Journal of Veterinary Internal Medicine
Open Access

Standard Article

J Vet Intern Med 2017;31:1724–1729

Opportunistic Invasive Cutaneous Fungal Infections Associated with Administration of Cyclosporine to Dogs with Immune-mediated Disease

B.B. McAtee, K.J. Cummings, A.K. Cook, J.A. Lidbury, J.C. Heseltine, and M.D. Willard

Background: Opportunistic invasive fungal infections (OIFIs) occur in dogs administered immunosuppressive medications. However, the epidemiology of OIFIs among dogs undergoing immunosuppressive treatment is poorly understood. The aims of this study were to (1) estimate the incidence of OIFIs among dogs diagnosed with certain immune-mediated diseases and treated with immunosuppressive drugs, and (2) determine if administration of particular drug(s) was a risk factor for OIFIs.

Hypothesis: Dogs receiving cyclosporine treatment (alone or as part of a multidrug protocol) are at higher risk of developing OIFIs.

Animals: One hundred and thirteen client-owned dogs diagnosed with select immune-mediated diseases: 42 with IMHA, 29 with ITP, 34 with IMPA, and 8 with Evans syndrome.

Methods: Retrospective cohort study. Medical records of dogs presenting to the Texas A&M University, Veterinary Medical Teaching Hospital between January 2008 and December 2015, and treated for 1 or more of IMHA, IMPA, ITP, or Evans syndrome were retrospectively reviewed. Dogs that did not develop an OIFI were excluded if they died, were euthanized, or were lost to follow-up within 120 days of initiation of immunosuppressive treatment.

Results: Fifteen dogs of 113 (13%) were diagnosed with an OIFI based on 1 or more of cytology, culture, or histopathology. The odds of developing an OIFI were greater among dogs that were treated with cyclosporine (OR = 7.1, $P = 0.017$; 95% CI, 1.5–34.4) and among male dogs (OR = 5.1, $P = 0.018$; 95% CI, 1.4–17.9).

Conclusions and Clinical Importance: OIFIs were significantly more likely in male dogs and those receiving cyclosporine. It is important to consider OIFIs as a potential complication of immunosuppressive treatment, particularly cyclosporine.

Key words: Fungal; Infectious disease.

Immune-mediated diseases in dogs, including immune-mediated thrombocytopenia (ITP), immune-mediated hemolytic anemia (IMHA), and immune-mediated polyarthritis (IMPA), are commonly treated with glucocorticoids and adjunctive immunosuppressive medications including cyclosporine, leflunomide, and mycophenolate. Adverse effects of these drugs can include opportunistic infections, including opportunistic invasive fungal infections (OIFIs).[1] A human international consensus defining OIFIs in human patients with cancer and stem cell transplants stated a general agreement among committee members that the highest level of certainty in diagnosing an invasive fungal infection is defined by the presence of fungi in tissue documented by biopsy or needle aspirate.[2] Invasive infections, defined as fungal elements penetrating tissues, should be differentiated from noninvasive infections, such as sinonasal aspergillosis. The majority of OIFIs in people receiving immunosuppressive treatment after organ transplantation are caused by infection with *Candida* spp. or *Aspergillus* spp. with other opportunistic fungi accounting for 1–2% of fungal infections.[3] The overall incidence of phaeohyphomycosis in 1 study of human solid organ transplant recipients between 1988 and 2009 is 0.7%.[4] Factors predisposing people to OIFIs include immunosuppressive drug treatment, infection with human immunodeficiency virus (HIV), diabetes mellitus, neutropenia secondary to chemotherapy, autoimmune diseases, and critical illness with ventilator support.[5,6]

Most cases of OIFIs reported in the veterinary literature involve immunocompromised and immunosuppressed animals. Disseminated OIFIs occur in dogs without evidence of immunosuppression, such as a Labrador retriever with systemic *Bipolaris* spp. infection[7]; however, this appears to be uncommon. Infections with nonpigmented filamentous ascomycetes (aspergillosis and hyalohyphomycoses) and pigmented fungi (phaeohyphomycosis) are typical OIFIs in dogs.[1,8–36] These organisms are ubiquitous soil saprophytes. The primary mode of infection for invasive aspergillosis and hyalohyphomycosis is thought to be via inhalation; however, cutaneous contamination or inhalation can be the mode of infection for phaeohyphomycoses.[37]

Abbreviations:

OIFI	opportunistic invasive fungal infection
IMHA	immune-mediated hemolytic anemia
ITP	immune-mediated thrombocytopenia
IMPA	immune-mediated polyarthritis
CI	confidence interval
OR	odds ratio

From the Texas A&M University, College Station, TX (McAtee, Cummings, Cook, Lidbury, Heseltine, Willard).

