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INTERNAL MEDICINE

Approaches to Opportunistic Fungal Infections in Small Animals

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Opportunistic fungal infections are of increasing importance in veterinary medicine, especially for patients receiving immunosuppressant therapy or those that are otherwise immunocompromised.[1-3] Opportunists are ubiquitous in the environment and are transmitted by either spore inhalation or percutaneous inoculation. Infections can be localized, causing superficial cutaneous nonhealing wounds that are refractory to antibiotic therapy, or they can cause life-threatening systemic illness.[1,2] Patients often have superficial ulcers/erosions or nodules that may have an associated draining tract on the feet, ears, and/or nose.[1-5]

In human medicine, opportunistic fungal infections have been reported for up to 0.7% of organ transplant patients and 20% of patients receiving immunosuppressant cyclosporine.[6] In veterinary medicine, the reported prevalence among dogs receiving immunosuppressant therapy is 13%; opportunistic fungal infections are significantly more likely to develop in dogs receiving immunosuppressant cyclosporine (20% prevalence).[3] Predisposition to opportunistic fungal infections can also be found in dogs and cats with naturally occurring causes of immunosuppression, such as diabetes mellitus, retrovirus infection (e.g., feline leukemia virus, feline immunodeficiency virus), cobalamin deficiency, and familial multifactorial immunodeficiency in German shepherd dogs.[2] The opportunistic fungal infections seen in veterinary medicine are categorized as phaeohyphomycosis, hyalohyphomycosis, and eumycotic mycetomas (**TABLE 1**).

Phaeohyphomycosis (**FIGURE 1**) is a rare infection caused by ubiquitous, pigmented saprophytic fungi of a number of genera, including but not limited to *Alternaria*, *Bipolaris*, *Cladophialophora*, *Curvularia*, and *Exophiala* (**TABLE 1**).[1,2] Pigment, seen within tissue and in culture, is derived from melanin in the cell wall of hyphal elements and conveys virulence.[1,2,7] Clinical infection is rare; both yeast (unicellular) and hyphal (multicellular) forms exist in tissue.[1,2] Phaeohyphomycosis is most commonly seen as locally invasive subcutaneous lesions, especially on areas exposed to soil (i.e., nose, ears, digits).

ON THE DEFENSE
While treatment of opportunistic fungal infections is challenging, early recognition and aggressive treatment can enhance the potential for success.

Among immunocompetent animals, it is more likely to cause cutaneous lesions in cats than dogs. Phaeoid fungi rarely cause central nervous system (CNS) or disseminated systemic disease.[1,2]

Hyalohyphomycosis (FIGURE 2) is caused by ubiquitous, nonpigmented saprophytic fungi that are transparent, or hyaline, in tissues. This heterogenous group of fungi includes *Fusarium*, *Penicillium*, *Paecilomyces*, and *Acremonium* species (TABLE 1). Hyalohyphomycosis most commonly affects young, large breed dogs.[1,2] In cats, hyaline fungi are the most common cause of nodular fungal granulomatous skin lesions.[8,9] Disease is hyphal in origin, occurring as either local cutaneous/osseous infection or disseminated disease involving one or multiple organs.[1] In immunosuppressed animals, disseminated illness is associated with a guarded to poor prognosis.[1,2] In immunocompetent animals, disease is usually confined to the skin and may respond to medical therapy alone.

Eumycotic mycetomas are tumor-like subcutaneous swellings that form within tissue. Infection is characterized by chronic pyogranulomatous inflammation with aggregates of fungal hyphae that form "grains," or aggregations of fungal organisms, within the draining tracts of the lesions.[1,2] These grains enable differentiation of pigmented and nonpigmented fungi within the tissue. Mycetomas are further classified as pigmented (black grain mycetoma) or nonpigmented (white grain mycetomas); color depends on the organism causing the lesion.[1,2]

FIGURE 1. Phaeohyphomycosis, seen in a 3-year-old spayed female boxer dog with nonhealing cutaneous skin lesions on her ventral abdomen and inguinal region; diagnosed by cytology and culture.

