Fungal Infections of the Upper Respiratory Tract

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ABSTRACT: Fungal infection of the upper respiratory tract presents diagnostic challenges and therapeutic dilemmas. Diagnosis of upper respiratory tract granuloma is based on clinical signs, identification of mass lesions during endoscopic examination, and collection of tissue samples by biopsy or by mucosal scraping. Cytologic or histologic examination of lesions may identify characteristic morphologic features of fungal organisms. The etiologic agent can be definitively identified by microbiologic culture, immunohistochemistry, polymerase chain reaction, or serology.

No retrospective or prospective studies have compared various surgical (debulking, laser, cryotherapy) and medical (topical, intralesional, systemic) treatment options for fungal granulomas in horses. Isolated case reports, small case series, and a limited number of review articles describe empirical therapies. A multimodal approach is often successful, but the relative benefits of the individual treatment components are unknown. Treatment options depend on the site and extent of the infection, accessibility to surgical intervention, the etiologic agent, the known antifungal susceptibilities, evidence-based study results from human medicine, and the financial resources of the owner.

Although results of several small comparative studies on treating guttural pouch mycosis have been reported, to date, no comparative studies have been conducted to determine the ideal therapeutic plan to treat mucosal conidiobolomycosis or cryptococcal infections in horses. In human medicine, new antifungals with good efficacy and reduced toxicities have become available within the past decade. Pharmacokinetic studies on newer drugs are being conducted in horses, and as more drugs become available in generic form, the cost of relatively more efficacious medical therapy will be dramatically reduced. This article reviews the reported etiologies of, as well as the diagnostic techniques and the medical and surgical therapies for, equine respiratory tract fungal granulomas.

FUNGI

The fungal kingdom comprises yeasts, molds, fungal rusts, and mushrooms. Fungi are eukaryotic organisms with a definitive cell wall made up of chitins, glucans, and mannans. Within the cell wall, the plasma membrane contains ergosterol, a cell membrane sterol that is frequently targeted by antifungals. Ergosterol regulates the permeability of the cell membrane and activity of membrane-bound enzymes. There are more than 70,000 species of fungi, but only 50 species have been identified as causes of disease in people or animals. Pathogenic fungi can be
Fungal infections of the upper Respiratory Tract

Dimorphic fungi can change between forms, depending on environmental conditions. In soil and decaying matter, the mycelial form usually is present and is composed of a collection of hyphae. The mycelia produce infective spores that can inoculate vertebrate tissue.

**CLINICAL SIGNS AND GROSS LESIONS**

Mycotic granulomas of the upper respiratory tract have been found in the nasal passages, paranasal sinuses, nasopharynx, gullet pouch, and trachea of infected horses. The most common clinical signs of upper respiratory fungal infection include unilateral or bilateral serosanguineous or mucopurulent nasal discharge as well as inspiratory or expiratory noise. Other clinical signs include coughing, facial deformation, and dyspnea caused by partial blockage of nasal passages by granulomatous masses. Fungal plaques in the gullet pouch are often located over the arterial blood supply. Horses with gullet pouch mycosis often have episodic serosanguineous nasal discharge. This may progress to potentially fatal epistaxis if there is erosion into an artery. The duration of clinical signs can vary from days to many months. Differentials for fungal granulomas of the respiratory tract include ethmoidal hematoMA, squamous cell carcinoma, amyloidosis, or exuberant granulation tissue.

**DIAGNOSIS**

**Diagnostic Samples**

Lesions in the nasal passages, turbinates, nasopharynx, gullet pouch, trachea, and bronchioles can usually be observed directly during endoscopic examination. Masses in the paranasal sinuses may be observed using radiography. Computed tomography or magnetic resonance imaging provides detailed imaging of the equine skull and can determine the extent of lesions and degree of bony invasion. A sterile rigid arthroscope or flexible endoscope can be passed through an 8- to 20-mm trephine that is drilled into the conchofrontal or maxillary sinus to directly view some lesions within the paranasal sinuses.

