found the yield of sputum for KOH preparation in human pulmonary blastomycosis to be 25% for a single specimen (Martynowicz and Prakash 2002). Nonetheless, examination of multiple specimens often leads to the correct diagnosis. For example, in a series of 100 persons with pulmonary blastomycosis, KOH preparation of respiratory samples (invasively and noninvasively collected) led to the immediate diagnosis in 66% of cases (Patel et al. 1999).

Visualization of *Blastomyces* yeast-like cells is enhanced with cytologic and histopathologic preparations. Cytology stains like Papanicolaou and Wright stains can be used to identify the organism in respiratory specimens (usually sputum and bronchoalveolar lavage in humans and transtracheal lavage or transthoracic fine-needle aspirates in dogs), lymph node aspirates, and impression smears or discharge from cutaneous lesions (Martynowicz and Prakash 2002). In tissue, the yeast-like

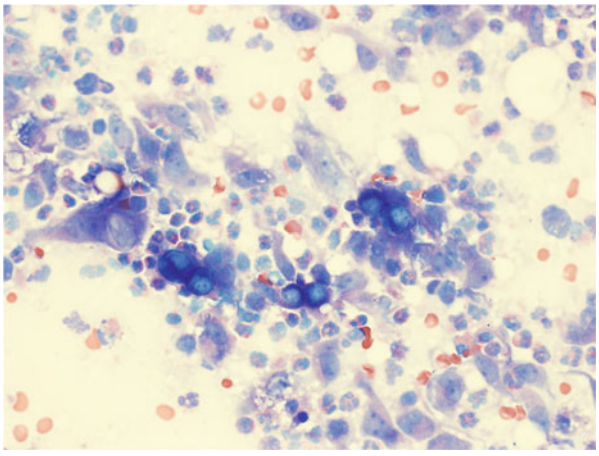

Fig. 8.3 Modified Wright's stain of impression smears collected from a hilar mass during necropsy of a 4-year-old mixed breed male dog, viewed at 60×. Note the large, round yeast-like cells with thick, double refractile walls and broad-based budding (Courtesy of Dr. Angelica Galezowski, DVM, MVetSc, DACVP, Faculty of Veterinary Medicine, University of Calgary, Canada)

cells may first be visualized with hematoxylin and eosin, although sensitivity and specificity are greatly improved by use of fungal stains like periodic acid-Schiff (PAS) or Grocott-Gomori methenamine-silver nitrate (GMS) (Saccente and Woods 2010). The host response is characterized by mixed inflammatory reaction, predominated first by neutrophils and eventually by noncaseating granulomas (Saccente and Woods 2010).

Cytologic and histopathologic examinations are frequently used in medical and veterinary practice. These tests perform well in diagnosing blastomycosis compared to culture (Patel et al. 2010), and with faster turnaround time. Cytologic examination led to the diagnosis in 71% of cases of canine disease from Louisiana, and histopathologic examination diagnosed an additional 9% (Arceneaux et al. 1998).

8.4.3 Antigen and Antibody Detection

An antigen enzyme immunoassay (EIA) for *B. dermatitidis* galactomannan is commercially available for the diagnosis of blastomycosis in humans and animals (MiraVista Diagnostics, Indianapolis, IN, USA). In a study of 89 people with blastomycosis proven by histopathology or culture, the quantitative detection of antigenuria had a sensitivity of 90% (Connolly et al. 2012). Sensitivity was higher in patients with pulmonary disease (with or without extrapulmonary dissemination) compared to isolated extrapulmonary disease. The specificity was 99% in controls without fungal infections, but cross-reactivity occurred in 96% of controls with histoplasmosis (Connolly et al. 2012). However, another study from Marshfield, Wisconsin, evaluated antigen tests in persons with blastomycosis over a course of 10 years and found the sensitivity of antigenuria to be 76% (Frost and Novicki 2015).

The use of the antigen EIA has also been studied for the diagnosis of canine blastomycosis (Spector et al. 2008). In a study of 46 dogs with blastomycosis, the sensitivities of antigen detection in urine and blood were 93 and 87%, respectively; false-positive results occurred in 2% of controls (Spector et al. 2008). Antigen detection is commonly used by veterinarians for the diagnosis of blastomycosis: Wisconsin veterinarians reported relying on this test more than any other to diagnose the disease (Anderson et al. 2014).

There is not currently a role for serological testing for *Blastomyces*-specific antibodies due to poor sensitivity (Smith and Gauthier 2015). An investigational EIA for antibodies against *Blastomyces adhesion-1* (BAD-1) was reported to have sensitivities and specificities of 88% and 95–99%, respectively (Richer et al. 2014). Confirmatory studies are warranted.