TABLE 1 Summary of Opportunistic Fungal Infections and First-Line Treatment Recommendations

TYPE	COMMON GENERA	CLINICAL MANIFESTATIONS	CYTOLOGIC FINDINGS	EMPIRIC THERAPY
Phaeohyphomycosis	*Alternaria*, *Aureobasidium*, *Bipolaris*, *Cladophialophora*, *Cladosporium*, *Curvularia*, *Exophiala*, *Fonsecaea*, *Ramichloridium*, *Scolecobasidium*, *Scytalidium*, *Ulocladium*	Cutaneous lesions: ulcerated or nonulcerated	Pigmented fungi; may need Fontana-Masson stain to highlight melanin pigment; dark, irregularly septate hyphae or yeast	Itraconazole + decrease immunosuppression
Hyalohyphomycosis	*Acremonium, Chrysosporium, Fusarium, Geosmithia, Lecythophora, Oxyporus, Paecilomyces, Penicillium*, *Purpureocillium*, *Pseudallescheria*, *Scedosporium*, *Sagenomella*, *Geomyces*, *Geotrichum*, *Paecilomyces*, *Schizophyllum*, *Scopulariopsis*, *Westerdykella*	Systemic illness: fever, lameness, lymphadenopathy, poor body condition score, central nervous system signs, ocular signs	Nonpigmented, hyaline; septate with branching at acute angles and globose swelling	Amphotericin B + itraconazole + decrease immunosuppression
EUMYCOTIC MYCETOMA				
Black grain	Dematiaceous fungi	Nodular lesion with draining tract in skin/subcutaneous tissue; exudate may contain black grains	Chronic pyogranulomatous lesions with formation of colonies that appear as aggregates of fungal hyphae	Surgery + decrease immunosuppression
White grain	*Pseudallescheria boydii*, *Acremonium*	Chronic body wall or intra-abdominal granuloma		

- **Black grain mycetomas** are caused by dematiaceous (brown-pigmented) fungi such as *Curvularia.* They result in chronic nonhealing, nodular cutaneous lesions with draining tracts.[1] Infection is often associated with trauma, although lesions may not develop until weeks to months after the event.
- **White grain mycetomas** are caused by organisms such as *Pseudallescheria boydii* or *Acremonium*.[1] They form chronic body wall and intra-abdominal granulomas. Infection typically occurs secondary to surgical wound contamination or wound dehiscence, months to years after surgery.[1,2]

DIAGNOSTICS

Historically, disseminated opportunistic fungal infection carries a guarded to poor prognosis, and because infection initiating in the skin has the potential

FIGURE 2. Hyalohyphomycosis in a 2-year-old neutered male French bulldog seen for meningoencephalitis of unknown etiology. Hyalohyphomycosis diagnosed by cytology; *Sporotrichum* species diagnosed by culture. Immunosuppressive therapies at the time of diagnosis included cytosar, prednisone, and cyclosporine. **(A)** Skin lesions on the forearm and between the toes noted during physical examination. **(B)** Interdigital skin lesion caused by hyalohyphomycosis fungal infection. **(C)** Hyalohyphomycosis fungal spore **(arrow)** observed on cytology slide of a cutaneous skin lesion. **(D)** Hyalohyphomycosis fungal hypha **(arrow)** observed on cytology slide of a cutaneous skin lesion. The fungal hypha is nonpigmented and branches at an acute angle.

to disseminate, early recognition is imperative for achieving disease remission and a successful outcome. Yet, early, reliable, and definitive diagnosis of opportunistic fungal infections can be challenging (**FIGURE 3**).

Clinical manifestations of fungal infection are not specific. Opportunistic fungal infections should be considered in cases of nonhealing cutaneous lesions (i.e., digits, pinnae, nasal planum)—with or without regional lymphadenopathy—that are refractory to empiric antibiotic therapy. Fungal infection should also be considered as a differential diagnosis for patients with nasal or osseous disease or patients with any unexplained systemic illness for which other infections (i.e., viral or bacterial) have previously been ruled out.

Cytology

The first, and relatively cost-effective, diagnostic step for fungal disease screening is cytology. For any patient receiving immunosuppressant medications and showing new skin lesions, at a minimum, cytology of the lesions should be performed.