**Fungal diseases of the upper respiratory tract include conidiobolomycosis, cryptococcosis, rhinosporidiosis, coccidioidomycosis, pseudallescheriosis, and aspergillosis.**

For nasal and nasopharyngeal lesions, specimens for cytology, histopathology, and culture can be obtained by use of an endoscopically guided biopsy instrument. However, these samples tend to be small, superficial, and often nondiagnostic. In cultures, mucosal contaminants may overgrow the organism of interest. Larger biopsy samples from the nasal passages or the nasopharynx can often be obtained by use of a uterine biopsy instrument, which can be passed nasally with visual guidance from a flexible endoscope. Excisional biopsy or surgical debulking may be performed through a sinus flap or via laryngotomy.

**Cytology**

Fungal hyphae may be identified in airway fluid or in impression smears from masses obtained by biopsy. Some fungi have characteristic morphologic features that can allow an early presumptive identification (Table 1).

**Histopathology**

Hyphae of certain fungi may be poorly visualized using routine hematoxylin–eosin staining. Therefore, special stains (e.g., periodic acid–Schiff, Gridley’s fungus, Grocott-Gomori methenamine-silver nitrate) can be useful in staining histopathologic specimens. In patients with chronic fungal infections, there is often evidence of extensive fibrosis on histopathology.

**Microbiologic Culture**

Some fungi have fastidious growth requirements and may take up to several weeks to grow on culture media or may be overgrown by contaminant bacteria. Tissue samples submitted for microbiologic culture should be placed in a prepared culture media and transported at room temperature. Specific culture media such as Sabouraud’s dextrose agar (Remel, Lenexa, KS), inhibitory mold agar, or Mycobiotic (Remel), which contains cycloheximide and chloramphenicol, are useful.

**Molecular Techniques**

Serologic tests that use immunodiffusion, radioimmunoassays, latex agglutination, complement fixation, or ELISAs are available to detect circulating antigens or
Table 1. Characteristic Morphologic Features of, and Availability of Serologic Tests for, Fungal Organisms Reported to Cause Fungal Granulomas in the Equine Upper Respiratory Tract

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cytologic Morphology</th>
<th>Serologic Test</th>
<th>Cost and Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcus neoformans</td>
<td>Round, thin-walled, yeast-like fungus (5–10 μm) with a large heteropolysaccharide capsule (1–30 μm) that does not take up common cytologic stains. The capsule is best stained with mucicarmine stain. The organisms show narrow-based budding and lack endospores.</td>
<td>Capsular antigen ELISA (antigen)</td>
<td>$16 at UGA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Latex agglutination (antigen)</td>
<td>$18 at NMDA</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>$20 at CSU</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>$30 at UT</td>
</tr>
<tr>
<td>Conidiobolus coronatus</td>
<td>Broad, thin-walled, highly septate, irregularly branched hyphae (5–13 μm)³; often surrounded by acidophilic-staining, glycoprotein antigen–antibody complexes known as Splendore–Hoeppli material.</td>
<td>Immunodiffusion is highly sensitive and specific. A decreasing titer correlates with disease resolution in horses.⁸ ⁹</td>
<td>Serologic testing is not widely available.</td>
</tr>
<tr>
<td>Pseudallescheria boydii</td>
<td>Hyaline, nonpigmented, septate, randomly branched hyphae (2–5 μm) with regular hyphal contours. The asexual form has nonbranching conidiophores with terminal conidia. The sexual form in culture has a cleistothecium (large, round body) and ascospores.²⁸</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Coccidioides immitis</td>
<td>Relatively large, round spherules (20–80 μm; up to 200 μm) with a double-contoured cell wall. The mature spherules are called sporangiospheres (2–5 μm).</td>
<td>Agar gel immunodiffusion (antibody) for IgM and IgG⁴⁷,⁵²,²</td>
<td>$8 at NMDA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CF (antibody)⁴⁷,⁵¹,⁶; may have some false-positive results⁶</td>
<td>$12 at CSU</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$12 at NMDA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$15 at UT</td>
</tr>
<tr>
<td>Aspergillus spp</td>
<td>Broad (2–4 μm), septate hyphae with parallel sides and acute, right-angled branching.</td>
<td>Aspergillus Galactomannan enzyme immunooassay (sandwich immunoassay) antigen test; 80.7% sensitive and 89.2% specific; some reactivity to Penicillium, Alternaria and Paecilomyces spp</td>
<td>Platelia Aspergillus antigen enzyme immunoassay by MDL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agar gel immunodiffusion (antibody): <em>A. fumigatus only</em></td>
<td>$15 at UT</td>
</tr>
<tr>
<td>Fungal panel</td>
<td>—</td>
<td>Agar gel immunodiffusion</td>
<td>$28 at MDL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Aspergillus, Blastomyces, Coccidioides, and Histoplasma spp)</td>
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<td></td>
<td></td>
<td></td>
<td>$40 at CSU</td>
</tr>
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<td></td>
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<td></td>
<td>$55 at CU</td>
</tr>
</tbody>
</table>