Work was performed at Texas A&M University, Veterinary Medical Teaching Hospital.

Corresponding author: B.B. McAtee, Texas A&M University, 4474 TAMU College Station, TX 77843; e-mail: bmcatee@cvm.tamu.edu

Submitted January 30, 2017; Revised June 29, 2017; Accepted August 3, 2017.

DOI: 10.1111/jvim.14824

There have been individual case reports[7–34,36] and 1 case series of 8 dogs[1] describing OIFIs in immunosuppressed dogs. The case series of 8 dogs with OIFIs that had received cyclosporine and prednisone treatment emphasized the severe and occasionally fatal consequences of these infections.[1] The goal of our study was to estimate the incidence of OIFIs among dogs at the Texas A&M University, Veterinary Medical Teaching Hospital that were diagnosed with select immune-mediated diseases and subsequently treated with immunosuppressive drugs. A secondary goal was to determine if particular drug(s) were associated with a greater risk for development of an OIFI. Our hypothesis was that dogs receiving cyclosporine treatment, either alone or as part of a multidrug protocol, were at higher risk of developing OIFIs compared to dogs given other immunosuppressive agents.

Materials and Methods

The electronic medical records database at Texas A&M University, Veterinary Medical Teaching Hospital between January 2008 and December 2015, was searched for dogs diagnosed with selected immune-mediated conditions: IMHA, ITP, Evans syndrome, and IMPA. Inclusion criteria were as follows: (1) diagnosis of immune-mediated hemolytic anemia (IMHA), immune-mediated thrombocytopenia (ITP), immune-mediated polyarthritis (IMPA), or Evans syndrome; (2) immunosuppressive treatment with 1 or more of cyclosporine, azathioprine, chlorambucil, mycophenolate, or leflunomide with or without glucocorticoids; and (3) a minimum 120-day follow-up period after initiation of immunosuppressive treatment except for dogs that developed an OIFI before 120 days. Dogs were excluded if they died, were euthanized, or were lost to follow-up within 120 days of initiation of immunosuppressive treatment, with the exception noted above. This was done to ensure that the dogs were followed up for a sufficient duration of time to allow development of an OIFI.

Data Collection

Data collected from medical records of dogs meeting inclusion criteria were: sex, age, breed, body weight, type of immune-mediated disease, the presence/absence of diabetes mellitus, type and dose of immunosuppressive drug(s) administered, the presence of an OIFI and etiologic agent (if identified), time to development of an OIFI, diagnostic method for the OIFI, and results of fungal culture, fungal identification, cytology, or histopathology (biopsy or necropsy). Protocols for treating the OIFIs and outcomes were recorded, if available.

Statistical Analysis

Data were imported into a commercial statistical software program (SAS, version 9.4[a]) for variable coding and analysis. Age in years was used to create a dichotomous variable for age group (<3 years of age versus ≥3 years). After descriptive analysis of all variables, chi-squared testing was used to determine whether each variable (including signalment, disease, and the immunosuppressive drugs administered) was independently associated with OIFI status. A multivariable logistic regression model was used to identify risk factors for OIFIs. Initial variable selection was based on the bivariable analysis (Table 1) screening ($P < 0.25$), and a backward elimination approach was used to establish a final multivariable model (Table 2). For all analyses, P-values <0.05 were considered significant.

Results

Four hundred and fifty-five dogs were identified in the initial electronic record search. Of these, 342 were excluded because of loss to follow-up or death/euthanasia within 120 days. One hundred and thirteen dogs met our inclusion criteria: 42 with IMHA, 29 with ITP, 34 with IMPA, and 8 with Evans syndrome.