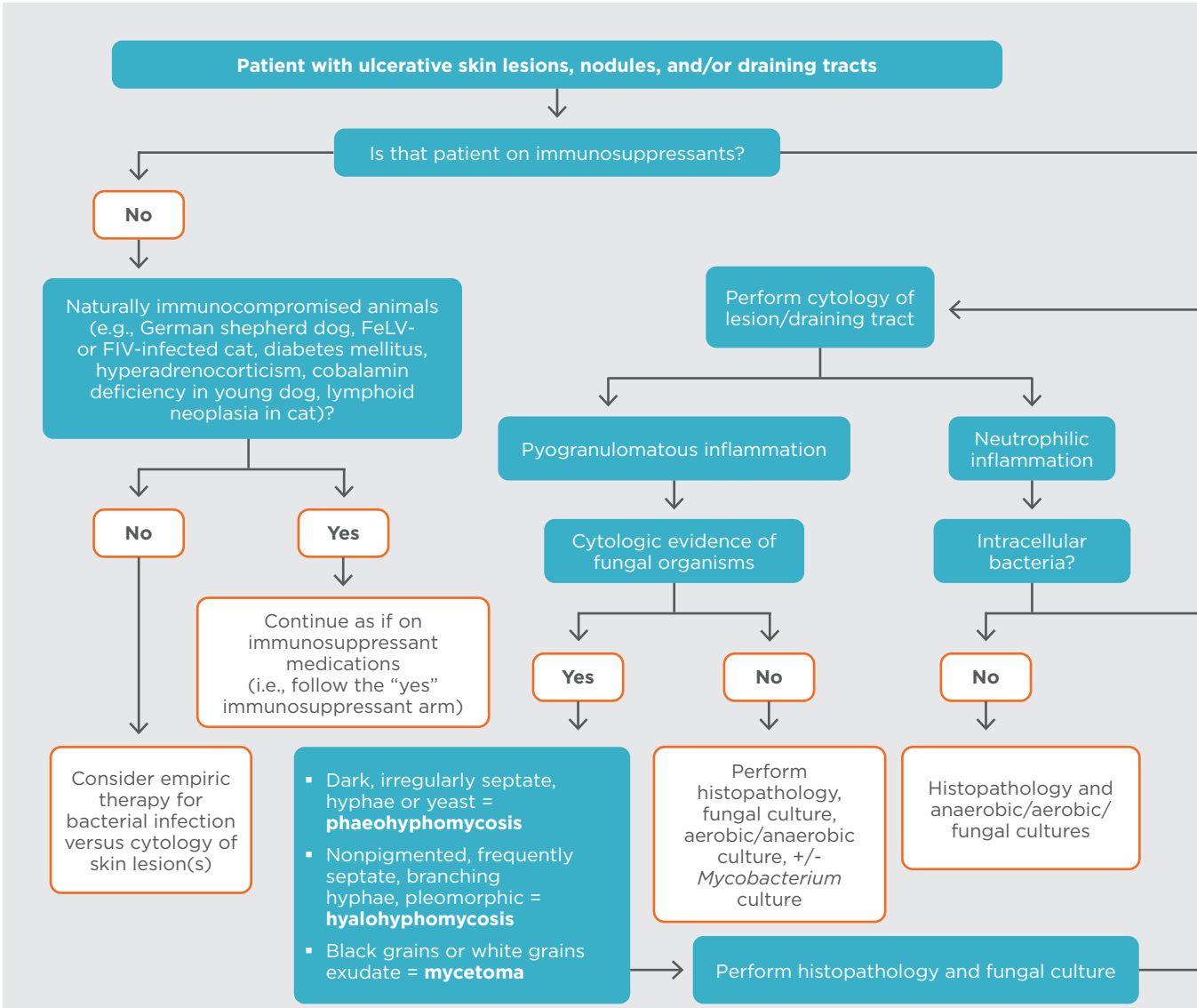
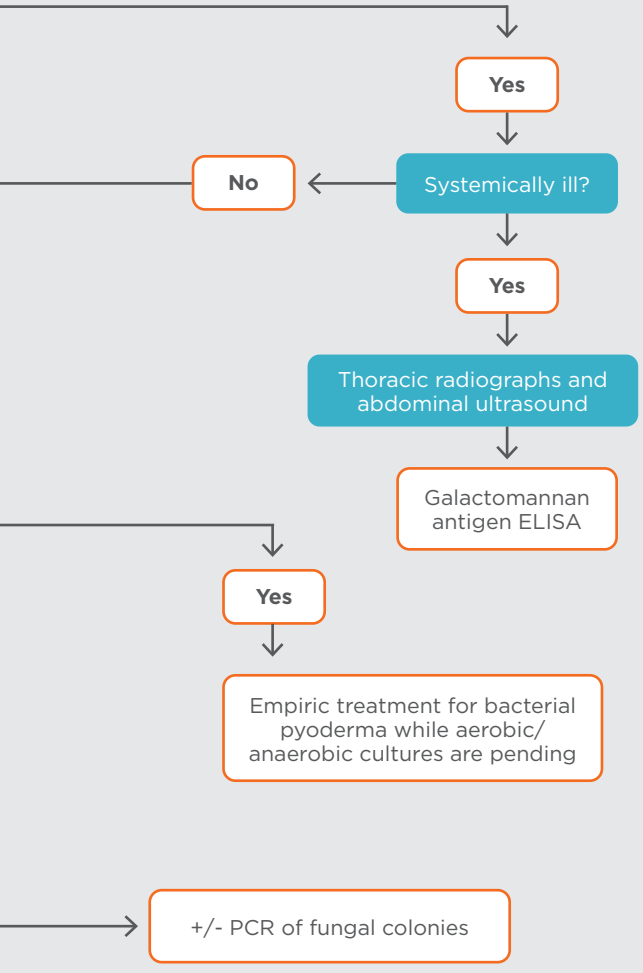