³CF = Complement fixation.
⁴CSU = Colorado State University College of Veterinary Medicine and Biomedical Sciences. Phone 970-297-1281; fax 970-297-0320; www.dlab.colostate.edu.
⁶MDL = MiraVista Diagnostics Laboratory, Indianapolis, IN. Phone 317-856-2681; fax 317-856-3685; www.miravistalabs.com.
⁷NMDA = New Mexico Department of Agriculture Veterinary Diagnostic Services. Phone 505-841-2576; www.nmda.nmsu.edu/animal-and-plant-protection/veterinary-diagnostic-services.
⁸UGA = The University of Georgia College of Veterinary Medicine. Phone 706-542-5568; fax 706-542-5233; www.vet.uga.edu/dlab/index.php.
⁹UT = University of Tennessee College of Veterinary Medicine. Phone 865-974-5639; fax 865-946-1788; www.vet.utk.edu/diagnostic/bacteriology.
antibodies against several fungal organisms (Table 1). These tests have been used to assist in the diagnosis of equine fungal infections caused by Cryptococcus spp., Conidiobolus coronatus, and Aspergillus spp. Because of cross-reactivity between some related fungal species, care must be taken in interpreting test results. Many healthy horses have antibodies against Aspergillus spp. as a result of environmental exposure. The development of a commercial ELISA with less reactivity is promising. Serologic testing is especially useful if biopsy samples are difficult to obtain.

Immunohistochemistry, fluorescent in situ hybridization, and DNA probes can also be used to positively diagnose fungal organisms in histopathologic sections.

**ANTIFUNGAL THERAPEUTICS**

During the past decade, there has been significant progress in the development of new antifungals in human medicine and in the subsequent empirical use and determination of pharmacokinetic profiles in horses. Although systemic therapy is expensive, it has resulted in an increased incidence of successful treatment of fungal diseases in horses. As various antifungals become available in generic form, the cost of antifungal therapy for horses will become more affordable. New antifungals differ in their mode of activity, toxicity, and propensity to interact with other drugs. Therefore, antifungal therapy must be tailored to the etiologic agent, site and extensiveness of infection, adjunctive therapies, and financial resources.

**In Vitro Sensitivity Testing**

For many years, clinically relevant antifungal susceptibility testing was nonexistent. Consequently, antifungal therapy in human medicine was largely empirical and based on evidence-based medicine rather than guided by susceptibility data. Selection of antifungal therapy for horses was based on recommendations from human literature, although it was limited by high expense and lack of pharmacokinetic information specific to horses. Currently, the National Committee for Clinical Laboratory Standards (NCCLS) has a published, approved reference method for susceptibility testing for yeasts (M27-A). This method is useful for interpreting susceptibility data forazole antifungals and fluycytosine in human medicine, but interpretation of results for amphotericin B has been problematic. To date, no interpretable breakpoints exist for any antifungal agent against Cryptococcus neoformans or for azoles against any of the molds. The NCCLS has published a proposed reference method for molds (M38-P), but clinical applicability is in its infancy. It is likely that in vitro susceptibility testing for yeasts and molds will evolve to allow more selective use of antifungals, but to date, clinicians should not rely solely on results of these methods to guide therapy.