Dogs with the specified immune-mediated diseases ranged from 1 to 12 years of age at the time of diagnosis (median of 6.0 years). Forty-one breeds were recorded, including 13 mixed breed dogs, 12 Labrador retrievers, 7 dachshunds, 6 Chihuahuas, 5 beagles, and 5 shih-tzus. All other breeds had fewer than 5 dogs in each group. There were 51 males (45%; 12 sexually intact and 39 neutered) and 62 females (55%; 4 sexually intact and 58 spayed). The median body weight was 12.3 kg (range 1.8–56 kg).

Three dogs had diabetes mellitus, which was diagnosed after starting immunosuppressive medications. One of the 3 dogs was diagnosed with an OIFI 36 days after diagnosis of diabetes mellitus. An association between diabetes mellitus and the development of an OIFI was not detected.

An OIFI was diagnosed in 15 of 113 (13%) dogs based on 1 or more of cytology of skin lesions, histopathology of skin lesions or disseminated lesions, or fungal cultures of skin lesions. Skin lesions were cultured in 9 of 15 (60%) dogs, skin cytology was performed in 9 of 15 (60%) dogs, skin biopsy was

Table 1. Results of bivariable analysis of potential risk factors for OIFI occurrence among dogs with immune-mediated diseases.

Variable	Diagnosed with OIFI, % (n)	Not Diagnosed with OIFI, % (n)	*P*
Sex			
Female	6 (4)	94 (58)	0.018
Male	22 (11)	78 (40)	
Age group			
<3 years of age	19 (3)	81 (13)	0.44
≥3 years of age	12 (12)	88 (85)	
Azathioprine			
Yes	11 (4)	89 (34)	0.54
No	15 (11)	85 (64)	
Cyclosporine			
Yes	20 (13)	80 (53)	0.017
No	4 (2)	96 (45)	
Leflunomide			
Yes	0 (0)	100 (3)	1.0
No	14 (15)	86 (95)	
Mycophenolate			
Yes	19 (5)	81 (21)	0.33
No	11 (10)	89 (77)	
Prednisone			
Yes	13 (15)	87 (97)	1.0
No	0 (0)	100 (1)	

Table 2. Association between OIFI occurrence and cyclosporine administration/patient sex among dogs with immune-mediated diseases, as estimated by a logistic regression model.

Variable	Odds Ratio	95% Confidence Interval	*P*
Cyclosporine			
Yes	7.1	1.5, 34.4	0.015
No	1.0	–	–
Sex			
Male	5.1	1.4, 17.9	0.011
Female	1.0	–	–

performed in 4 of 15 (27%) dogs, and renal capsule biopsy in 1 of 15 (7%) dogs. Median time to diagnosis of an OIFI was 43 days (range: 21–390 days) after beginning immunosuppressive treatment.

Only 1 of 15 dogs (7%) had a solitary lesion, which was located on a distal extremity. The remainder of dogs (14 of 15, 93%) had multiple lesions. One of 15 (7%) of the dogs was diagnosed with disseminated fungal disease with the presence of a renal capsular granuloma. This dog also had visible multifocal skin/subcutaneous lesions. The remaining 14 of 15 (93%) dogs were diagnosed with OIFIs based on grossly visible lesions confined to the skin/subcutaneous tissues and were commonly found on the distal extremities (14 of 15 dogs). Lesions affected 1 limb in 4 of 15 (27%) dogs, more than 1 limb in 5 of 15 (33%) dogs, and were multifocal cutaneous lesions (truncal and multiple extremities) in 5 of 15 (33%) dogs. The gross appearance of cutaneous lesions varied from obvious ulcerative lesions (5 of 15, 33% of dogs) to subtle, small, nonulcerated nodules often initially assessed as "ant bites" due to their wheal-like appearance by the dogs' owners (10 of 15, 67% of dogs).