FIGURE 3. Algorithm for diagnosis of opportunistic fungal infection. ELISA=enzyme-linked immunosorbent assay, FeLV=feline leukemia virus, FIV=feline immunodeficiency virus, PCR=polymerase chain reaction

For ulcerated skin lesions, impression smears are usually recommended. For nodules, fine-needle aspirations are recommended, including aspiration of adjacent draining lymph nodes even with no evidence of concurrent lymphadenopathy. In the absence of concurrent pyogranulomatous inflammation (i.e., neutrophilic and macrophagic inflammation), cytologic identification of fungal organisms is not sufficient for a diagnosis; fungal organisms may merely be contaminants because they are ubiquitous in the environment and common commensals of the skin and nasal cavity.[1-3,5,7,10] Diff-Quik or Gram stains should be used for in-house cytology.



Phaeohyphomycosis: The traditional stains mentioned above may not demonstrate the variable amounts of pigment of phaeohyphomycosis organisms.[1,2] Diagnostic sensitivity for phaeohyphomycosis organisms may be increased by using an unstained sample slide and lowering the condenser of the microscope or by using special fungal stains (e.g., Gömöri methenamine silver [GMS], periodic acid-Schiff [PAS]).[8,11] Fungal hyphae are thin (2 to 6 µm) with irregular swellings and prominent septate constrictions.[11] Hyphae or yeast-like cells may appear brown, reflecting their high melanin content; Fontana-Masson staining for melanin confirms their presence (**TABLE 1**).

Hyalohyphomycosis: These infections are denoted by nonstaining hyphae (3 to 12 µm) that are septate and demonstrate acute angular (45°) branching.[11] Hyphal contours and the presence of septae may be highlighted by using GMS or PAS stains. Hyphae will occasionally swell and appear globose. Organisms may be indistinguishable from each other or from *Aspergillus* species (e.g., *A caninus*, *A alabamensis*).[2,11]

Mycetomas: The black or white grains produced by mycetomas[1,2,11] are usually visualized in the discharge from a draining tract. Microscopically, they appear as interwoven mycelial aggregates lined with eosinophilic material.[11] Grains are found in abscesses and the sinus tracts connecting abscesses to the skin surface. Sinus tracts are usually surrounded by granulation tissue and granulomatous inflammation.

Biopsy

Because fungi may be absent from cytology samples or the presence of hyphae may be masked by necrotic debris, cytology alone may not lead to a definitive diagnosis.[12,13] Biopsies enable evaluation by histopathology, culture, and polymerase chain reaction (PCR).

Before performing the biopsy, lesions of interest should be clipped. If submitting samples for histopathology, no further preparation is necessary. When samples are being submitted for fungal culture, the site should be aseptically prepared to remove any superficial contaminants. Biopsy punches (4 to 6 mm) should be used to obtain samples from the center and edge of the lesion. Deeper lesions can be sampled by performing a second biopsy punch through the initial biopsy site. To obtain representative samples of diseased tissue,

collection of 2 to 4 samples is recommended. Samples should be apportioned for histopathology (1 to 2 samples) and culture (aerobic/anaerobic bacteria and fungi). If samples need to be prioritized because of limited number or financial concerns, cultures for fungi and aerobic bacteria should be chosen. Samples for fungal culture should be stored at room temperature and submitted to laboratories that can perform molecular identification and susceptibility testing with results available in 2 to 4 weeks. Meanwhile, if cytology has provided enough evidence of a fungal infection, empiric treatment should be started immediately and then later adjusted pending culture and sensitivity results (**TABLE 1**).

Molecular Diagnostics

A newer, commercial, nonculture way to diagnose opportunistic fungal infections is PCR. PCR amplifies fungal DNA extracted from paraffin-embedded tissues; sensitivity is 54% to 94%.[2] Panfungal PCR, offered by specialized laboratories (Texas A&M and Illinois Veterinary Medical Diagnostic Laboratory), has the unique ability to identify fungal species. Test results should be interpreted in light of clinical, cytopathologic, and histopathologic findings.