**Amphotericin B**

Amphotericin B is a polyene antibiotic that combines with ergosterol in the fungal cell membrane and causes an increase in cell permeability. Intravenous amphotericin B is one of the most efficacious antifungal therapies but can cause nephrotoxicity and phlebitis. Other possible adverse effects include anorexia, anemia, cardiac arrhythmias, hepatic and renal dysfunction, and hypersensitivity reactions. Reported doses range from 0.3 to 0.9 mg/kg (diluted in saline) IV administered over 1 hour for approximately 30 days. Topical amphotericin B can also be used.

**Azoles**

Benzimidazole derivatives in the azole class (e.g., clotrimazole, econazole, miconazole, enilconazole, ketoconazole, isoconazole, itraconazole, fluconazole, voriconazole) kill fungi by inhibition of ergosterol biosynthesis in the fungal cell membrane. Ketoconazole is absorbed poorly in the nonacidified form but can be acidified for better absorption (30 mg/kg via nasogastric tube q12h mixed with 0.2 normal hydrochloric acid). Itraconazole (Sporanox; Janssen-Ortho, Toronto Ontario, Canada) solution is absorbed well orally (bioavailability: 60%). A dose of 5 mg/kg PO q24h maintains concentrations above minimum inhibitory concentration for susceptible yeasts and Aspergillus spp, with no detectable adverse effects. Itraconazole (Sporanox) suspension is very expensive, and because of the large volume required, administration by nasogastric tube is recommended. The use of compoundeditraconazole is not recommended. Itraconazole is very unstable (requires a low pH) and, owing to its lipophilic nature, is difficult to formulate in aqueous solution.

Oral fluconazole at a loading dose of 14 mg/kg, followed by 5 mg/kg q24h, yields concentrations in plasma, cerebrospinal fluid, synovial fluid, aqueous humor, and urine above the minimum inhibitory concentration reported for several equine fungal pathogens. However, fluconazole reportedly has minimal activity against filamentous fungi (Aspergillus and Fusarium spp). Low-dose oral fluconazole (1 mg/kg PO
q24h) for at least 10 to 15 days has been anecdotally successful in treating fungal keratitis. Compounded fluconazole formulations are very stable.

Voriconazole, a new broad-spectrum triazole antifungal, is preferred for initial treatment of invasive aspergillosis, candidiasis, and cryptococcosis in human patients who cannot tolerate or have infections that are refractory to other therapeutic agents. A recently published pharmacokinetic study of voriconazole in horses showed excellent oral bioavailability and a long half-life. The authors proposed a dose of 4 mg/kg PO q24h to achieve plasma concentrations greater than 1 µg/mL but recommended that because of potential accumulation, multiple-dosing studies should be conducted before clinical use in horses.

Voriconazole is presently very expensive but is likely to achieve therapeutic concentrations in the brain, retina, and lungs. Topical miconazole and enilconazole have successfully been used to treat guttural pouch mycosis. Miconazole is suitable only for topical administration because it is toxic when given intravenously.

Systemic Iodide Therapy

Iodides have very little, if any, in vitro antibiotic effect, but they seem to have a beneficial effect on the granulomatous inflammatory process. Although the exact mode of action is unknown, in several successfully treated cases, iodides were used as primary or adjunctive therapy for fungal granulomas. However, overall, the efficacy of iodides is considered limited at best. The treatment is inexpensive, but toxicity and resistance can occur. Iodide toxicity is characterized by excessive lacrimation, a nonproductive cough, increased respiratory secretions, and dermatitis. The recommended dose of 20% sodium iodide is 20 to 40 mg/kg/day IV for 7 to 10 days. Orally administered iodide is available in two forms:

- **Inorganic potassium iodide** (10 to 40 mg/kg/day) is available only in a chemical grade and is unstable in the presence of light, heat, and excessive humidity.