Of the OIFI dogs, 10 of 15 (67%) were diagnosed with phaeohyphomycosis with infection by *Paraconiothyrium* spp., *Bipolaris* spp., *Cladosporium* spp., *Alternaria* spp., or *Curvularia* spp., 3 of 15 (20%) were diagnosed with unclassified mold infections, 1 of 15 (7%) was diagnosed with hyalohyphomycosis (*Chrysosporum* spp.), and 1 of 15 (7%) had both phaeohyphomycosis (*Curvularia* spp.) and hyalohyphomycosis (*Scedosporium* spp.).

A total of 66 of 113 (58%) dogs received cyclosporine as part of their immunosuppressive regimen. Upon bivariable analysis (Table 1), OIFIs were significantly ($P = 0.017$; 95% CI, 1.5–34.4) more common among dogs that were treated with cyclosporine (13/66, 20%) than among dogs that were not (2/47, 4%). No other drugs were significantly associated with development of OIFI. Average dosages of immunosuppressive medications at the time OIFI was diagnosed are as follows: cyclosporine 11.5 mg/kg/day (range 8.8–17.9); prednisone 2.1 mg/kg/day (range 0.77–3.5); mycophenolate 19 mg/kg/day (range 12.5–30); and azathioprine 2 mg/kg/every other day (range 2–3.2). OIFIs were significantly ($P = 0.018$; 95% CI, 1.4–17.9) more common among male dogs (11/51, 22%) than females (4/62, 6%). Occurrence of OIFIs did not vary significantly by age group, and there was no significant association between any of the specific immune-mediated diseases and development of an OIFI. As estimated by multivariable logistic regression model (Table 2), the odds of developing an OIFI were 7.1 times greater among dogs that received cyclosporine compared to dogs that did not ($P = 0.017$; 95% CI, 1.5–34.4). The odds of developing an OIFI were 5.1 times greater among male dogs compared to female dogs ($P = 0.018$; 95% CI, 1.4–17.9). There was not a significant interaction between cyclosporine administration and sex, age group, or any of the other drug treatment variables.

Treatment of the OIFIs was attempted in 13 (87%) of the 15 affected dogs, while 1 of 15 (7%) of dogs was euthanized and 1 of 15 (7%) of dogs died without treatment. None of the dogs were treated with surgical excision; however, 3 of the 13 received wound care with prolonged bandaging until the lesions resolved. Medical treatment protocols varied and were decided by the attending clinician. Antifungal therapies included 1 or more of fluconazole, itraconazole, voriconazole, or terbinafine. Resolution of dermal lesions occurred in 12 of 13 (92%) of the treated OIFI dogs after a median of 4.9 months (range 2–9 months); the remaining dog was lost to follow-up. Resolution was defined by the absence of visible skin lesions.

Discussion

An OIFI was diagnosed in 15 of 113 (13%) of dogs with selected immune-mediated diseases treated with immunosuppressive drugs and represents an important complication in this population of dogs. This retrospective analysis included dogs with selected immune-mediated diseases (e.g., IMHA, ITP, Evans syndrome, and IMPA) because these diseases are routinely treated with immunosuppressive drugs and glucocorticoids. Dogs with other immune-mediated conditions were not included to lessen the confounding effects of many different disease processes, and dogs with cutaneous diseases commonly treated with cyclosporine (in particular atopy) were excluded because of the confusion that would arise when trying to decide if cutaneous fungal infections were due to the drug treatment or the underlying cutaneous disease or both. Dogs were significantly more likely to develop an OIFI if they had been treated with cyclosporine.

Cyclosporine is a T-lymphocyte inhibitor approved by the United States Food and Drug Administration for the treatment of canine atopy. However, it is routinely used extralabel for anal furunculosis, inflammatory bowel disease, meningoencephalitis of unknown etiology (MUE), mitigation of rejection after organ transplantation, and immune-mediated anemia, thrombocytopenia, and polyarthritis.[38] OIFIs associated with cyclosporine administration occur with 8 dogs treated with cyclosporine and prednisone developing OIFIs,[1] and 4 of the 8 develop severe systemic OIFIs, which lead to euthanasia in 2 of 8 dogs and death in 2 of 8 dogs. Fifteen dogs in our study (13%) developed an OIFI, and all except 1 had cutaneous lesions without

obvious evidence of systemic involvement. One dog in our study had disseminated phaeohyphomycosis diagnosed incidentally on renal biopsy of a capsular granuloma during an exploratory laparotomy and splenectomy. This dog died 6 days after diagnosis of the mycotic infection. The difference in case fatality between the current and prior series might be due to the number of dogs with systemic involvement, the fungal species involved, time to recognition of the fungal infection, or concurrent disease.