Other Diagnostic Techniques

If hyalohyphomycosis is a concern (on the basis of clinical signs of nonhealing cutaneous lesions, systemic illness in animals receiving immunosuppressive

TABLE 2 Antifungal Drugs

DRUG	DOSE[a]	COMMON ADVERSE EFFECTS	MONITORING	COST
Itraconazole	▪ Capsule: 5 mg/kg PO q12–24h ▪ Dogs: Administer with food to improve absorption ▪ Cats: Suspension, 5 mg/kg PO q12–24h	▪ Vomiting, anorexia (may decrease with q12h administration) ▪ Hepatotoxicity (less common)	▪ Liver panel every 3 months ▪ If no clinical response in 2 weeks, measure trough levels	$$
Fluconazole	▪ 5–10 mg/kg PO q12–24h	▪ Mild and transient gastrointestinal signs ▪ Hepatotoxicity (less common)	▪ Liver panel every 3 months (increased ALT is common)	$$
Voriconazole	▪ 4–5 mg/kg PO q12h ▪ Decreased absorption with food ▪ Do **NOT** use in cats	▪ Inappetence, increased liver enzymes, ataxia and other central nervous system signs	▪ Liver enzymes, electrolytes	$$$
Posaconazole	▪ Dogs: 5–10 mg/kg PO q12–24h ▪ Cats: 5 mg/kg PO q24h	▪ Limited knowledge (lack of studies)	▪ Limited knowledge (lack of studies)	$$$
Terbinafine	▪ 30–40 mg/kg PO q24h with food	▪ Vomiting, increased liver enzymes ▪ Cats: Facial pruritus	▪ Baseline liver enzymes, then every 3 months	$
Amphotericin B (AMB)	IV or SQ			

▪ AMB deoxycholate (conventional)	▪ Q48h
	  ▪ Dogs: 0.5 mg/kg IV
	  ▪ Cats: 0.25 mg/kg IV
	▪ Cumulative
	  ▪ Cumulative dose should not exceed 12 mg/kg IV
	  ▪ SQ cumulative doses reported at 15 mg/kg
		▪ Nephrotoxicity; sterile abscesses with subcutaneous administration	▪ Monitor BUN, creatinine, urine sediment, and potassium with each administration.	$$–$$$

▪ AMB lipid-complex with cholesteryl sulfate
▪ AMB lipid complexed
▪ AMB encapsulated unilamellar liposomes
	▪ Q24h
	  ▪ Dogs: 1–3.3 mg/kg IV
	  ▪ Cats: 1 mg/kg IV
	▪ Cumulative
	  ▪ Dogs: 24–30 mg/kg IV
	  ▪ Cats: 12 mg/kg IV
				$$–$$$

Caspofungin	▪ 1 mg/kg IV q24h[b]	▪ Fever, phlebitis, and increased ALT in humans has been reported	▪ CBC, electrolytes, and liver function	$$$

[a]All doses are for dogs and cats unless otherwise indicated.
[b]Anecdotal reports. No safety and efficacy studies in dogs and cats have been performed.
ALT=alanine aminotransferase, BUN=blood urea nitrogen, CBC=complete blood count

medications [e.g., fever, lameness, chorioretinitis, lymphadenomegaly], and cytology), a systemic workup (thoracic and abdominal imaging) should be performed. If systemic hyalohyphomycosis is suspected, *Aspergillus* galactomannan antigen enzyme-linked immunosorbent assay (ELISA) can be considered. Often used to test for hyalohyphomycosis in humans, this ELISA can be considered for animals because of its cross-reactivity with fungi of multiple genera (e.g., *Penicillium*, *Geotrichum*, *Paecilomyces*, *Cladosporium*).

THERAPEUTIC APPROACHES

Fungal infections are quite challenging to treat; therapy consists of aggressive resection and prolonged treatment with antifungals (≥6 months for some, **TABLE 2**).[1-3,5,10] Empiric therapy is initiated when diagnosis of fungal disease is confirmed (i.e., cytology/histopathology) or when suspicion of fungal infection is increased and other types of infections have been ruled out (e.g., leukemia virus–associated dermatoses, feline herpesvirus–associated dermatoses, Bowenoid in situ carcinoma, cutaneous inverted papilloma, or bacterial infection).

Because of the limited number of cases reported, treatment guidelines in the literature are arbitrary. However, treatment for 3 months beyond clinical resolution of grossly detectable disease is recommended due to the risk for recurrence, especially in immunosuppressed patients. For patients receiving immunosuppressants, especially cyclosporine, these drugs should be discontinued immediately or tapered (e.g., prednisone) to allow the immune system to fight infection.[1-3,5,6,10] Failure to do this at the time of diagnosis, even if fungal infections are localized to the skin, may result in progression of disease or death since fungal infections tend to disseminate throughout the body. In patients that have severe immune-mediated disease and still require immunosuppressive therapy, alternative therapies (e.g., splenectomy and human immunoglobulin for immune-mediated hemolytic anemia or liposomal clodronate for immune-mediated thrombocytopenia) may be considered.[14-16] Another possible treatment strategy is therapeutic plasma exchange to help decrease the amount of medical immunosuppression needed.[17] These alternative therapies have not been evaluated in cats.