8.4.4 Nucleic Acid Detection

Nucleic acid detection is not yet a part of routine diagnostics for blastomycosis, and the role for this tool in clinical laboratories has not been defined. Theoretically,

nucleic acid detection could reduce turnaround time compared with culture while obviating laboratory-associated hazard. It could also improve sensitivity compared to cytology or histopathology (Babady et al. 2011).

8.5 Treatment

8.5.1 In Humans

Clinical guidelines have been published for the management of human blastomycosis by the Infectious Diseases Society of America (IDSA) updated in 2008 (Chapman et al. 2008) and of human fungal pneumonias including blastomycosis by the American Thoracic Society (ATS) in 2011 (Limper et al. 2011). In humans, the recommended treatment for mild to moderate pulmonary or extrapulmonary blastomycosis (other than osteoarticular or CNS disease) is itraconazole 200 mg once or twice daily for 6–12 months; treatment of osteoarticular disease should be for 12 months. Moderately severe to severe pulmonary or extrapulmonary disease should be treated preferably with lipid formulation amphotericin B (3–5 mg/kg) or alternatively amphotericin deoxycholate (0.7–1.0 mg/kg) until clinical improvement, followed by de-escalation to a triazole for 6–12 months (Chapman et al. 2008). Central nervous system disease should be treated with a lipid formulation of amphotericin B (3–5 mg/kg) (for 4–6 weeks or until clinical improvement) followed by step-down to a triazole for 12 months (Chapman et al. 2008; Limper et al. 2011). Recent interest in the use of voriconazole for CNS blastomycosis has been driven by improved CSF and brain tissue penetration (Ta et al. 2009); accumulating published clinical experience provides anecdotal support for its use for this indication (Bakleh et al. 2005; Borgia et al. 2006; Bariola et al. 2010; Bush et al. 2013). Therapeutic drug monitoring is recommended for itraconazole and possibly voriconazole to ensure adequate levels are maintained (Chapman et al. 2008; Limper et al. 2011).

Acute respiratory distress syndrome due to blastomycosis occurs in 8–15% of persons with symptomatic blastomycosis (Meyer et al. 1993; Vasquez et al. 1998; Lemos et al. 2001; Azar et al. 2015), but it portends a grave prognosis with case fatality rates of at least 40% (Meyer et al. 1993; Vasquez et al. 1998; Lemos et al. 2001; Azar et al. 2015; Schwartz et al. 2016). Consequently, the roles of adjunctive, rescue therapies for ARDS caused by blastomycosis are an area of great interest, but little data. Some investigators have suggested a role for adjunctive corticosteroids considering the inflammatory cascade involved in the pathogenesis ARDS (Hough 2014). Anecdotal support has come from case reports and series (Lahm et al. 2008; Plamondon et al. 2010; Azar et al. 2015; Schwartz et al. 2016), although sufficiently powered prospective or retrospective studies are unlikely to be forthcoming (Schwartz et al. 2016). Extracorporeal membrane oxygenation (ECMO) is another promising adjunctive rescue therapy for ARDS due to blastomycosis (Dalton et al. 1999; Resch et al. 2009; Bednarczyk et al. 2015; Schwartz et al. 2016) and should be considered in centers where the capacity exists.

8.5.2 In Animals

Guidelines for the management of veterinary blastomycosis are currently available for cats as part of guidelines for the prevention and management of rare systemic mycoses published in 2013 by the European Advisory Board on Cat Diseases (Lloret et al. 2013). These suggest that itraconazole (10 mg/kg once daily) should be the preferred therapy for most cases, usually given for >3 months and that amphotericin B (0.25 mg/kg every 48 h to a total dose of 4–16 mg/kg) or fluconazole (2.5–10 mg/kg twice daily) are preferred for severe cases or those with CNS involvement (Lloret et al. 2013).

No guidelines currently exist for the diagnosis or management of canine blastomycosis. Randomized controlled trials do not exist to guide management decisions, but several prospective and retrospective studies of canine blastomycosis are instructive.

Legendre et al. prospectively treated 112 dogs with blastomycosis with itraconazole at doses of 5 or 10 mg/kg daily for 60 days and compared outcomes to historical controls treated with amphotericin B (at a cumulative dose of 8–9 mg/kg) in a study setting (Legendre et al. 1996). No differences were observed in outcomes between dogs treated with either of the itraconazole doses and amphotericin B: cure was achieved in 54–57% of all dogs, with disease recurring in 20–21% and death in 23–26% (Legendre et al. 1996). These observations are for the most part congruent with other reports (Arceneaux et al. 1998).