The majority of dogs in this study were diagnosed with phaeohyphomycosis, hyalohyphomycosis, or both. Inhalation is thought to be the most common mode of infection for aspergillosis and hyalohyphomycosis, while cutaneous penetration or inhalation is common for phaeohyphomycosis.[37] In distinction to previous reports,[1,7–9,11,13–16,18–27,29–34,36] our study had only 1 case of disseminated fungal infection with a renal capsular granuloma, and the remaining 14 of 15 dogs had cutaneous lesions as the sole manifestation of OIFI, which is unique. There are relatively few case reports of OIFIs in immunosuppressed dogs and many of these reports are of disseminated systemic OIFIs. One case series reports 5 cases with skin/subcutaneous OIFIs and 3 cases with confirmed disseminated systemic OIFIs.[1] The reason for this difference is unknown; however, it might be related to the different species of fungal organisms, as some species might be more likely to disseminate beyond cutaneous lesions. However, this hypothesis was not critically evaluated because we did not have definitive identification of fungi to species level. Phaeohyphomycoses are found worldwide in a variety of climates and environments,[37] and a relationship of geographic location and climate and an increased risk development of OIFIs seems unlikely; however, this also has not been specifically evaluated.

Innate immunity including physical barriers, such as intact skin and mucous membranes, is a first line of defense against OIFIs.[39] In immunocompetent animals, additional innate immunity initiates the immune response against fungal organisms[5]; however, T helper 1-type cell-mediated immunity is required for resolution of fungal infections.[39] Suppression of T-cell function and immunity, as with decreased interleukin-2 and interferon gamma expression with cyclosporine, is also associated with a blunting of the immune response,[38,40] which is especially detrimental to dogs that develop OIFIs while on immunosuppressive treatment.

A secondary goal was to investigate if diabetes mellitus increased the risk of OIFIs in our study population, as concurrent systemic illnesses can predispose people to OIFIs. There are reports of fungal urinary tract infections in dogs and cats with diabetes[41] and descriptions of human diabetic patients with OIFIs.[42] We found no association between diabetes mellitus and development of an OIFI, but only 3 of 113 (2.7%) of dogs were diabetic and only 1 of 3 (33%) of these dogs developed an OIFI.

The reason for the increased incidence in males is unknown and has not been described in previous studies. Possibilities include increased roaming behavior or increased time spent outside. This information could not be gathered in all dogs due to the retrospective nature of the study. Furthermore, this could be a spurious finding.

The majority of treated dogs in this study that developed an OIFI (12 of 13; 92%) were treated successfully, while the remaining 1 of 13 dogs; 8% was lost to follow-up.

Antifungal treatment recommendations could not be meaningfully evaluated in this study due to its retrospective nature and the relatively small number of dogs with OIFIs. However, some assumptions seem reasonable. Early diagnosis of OIFIs likely allows for timely treatment and a more favorable outcome. Stopping or reducing dosages of immunosuppressive drugs is probably desirable to improve cell-mediated defenses. Stopping cyclosporine and reducing prednisolone dosage did result in spontaneous resolution of a cutaneous *Alternaria* spp. infection in 1 dog.[17] However, the severity of some immune-mediated diseases precludes immediate cessation of immunosuppressive treatment, and these cases might have a more guarded prognosis. Surgical excision could be considered if lesions are solitary or on a distal extremity, although most dogs in our study (11 of 15) had multifocal cutaneous lesions not amenable to surgical excision.