Each patient should be evaluated on an individual basis; treatment decisions should be based on clinical assessment, severity of fungal disease, and which disease is more life-threatening. Before prescribing multiple (i.e., >2) immunosuppressants for a patient with immune-mediated disease, discuss with clients the risk for development of opportunistic fungal infection and the possibility of immune-mediated disease relapse if immunosuppressants are tapered or discontinued.

Surgical Procedures

Excision

The treatment of choice for phaeohyphomycosis, localized hyalohyphomycosis, and mycetomas is surgical excision with wide margins.[1,2] To remove diseased tissue, excision of wide surgical margins (≥2 cm) in all planes wherever possible should be attempted or the distal extremity amputated. For example, for a patient with a cutaneous lesion on its toe, amputation of the digit is recommended. For patients receiving immunosuppressant therapy, phaeohyphomycosis may respond to medical therapy alone if immunosuppressants can be discontinued.[2,5,10]

CO_2 Laser

At the University of Florida, the authors also use a CO_2 laser to treat cutaneous fungal infections of the digits and nasal planum on dogs and cats. Laser is an ideal alternative to traditional surgery of the digits, around the eyes, and of the nasal planum because it enables precise ablation of infected tissue while preserving surrounding healthy tissue.[18] Because the laser does not directly contact the lesion, seeding of the infective organisms into surrounding tissues is unlikely. The laser also "seals off" blood vessels and lymphatics, thereby reducing risk for organism spread.

Before laser treatment, the patient is anesthetized and the site is clipped. Laser ablation is then executed by applying a 15- to 20-watt continuous wave over the site

Use of a CO_2 laser has enabled successful treatment of cutaneous fungal infections while sparing patients' limbs and noses.

until the lesion is resurfaced to healthy tissue and fungal organisms are killed in the process. Wounds created from these procedures are left open to heal through secondary intention. Use of a CO_2 laser has enabled successful treatment of cutaneous fungal infections while sparing patients' limbs and noses.

Cryosurgery

The authors' institution has also used cryosurgery to treat fungal infections involving the digits, ears, or nasal planum. Applications for cryotherapy have been extrapolated from human medicine. As with CO_2 laser therapy, cryosurgery patients are anesthetized. Liquid nitrogen is applied by using a cryogun. For lesions smaller than 1 cm, liquid nitrogen is sprayed on the lesion for about 60 seconds until a halo forms around the lesion. The area is then allowed to thaw, and the treatment is repeated for 2 to 3 freeze/thaw cycles. Lesions larger than 1 cm are divided into smaller sections; each section is treated as above until the whole lesion has been effectively treated. Wounds are left to heal through secondary intention.

Currently, no veterinary literature supports use of this therapy for opportunistic fungal infections. However, cryotherapy may be an effective alternative for areas where margins cannot be surgically excised.

Medical Therapies

Triazole Antifungals

First-line medical treatment for fungal disease comprises triazole antifungals. These drugs inhibit synthesis of ergosterol, a component of the fungal cell wall,[1,19] resulting in cell wall damage and increased cell permeability, leading to eventual cell lysis. The triazoles commonly used in veterinary medicine are itraconazole, fluconazole, and voriconazole. Newer azoles (e.g., posaconazole) are generally cost prohibitive in veterinary medicine.[1,2]

First-line medical treatment for fungal disease comprises triazole antifungals.

Itraconazole: The most commonly used antifungal in veterinary medicine is itraconazole.[1,2] Because it is highly protein bound, it does not have good penetration into the CNS, eyes, or urine.[1]

Fluconazole: Although less effective against systemic fungal infections, fluconazole effectively penetrates the CNS, prostate, and urinary tract. It is usually considered for patients that experience adverse effects with itraconazole.

Voriconazole: This drug produces severe side effects in cats, and its use in cats should be avoided.[1]

Several azole antifungal drugs cross-inhibit mammalian cytochrome P450 enzymes; thus, triazoles may interact with other drugs that inhibit mammalian cytochrome P450 enzymes. Most adverse effects are dose related; hepatotoxicity, a potentially severe side effect, usually develops within the first 2 to 3 months of therapy. If progressively increasing transaminase activity is accompanied by concurrent clinical signs (lethargy, inappetence, vomiting, diarrhea), clinicians should immediately discontinue the medication. Other side effects include cutaneous reactions (e.g., itraconazole, voriconazole) and thrombocytopenia (fluconazole).