Fluconazole has been suggested by some authors as a reasonable (and cheaper) alternative to itraconazole in the treatment of canine blastomycosis (Mazepa et al. 2011). In vitro susceptibility testing on a small number of human *B. dermatitidis* isolates suggests fluconazole has less activity than itraconazole (Li et al. 2000; González et al. 2005). While no trial has compared these head-to-head, small single-arm trials in humans are informative. In a prospective, open-label trial of 48 persons with non-life-threatening, non-CNS blastomycosis, itraconazole (at a dose of 200–400 mg daily, for a mean of 6 months) resulted in 90% success (response with no relapse by 1 year follow-up) (Dismukes et al. 1992). In contrast, a trial of fluconazole at a dose of 400–800 mg daily (for a mean of 8.9 months) in 39 patients with non-life-threatening, non-CNS blastomycosis resulted in successful outcome in 87% (Pappas et al. 1997). Prospective trials are lacking in dogs, but Mazepa et al. (2011) retrospectively compared 36 and 31 dogs treated with fluconazole and itraconazole, respectively. The study was not powered to detect a difference in outcomes, but dogs treated with fluconazole required longer courses of therapy than those treated with itraconazole (median 183 vs 138 days, respectively). Nonetheless, costs for fluconazole were much less than for itraconazole, with median costs of $1223 and $3717, respectively (Mazepa et al. 2011). Taken together, this data suggests that fluconazole at higher doses and for longer courses may be reasonable alternatives to itraconazole for blastomycosis in animals.

For CNS and ocular disease, fluconazole achieves better penetration than itraconazole into these structures (Perfect et al. 1986; Savani et al. 1987), although both drugs were effective in animal models of non-blastomycotic fungal meningitis (Perfect et al. 1986) and endophthalmitis (Savani et al. 1987).

Adjunctive systemic corticosteroids have been suggested for ocular blastomycosis in dogs. In a retrospective study of 12 dogs with ocular involvement in 19 eyes, systemic corticosteroids were administered in addition to triazoles (Finn et al. 2007). The success rate in this series was 74% across all eyes involved, including 67% of eyes with endophthalmitis, the most common complication that generally carries a poor prognosis (Finn et al. 2007). For comparison, another retrospective study of itraconazole monotherapy for ocular blastomycosis reported favorable outcomes in just 13% of eyes with endophthalmitis (Brooks et al. 1992). In another study, amphotericin B plus ketoconazole resulted in favorable outcomes for 20% of eyes with endophthalmitis, although this improved to 43% if only non-severely affected eyes were considered (Bloom et al. 1996).

8.5.3 Monitoring Response to Therapy

Radiographic worsening is commonly observed soon after initiation of effective antifungal therapy for canine blastomycosis, occurring in almost a quarter of dogs (Crews et al. 2008b). However, this does not portend a worse outcome (Crews et al. 2008b) and—in the absence of other signs of clinical failure—should not alter management. For this reason, follow-up chest radiography is recommended no sooner than 4–6 weeks after therapy initiation in stable patients (Crews et al. 2008b).

Quantitative *Blastomyces* antigen detection by EIA has been evaluated for monitoring of remission in dogs during and after treatment for blastomycosis (Foy et al. 2014). Foy and colleagues prospectively studied 27 dogs with blastomycosis who were monitored clinically, radiographically, and with detection and quantification of *Blastomyces* antigen in urine and serum following discontinuation of antifungal therapy; among these, 12 dogs were also monitored from time of therapy initiation (Foy et al. 2014). The investigators found that urine antigen levels dropped dramatically within several months of initiation of antifungal therapy. Seven of 27 dogs (26%) relapsed at a median of 4 months following treatment discontinuation. Five of these had detectable antigenuria at the time of clinical relapse, but only one had rising levels of antigenuria preceding clinically detectable relapse. Moreover, persistence of positive urinary antigen at treatment discontinuation did not predict relapse: only two of seven dogs that relapsed had detectable antigenuria at that treatment discontinuation. On the other hand, five of eight of dogs with antigenuria at the end of therapy did not relapse (Foy et al. 2014). In summary, monitoring urine antigen levels during and/or after discontinuation of therapy is unlikely to add significant value to serial clinical and radiographic evaluations for most dogs with blastomycosis.

8.6 Prevention

A commercially available vaccine against blastomycosis does not currently exist, although the science is advancing. Wüthrich et al. (2000, 2011) developed a recombinant, live-attenuated vaccine using an avirulent, genetically engineered

strain of *B. dermatitidis* lacking *Blastomyces* adhesin-1 (*BAD-1*, previously called *WI-1*), an essential virulence factor. This vaccine has been demonstrated to be protective against experimental blastomycosis in mice (Wüthrich et al. 2000), although efficacy in dogs has not yet been established. Experimental infection and a field study of beagles and foxhounds, respectively, demonstrated acceptable safety and immunogenicity (Wüthrich et al. 2011). Adverse reactions included fever, lymphadenopathy, and draining cutaneous lesions at the site of inoculation (Wüthrich et al. 2011); these may limit use in all but highly enzootic regions.

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