Opportunistic fungal infections can be treated with fungicidal drugs, fungistatic medications, or newer classes of antifungal medications including echinocandins and terbinafine.[43,44] Long-term treatment (often 6–12 months) is typically recommended due to risk of recurrence.[45] Response to treatment varies depending on the infecting fungus, the extent of disease, and the ability to wean dogs off immunosuppressive drugs.[46] Fortunately, the majority of dogs in this study had resolution of their lesions although most required prolonged antifungal treatment and a few required wound care. Death related to cutaneous infections in humans is also extremely rare.[4]

In the previous report of 8 dogs with OIFIs,[1] the median interval from initiating immunosuppressive treatment to diagnosis of OIFI was 31 days (range 13 to 201). In our study, the median time to diagnosis of OIFI was 43 days (range 21 to 390 days). However, the range in both studies was wide, with 1 dog developing an OIFI 390 days after initiation of immunosuppressive treatment. The average duration of time between organ transplantation and onset of OIFIs in 27 human patients is about 20 months (range: 2–128 months).[4,47] Continued monitoring for OIFIs throughout immunosuppressive treatment seems warranted. Recommendations in human medicine are to biopsy new or unresponsive skin lesions for histopathology and culture.[4]

Limitations of this study stem from its retrospective nature. In particular, there was a lack of definitive identification of fungi to species level and only 5/15 (33%) of our dogs with OIFIs had biopsies of the skin lesions. Molecular identification techniques are becoming more widely available for identification of

veterinary isolates[48]; however, these techniques were not as widely available at the time of diagnosis in this retrospective report. Also, while broad range PCR can detect rare and unreported pathogens, PCR tests are susceptible to contamination during sampling, handling or storage of specimens, making this a potential drawback as this would increase false positives.[49] Therefore, results of fungal culture and PCR should be interpreted in conjunction with clinical findings and cytologic or histopathologic findings.[50] Given the combination of fungal culture results, clinical lesions, and corresponding positive cytology results in this study, false-positive results of the fungal culture seem unlikely. Lack of standardization of treatment of immune-mediated diseases or OIFIs (i.e., drugs, dosages, monitoring frequency) made it impossible to meaningfully compare different protocols. Many dogs were lost to follow-up and it is possible that more of the dogs in our study could have developed an OIFI if followed for a longer period of time. Also, OIFIs were not very common overall and the power of the study to detect weaker associations might have been low.

This report underscores the importance of informing clients of OIFIs as potential complications of immunosuppressive treatment, especially if cyclosporine is administered. In addition, veterinarians should realize that small, subtle, nonulcerated/ulcerated cutaneous lesions might represent an OIFI in dogs receiving immunosuppressive treatment. Although most of the dogs in our study survived their OIFI, additional medications were needed and immunosuppressive regimens were adjusted. Frequent monitoring for cutaneous lesions is recommended to allow early diagnosis, and any new skin lesions should be evaluated by cytology or histopathology.

While multi-agent protocols are often necessary when treating severe immune-mediated diseases, dogs receiving cyclosporine were 7.1 times more likely to develop an OIFI compared to dogs receiving other immunosuppressive medications in this study. Future multicenter prospective cohort studies are necessary to determine best treatment protocols for immune-mediated diseases, treatment options for OIFIs, as well as effective prevention strategies for OIFIs for dogs on immunosuppressive treatment.

Footnote

[a] SAS Institute Inc., Cary, NC

Acknowledgments

Grant support: Study was not supported by a grant.

Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

References

1. Dowling SR, Webb J, Foster JD, et al. Opportunistic fungal infections in dogs treated with ciclosporin and glucocorticoids: Eight cases. J Small Anim Pract 2016;57:105–109.

2. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: An international consensus. Clin Infect Dis 2002;34:7–14.

3. Husain S, Alexander BD, Munoz P, et al. Opportunistic mycelial fungal infections in organ transplant recipients: Emerging importance of non-Aspergillus mycelial fungi. Clin Infect Dis 2003;37:221–229.

4. Schieffelin JS, Garcia-Diaz JB, Loss GE Jr, et al. Phaeohyphomycosis fungal infections in solid organ transplant recipients: Clinical presentation, pathology, and treatment. Transpl Infect Dis 2014;16:270–278.

5. Ramana KV, Kandi S, Bharatkumar V, et al. Invasive fungal infections: A comprehensive review. Am J Infect Dis Microbiol 2013;1:64–69.

6. Richardson MD. Changing patterns and trends in systemic fungal infections. J Antimicrob Chemother 2005;56(Suppl 1):i5–i11.