Amphotericin B

Amphotericin B is a fungistatic polyene macrolide. It irreversibly binds and forms micelles with fungal ergosterol, forming pores/channels within the fungal membrane, thereby altering the fungal cell permeability, which then allows leakage of ions and cellular components.[1,7] At higher doses, amphotericin B is fungicidal.[1] Amphotericin B has immunomodulatory effects that activate macrophages and enhance macrophage-killing capacity. It is administered intravenously or subcutaneously[1] and is the initial treatment of choice for rapidly progressive fungal disease or when conventional antifungal therapy has failed. Adverse effects are associated with dose-dependent nephrotoxicity, attributable to the drug's vasoconstrictive and tubulotoxic effects.[1] Newer lipid formulations are less nephrotoxic, allowing for higher cumulative drug doses and improved effectiveness. Amphotericin B is often used in combination with itraconazole to treat hyalohyphomycosis.[1,2]

Echinocandins

Echinocandins are a newer parenteral group of

antifungals that inhibit glucan synthase and inhibit β-(1,3)-D glucan in the fungal cell wall, leading to fungal cell lysis.[1,7] Echinocandins such as caspofungin are effective against hyalohyphomycosis.[1,2] Their use in veterinary medicine is limited because they must be administered in the hospital and are expensive.

Terbinafine

Terbinafine, a lipophilic synthetic allylamine, noncompetitively inhibits fungal squalene epoxidase, blocking fungal lanosterol and ergosterol synthesis and resulting in the accumulation of toxic squalene and fungal cell lysis.[1] It concentrates in hair follicles, skin, nail plates, and adipose tissue and is most commonly used to treat dermatophytosis.[1] Side effects are mild (e.g., limited gastrointestinal upset, rare hepatotoxicity and neutropenia). Terbinafine is usually combined with other antifungal agents because of its synergistic activity with azoles.[1,7] It has been used in combination therapy to treat phaeohyphomycosis and hyalohyphomycosis.

Other Therapies

Hyperbaric Oxygen Therapy

Opportunistic fungi, although considered obligate aerobes, have evolved mechanisms that enable them to tolerate and adapt to low-oxygen environments.[20] Hyperbaric oxygen therapy (HBOT) to treat fungal infections has rarely been described in veterinary literature; clinical applications have been extrapolated from accepted indications in human medicine. Reported theorized antifungal benefits from HBOT include increased production of oxygen free radicals, leading to enzyme inactivation, damage to cell membranes, and reduced protein synthesis resulting from increased oxygen delivery to peripheral tissues and increased cellular oxygenation.[21] HBOT also inhibits the growth of some fungi and potentiates the antifungal effects of amphotericin B.[21,22] At the University of Florida, HBOT is considered an adjunctive treatment on a case-by-case basis. Further investigation is needed to determine whether or how these treatments affect clinical outcomes and to determine which patients or infections are the best candidates.

Future Therapies

Given the association between opportunistic fungal infection and immunodeficiency/immunosuppression, investigation into locally controlling disease while fortifying the immune system is at the forefront of human and veterinary research. Areas of research include use of cytokine therapies to strengthen defenses against disseminated fungal infections in patients with chemotherapy-induced neutropenia,[23] transfusion of leukocytes loaded with an antifungal in human medicine, and experimental laboratory models (e.g., mice) to treat invasive aspergillosis via transfusion of granulocytes loaded with posaconazole.[23] Other areas of research include use of monoclonal antibodies and autologous vaccinations with fungal cell wall components and fungal antigens.

In addition to these therapies, a newer azole drug that has successfully treated resistant mold infections has become available in human medicine;[19] however, it is not readily available in the veterinary market at this time due to cost. Isavuconazonium sulfate is a broad-spectrum prodrug of isavuconazole, a second-generation triazole that is less toxic than the other azoles.[19] This newer drug may be a future option in the treatment of opportunistic fungal infections in veterinary medicine.

If surgery is not performed, pictorial documentation of gross lesions (e.g., photos and body mapping) and restaging lesions every 3 months may be beneficial.

MONITORING

In the absence of consensus as to the timing or staging of patients with opportunistic fungal infections, monitoring for recurrence can be difficult. Recommended monitoring includes surveillance of the skin and previous surgical sites for evidence of recurrence. If surgery is not performed, pictorial documentation of gross lesions (e.g., photos and body mapping) and restaging lesions (i.e., repeat cytology, thoracic radiography, abdominal ultrasonography) every 3 months may be beneficial. Thorough palpation of the surgical scar and skin around the primary lesion

as well as regional lymph nodes may also help detect early disease spread or recurrence. Clients should be informed that any evidence of new skin lesions or discharge should be promptly investigated. Because the rate of recurrence of disseminated disease is high, any patient with disseminated disease should undergo routine restaging by thoracic radiography and abdominal ultrasonography every 3 months after clinical resolution or if they become systemically unwell while receiving treatment.

