Frustrating Fungi

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Introduction

In recent years, fungal infections have been recognized more frequently in both human and veterinary patients, and the use of antifungal drugs has increased, especially with the use of more potent immunosuppressive drug treatments for longer periods of time. Efforts have focused on the development of new, less toxic and more efficacious antifungal drugs, and antifungal drugs with novel mechanisms of action, and early diagnosis for more effective treatment.

Diagnosis of Fungal Infections

Although different fungal species vary in their organ tropism, fungal infections should be highly suspected in dogs with fever, nodular, cavitary, or lobar pulmonary lesions, osteolytic bone lesions, ocular inflammation such as uveitis or chorioretinitis, diskospondylitis, enlarged lymph nodes, or cutaneous nodules. A lack of response to antibacterial drugs may also suggest underlying fungal disease.

Major progress has been made in diagnostic testing for fungal disease. Cytology, histopathology and culture are useful but sometimes organisms are undetectable with cytology and histopathology, and culture may be dangerous to laboratory personnel. A history of antifungal drug use may render these assays falsely negative. In addition, these techniques may require invasive specimen collection techniques. Previously, with the exception of cryptococcosis, the only alternative tests available were assays that detect antibodies, which can lack sensitivity and/or etiologic predictive value due to subclinical exposure. A positive agar gel immunodiffusion assay titer in a dog suspected to have nasal aspergillosis is strongly suggestive of the disease, but a negative titer does not rule out the possibility of nasal aspergillosis. Over the last 5-10 years, additional assays that detect fungal antigens have been used more widely in veterinary patients. Point-of-care (POC) assays for cryptococcal antigen have recently become available that are highly sensitive tests for in-practice diagnosis of cryptococcosis (e.g., IMMY line immunoassay). Positive results using these tests should be followed up with a cryptococcal latex agglutination test. Other POC assays that detect *Aspergillus* antigen and beta-D-glucan are under study at the time of writing and have potential to improve diagnosis of disseminated mold infections in dogs.

Treatment of Fungal Infections

Cure with antifungal drug treatment is most likely to be achieved in dogs with localized pulmonary infections, or in dogs with mold infections that have occurred secondary to immunosuppressive drug treatment and the immunosuppression can be reversed. Prognosis is poorest for dogs with disseminated mycoses that are predisposed breeds or that lack a clear underlying cause for their disease. The inflammatory response that follows organism lysis with treatment may lead to significant worsening of clinical signs in the first few days of treatment. Use of NSAIDs or, when the brain is involved, a short period of anti-inflammatory doses of glucocorticoids, may be required until the signs begin to resolve.

Some fungal infections respond to treatment with single agent fluconazole or itraconazole. Molds such as *Aspergillus* have intrinsic resistance to fluconazole, so fluconazole should not be used to treat mold infections. Fluconazole penetrates the brain and the urinary tract, whereas itraconazole may not, unless significant inflammation is present. Many compounded formulations of fluconazole and itraconazole lack efficacy. When treatment failure occurs, serum drug levels can be performed. Itraconazole levels should be performed at least 2 weeks after initiating treatment.

For dogs with disseminated disease, treatment with amphotericin B (AMB) should be considered, although this can be expensive, especially when lipid formulations are used. AMB irreversibly binds sterols in fungal cell membranes, forming pores with subsequent leakage of ions. AMB is virtually unabsorbed from the gastrointestinal tract, so it is formulated for IV infusion (Fungizone®, AMB-D) as a complex with the bile salt deoxycholate. Penetration of the CSF and vitreous humor is poor, but we have still had clinical successes using AMB intravenously for treatment of CNS infections.

The major adverse effect of AMB-D is nephrotoxicity. Loading with IV 0.9% NaCl for 1 hour before the infusion decreases nephrotoxicity. Slow administration in a large volume of fluid also decreases nephrotoxicity. Fever, inappetence and vomiting also appear to occur in some dogs treated with AMB-D. Treatment with nonsteroidal anti-inflammatory drugs can be used to decrease pyrexia during therapy.

New Triazoles

Newer triazoles include voriconazole and posaconazole. Voriconazole has been used for treatment of refractory invasive mold infections in dogs. It penetrates the CNS, and can sometimes cause neurologic signs in dogs, as well as hepatopathy. Cats are very predisposed to neurologic adverse

effects and cardiac arrhythmias at the doses used in dogs and humans and so its use at those doses is contraindicated in cats. Posaconazole, an itraconazole analog, is a safer option for both dogs and cats - it is an itraconazole analog and has also shown efficacy for treatment of refractory fungal infections in dogs and cats. Absorption of the oral suspension has been shown to be variable in dogs, whereas use of the delayed-release tablet formulation has improved absorption and a longer half-life. A dose of 5 mg/kg q48h is recommended. Posaconazole suspension has also been used successfully to treat life-threatening fungal infections in cats. The pharmacokinetics of posaconazole in cats has been reported. Two treatment regimens using the oral suspension appeared to maintain targeted trough concentrations of 0.5-0.7 µg/mL; either 30 mg/kg PO loading dose followed by 15 mg/kg q48h, or 15 mg/kg PO loading dose followed by 7.5 mg/kg q24h.

Pneumocandins/Echinocandins

The echinocandins inhibit formation of beta(1,3)-D-glucans in the fungal cell wall. The prototype drug is *caspofungin acetate*. Other drugs in this class are micafungin and anidulafungin. Caspofungin is given once daily as a slow IV infusion. Caspofungin is effective against resistant *Candida albicans*, and it also has efficacy against *Aspergillus*. It is ineffective against *Cryptococcus*. Cost is slightly less than for lipid formulations of AMB, but nevertheless the need for daily IV infusion together with the cost means it is rarely used in veterinary medicine at this time. In addition, the optimum dose for dogs and cats and its adverse effects in these species are not known.

Terbinafine

Terbinafine (Lamasil®) inhibits fungal squalene epoxidase, blocking fungal ergosterol synthesis. In veterinary medicine, it has been most commonly used to treat dermatophytosis, and it is well tolerated. Its efficacy for invasive fungal infections has not been well investigated, although there are a few published and some anecdotal reports of its use to successfully treat some deep mycoses, especially when used in combination with other drugs.

Commonly used drugs for treatment of deep mycoses in dogs and cats

Drug	**Dose Range**	**Frequency**	**Route**
Deoxycholate amphotericin B	Dogs: 0.5 mg/kg in 1 L D5W Cats: 0.25 mg/kg in 250 mL D5W	Mon-Wed-Fri until a total dose of 4-6 mg/kg or azotemia occurs*	IV over 4-6 h

Abelcet® (amphotericin B lipid complex)	Dogs: 2-3 mg/kg Cats: 1 mg/kg	Mon-Wed-Fri for 9-12 treatments*	IV; dilute in D5W to 1 mg/kg; give over 1-2 h
Itraconazole	Cats: 3 mg/kg Dogs: 5 mg/kg	q24h (suspension) q12-24h	PO
Fluconazole	Cats: 50 mg/cat/d Dogs: 5-10 mg/kg/d	q24h; divide high doses and give q8-12 h	PO
Terbinafine	Cats: 10-30 mg/kg Dogs: 10 mg/kg	q24h	PO

- Check BUN and creatinine prior to each administration. Discontinue if azotemia occurs.