7. Giri DK, Sims WP, Sura R, et al. Cerebral and renal phaeohyphomycosis in a dog infected with *Bipolaris* species. Vet Pathol 2011;48:754–757.

8. Swift IM, Griffin A, Shipstone MA. Successful treatment of disseminated cutaneous phaeohyphomycosis in a dog. Aust Vet J 2006;84:431–435.

9. Waurzyniak BJ, Hoover JP, Clinkenbeard KD, et al. Dual systemic mycosis caused by *Bipolaris spicifera* and *Torulopsis glabrata* in a dog. Vet Pathol 1992;29:566–569.

10. Herraez P, Rees C, Dunstan R. Invasive phaeohyphomycosis caused by *Curvularia* species in a dog. Vet Pathol 2001;38:456–459.

11. Singh K, Flood J, Welsh RD, et al. Fatal systemic phaeohyphomycosis caused by *Ochroconis gallopavum* in a dog (*Canis familiaris*). Vet Pathol 2006;43:988–992.

12. Metry CA, Hoien-Dalen PS, Maddox CW, et al. Subcutaneous *Mycoleptodiscus indicus* infection in an immunosuppressed dog. J Clin Microbiol 2010;48:3008–3011.

13. Armstrong PF, Sigler L, Sutton DA, et al. Fungal myelitis caused by *Phialosimplex caninus* in an immunosuppressed dog. Med Mycol 2012;50:509–512.

14. Atencia S, Papakonstantinou S, Leggett B, et al. Systemic fungal infection in a dog: A unique case in Ireland. Ir Vet J 2014;67:17.

15. Hawkins EC, Grooters AM, Cowgill ES, et al. Treatment of *Conidiobolus* sp. pneumonia with itraconazole in a dog receiving immunosuppressive therapy. J Vet Intern Med 2006;20:1479–1482.

16. Taylor A, Talbot J, Bennett P, et al. Disseminated *Scedosporium prolificans* infection in a Labrador retriever with immune mediated haemolytic anaemia. Med Mycol Case Rep 2014;6:66–69.

17. Dedola C, Stuart APG, Ridyard AE, et al. Cutaneous *Alternaria infectoria* infection in a dog in association with therapeutic immunosuppression for the management of immune-mediated haemolytic anaemia. Vet Dermatol 2010;21:626–634.

18. Sutton DA, Wickes BL, Thompson EH, et al. Pulmonary *Phialemonium curvatum* phaeohyphomycosis in a Standard Poodle dog. Med Mycol 2008;46:355–359.

19. Ribas T, Pipe-Martin H, Kim KS, et al. Fungal myocarditis and pericardial effusion secondary to *Inonotus tropicalis* (phylum Basidiomycota) in a dog. J Vet Cardiol 2015;17:142–148.

20. Burrough E, Deitz K, Kinyon J, et al. Disseminated aspergillosis in a dog due to *Aspergillus alabamensis*. Med Mycol Case Rep 2012;1:1–4.

21. Murphy KF, Malik R, Barnes A, et al. Successful treatment of intra-abdominal *Exophiala dermatitidis* infection in a dog. Vet Rec 2011;168:217.

22. Jang SS, Dorr TE, Biberstein EL, et al. *Aspergillus deflectus* infection in four dogs. J Med Vet Mycol 1986;24:95–104.

23. Berry WL, Leisewitz AL. Multifocal *Aspergillus terreus* discospondylitis in two German shepherd dogs. J S Afr Vet Assoc 1996;67:222–228.

24. Robinson WF, Connole MD, King TJ, et al. Systemic mycosis due to *Aspergillus deflectus* in a dog. Aust Vet J 2000;78:600–602.

25. Kahler JS, Leach MW, Jang S, et al. Disseminated aspergillosis attributable to *Aspergillus deflectus* in a springer spaniel. J Am Vet Med Assoc 1990;197:871–874.

26. Kelly SE, Shaw SE, Clark WT. Long-term survival of four dogs with disseminated *Aspergillus terreus* infection treated with itraconazole. Aust Vet J 1995;72:311–313.