SUMMARY

- Opportunistic fungal infections can be quite challenging to definitively diagnose and treat.
- Therapeutic success may be enhanced by early recognition and aggressive treatment.
- For patients with nonhealing cutaneous lesions that are refractory to conventional antibiotic treatment, opportunistic fungal infections should be on the list of differentials.
- Treatment is long-term and multimodal; therapy is optimal when concurrent immunosuppressant medications can be rapidly tapered or discontinued.
- Prognosis for patients with underlying immunodeficiency or disseminated disease is guarded to poor. **TVP**

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References

1. Sykes JE, ed. *Canine and Feline Infectious Diseases.* St. Louis, MO: Elsevier; 2014.
2. Dedeaux A, Grooters A, Wakamatsu-Utsuki N, Taboada J. Opportunistic fungal infections in small animals. *JAAHA.* 2018;54(6):327–337.
3. McAtee BB, Cummings KJ, Cook AK, et al. Opportunistic invasive cutaneous fungal infections associated with administration of cyclosporine to dogs with immune-mediated disease. *J Vet Intern Med.* 2017;31(6):1724–1729.
4. Smith LN, Hoffman SB. A case series of unilateral orbital aspergillosis in three cats and treatment with voriconazole. *Vet Ophthalmol.* 2010;13(3):190–203.
5. 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(2):105–109.
6. 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(2):270-8.
7. Wong EH, Revankar SG. Dematiaceous molds. *Infect Dis Clin North Am.* 2016;30(1):165–178.
8. Lloret A, Hartmann K, Pennisi MG, et al. Rare opportunistic mycoses in cats: phaeohyphomycosis and hyalohyphomycosis: ABCD guidelines on prevention and management. *J Feline Med Surg.* 2013;15(7):628–630.
9. Miller RI. Nodular granulomatous fungal skin diseases of cats in the United Kingdom: a retrospective review. *Vet Dermatol.* 2010;21(2):130–135.
10. Swift IM, Griffin A, Shipstone MA. Successful treatment of disseminated cutaneous phaeohyphomycosis in a dog. *Aust Vet J.* 2006;84(12):431–435.
11. Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. *Clin Microbiol Rev.* 2011;24(2):247–280.
12. Kundu R, Handa U, Punia RS, et al. Phaeohyphomycosis: cytomorphologic evaluation in eleven cases. *Acta Cytol.* 2020;64(5):406–412.
13. Sangoi AR, Rogers WM, Longacre TA, et al. Challenges and pitfalls of morphologic identification of fungal infections in histologic and cytologic specimens: a ten-year retrospective review at a single institution. *Am J Clin Pathol.* 2009;131(3):364–375.
14. Scott-Moncrieff JC, Reagan WJ. Human intravenous immunoglobulin therapy. *Semin Vet Med Surg Small Anim.* 1997;12(3):178–185.
15. Mathes M, Jordan M, Dow S. Evaluation of liposomal clodronate in experimental spontaneous autoimmune hemolytic anemia in dogs. *Exp Hematol.* 2006;34(10):1393–1402.
16. Horgan JE, Roberts BK, Schermerhorn T. Splenectomy as an adjunctive treatment for dogs with immune-mediated hemolytic anemia: ten cases (2003–2006). *J Vet Emerg Crit Care.* 2009;19(3):254-61.
17. Crump KL, Seshadri R. Use of therapeutic plasmapheresis in a case of canine immune-mediated hemolytic anemia. *J Vet Emerg Crit Care.* 2009;19(4):375–380.
18. Agulian L, Mann FA, Middleton JR, Kim DY. A retrospective comparison of carbon dioxide surgical laser and non-laser excision for removal of cutaneous and subcutaneous soft-tissue sarcomas in dogs. *N Z Vet J.* 2020;68(6):340–344.
19. Lewis RE, Wurster S, Beyda ND, et al. Comparative in vitro pharmacodynamic analysis of isavuconazole, voriconazole, and posaconazole against clinical isolates of aspergillosis, mucormycosis, fusariosis, and phaeohyphomycosis. *Diagn Microbiol Infect Dis.* 2019;95(3):114861.
20. Grahl N, Shepardson KM, Chung D, Cramer RA. Hypoxia and fungal pathogenesis: To air or not to air? *Eukaryot Cell.* 2012;11(5):560–570.
21. Bitterman H. Hyperbaric oxygen for invasive fungal infections. *Isr Med Assoc J.* 2007;9(5):387–388.
22. Gudewicz TM, Mader JT, Davis CP. Combined effects of hyperbaric oxygen and antifungal agents on the growth of *Candida albicans*. *Aviat Space Environ Med.* 1987;58(7):673–678.
23. Scriven JE, Tenforde MW, Levitz SM, Jarvis JN. Modulating host immune responses to fight invasive fungal infections. *Curr Opin Microbiol.* 2017;40:95–103.