27. Perez J, Mozos E, de Lara FC, et al. Disseminated aspergillosis in a dog: An immunohistochemical study. J Comp Pathol 1996;115:191–196.

28. Day MJ, Penhale WJ, Eger CE, et al. Disseminated aspergillosis in dogs. Aust Vet J 1986;63:55–59.

29. Bruchim Y, Elad D, Klainbart S. Disseminated aspergillosis in two dogs in Israel. Mycoses 2006;49:130–133.

30. Dallman MJ, Dew TL, Tobias L, et al. Disseminated aspergillosis in a dog with diskospondylitis and neurologic deficits. J Am Vet Med Assoc 1992;200:511–513.

31. Mullaney TP, Levin S, Indrieri RJ. Disseminated aspergillosis in a dog. J Am Vet Med Assoc 1983;182:516–518.

32. Wood GL, Hirsh DC, Selcer RR, et al. Disseminated aspergillosis in a dog. J Am Vet Med Assoc 1978;172:704–707.

33. Pastor J, Pumarola M, Cuenca R, et al. Systemic aspergillosis in a dog. Vet Rec 1993;132:412–413.

34. Clercx C, McEntee K, Snaps F, et al. Bronchopulmonary and disseminated granulomatous disease associated with *Aspergillus fumigatus* and Candida species infection in a golden retriever. J Am Anim Hosp Assoc 1996;32:139–145.

35. Schultz RM, Johnson EG, Wisner ER, et al. Clinicopathologic and diagnostic imaging characteristics of systemic aspergillosis in 30 dogs. J Vet Intern Med 2008;22:851–859.

36. Butterworth SJ, Barr FJ, Pearson GR, et al. Multiple discospondylitis associated with *Aspergillus* species infection in a dog. Vet Rec 1995;136:38–41.

37. Naggie S, Perfect JR. Molds: Hyalohyphomycosis, phaeohyphomycosis, and zygomycosis. Clin Chest Med 2009;30:337–353, vii–viii.

38. Archer TM, Boothe DM, Langston VC, et al. Oral cyclosporine treatment in dogs: A review of the literature. J Vet Intern Med 2014;28:1–20.

39. Blanco JL, Garcia ME. Immune response to fungal infections. Vet Immunol Immunopathol 2008;125:47–70.

40. Archer TM, Fellman CL, Stokes JV, et al. Pharmacodynamic monitoring of canine T-cell cytokine responses to oral cyclosporine. J Vet Intern Med 2011;25:1391–1397.

41. Jin Y, Lin D. Fungal urinary tract infections in the dog and cat: A retrospective study (2001–2004). J Am Anim Hosp Assoc 2005;41:373–381.

42. Badiee P, Hashemizadeh Z. Opportunistic invasive fungal infections: Diagnosis & clinical management. Indian J Med Res 2014;139:195–204.

43. Turner MS, Drew RH, Perfect JR. Emerging echinocandins for treatment of invasive fungal infections. Expert Opin Emerg Drugs 2006;11:231–250.

44. Krishnan-Natesan S. Terbinafine: A pharmacological and clinical review. Expert Opin Pharmacother 2009;10:2723–2733.

45. Grooters AM. Miscellaneous fungal infections. In: Sykes JE, ed. Canine and Feline Infectious Diseases, 1st ed. St. Louis, MO: Saunders; 2013:660–667.

46. Greene CE. Infectious Diseases of the Dog and Cat, 4th ed. St. Louis, MO: Elsevier/Saunders; 2012.

47. Singh N, Chang FY, Gayowski T, et al. Infections due to dematiaceous fungi in organ transplant recipients: Case report and review. Clin Infect Dis 1997;24:369–374.

48. Bernhardt A, von Bomhard W, Antweiler E, et al. Molecular identification of fungal pathogens in nodular skin lesions of cats. Med Mycol 2015;53:132–144.

49. Khot PD, Fredricks DN. PCR-based diagnosis of human fungal infections. Expert Rev Anti Infect Ther 2009;7:1201–1221.

50. Borman AM, Johnson EM. Interpretation of fungal culture results. Curr Fungal Infect Rep 2014;8:312–321.