- **Organic ethylenediamine dihydroiodide (EDDI)** is commercially available (0.86 to 1.72 mg/kg of EDDI is equivalent to 20 to 40 mg/kg/day of the 4.57% dextrose powdered form).

Because of the risk for developmental congenital hypothyroidism in foals, administration of iodides should be avoided in pregnant mares.

Surgical Therapy

Surgical debulking, endoscopic laser surgery, and cryotherapy can be used as primary treatments or as premedical therapy in treating fungal granulomas. Surgical debulking can be performed through a conchofrontal or nasomaxillary sinus flap or through a laryngotomy incision. Surgery via a sinus flap can be performed with the use of either sedation and local anesthesia in standing patients (Figure 1) or general anesthesia in patients in lateral recumbency (Figure 2). As with all sinonasal surgeries, there is a significant risk for hemorrhage, and the need for blood transfusion is not uncommon.
hemorrhage is anticipated, a blood transfusion should be prepared for preoperatively. If marked hemorrhage occurs, temporary bilateral carotid artery occlusion can be used (up to 16 minutes) to reduce intraoperative hemorrhage. Direct pressure provided by gauze packing is often required for 48 to 72 hours after surgery. Surgery is often combined with local injection of amphotericin B or adjunctive medical therapy. Treatment has been unsuccessful in many horses that were treated for many months by medical and surgical means, thereby necessitating placement of a permanent tracheostomy as a salvage procedure to prolong life for breeding or for pasture soundness.

ETIOLOGIC AGENTS
Phycomycosis Disease Complex
Organisms within the phycomycosis (subcutaneous mass due to fungus or bacteria) disease complex include *C. coronatus*, *Basidiobolus* spp, and *Pythium insidiosum*, which are in the class Zygomycetes and order Entomophthorales. Fungi within this order are opportunistic. They infect immunocompetent animals and tend to form nondisseminating subcutaneous masses. In contrast, other members of Zygomycetes (*Rhizopus*, *Mucor*, and *Absidia* spp) often disseminate to cause systemic disease.

Conidiobolomycosis
*C. coronatus* is a saprophytic fungus that causes granulomatous lesions of the upper respiratory tract in horses. Single to multiple granulomatous lesions in the nasal passages, the trachea, or the soft palate can be observed endoscopically (Figure 3). The histologic appearance of conidiobolomycosis is similar to those of pythiosis and basidiobolomycosis. *Basidiobolus* spp and *P. insidiosum* tend to infect subcutaneous tissue of the limbs and trunk, whereas *C. coronatus* generally infects the mucous membranes of the upper respiratory tract. Although nasal pythiosis has occasionally been reported, *P. insidiosum* is not a true fungus but rather is classified among the Oomycetes and is discussed elsewhere. Hyphae of *C. coronatus* are thin-walled, highly septate, and irregularly branched (5 to 13 µm). The lesions typically have large numbers of eosinophils and fewer macrophages, neutrophils, plasma cells, and lymphocytes that surround hyphae (Figure 4). The definitive diagnosis is based on microbiologic culture, immunodiffusion, or polymerase chain reaction. Detection of serum antibodies by immunodiffusion is considered highly sensitive and specific and can be used to monitor response to treatment. A nested polymerase chain reaction pythiosis assay has also been used to identify *C. coronatus*.

Conidiobolomycosis lesions can be treated with surgical excision, cryotherapy, or long-term administration of iodides or antifungals. Pharyngeal masses can be approached via laryngotomy and visualized with a flexible endoscope. Surgical debulking followed by intraleSIONAL injection of amphotericin B (20 mg) via an 8-inch spinal needle through the surgical incision, followed by 10 days of a topical mixture of amphotericin B (20 mg), potassium penicillin (100,000 IU), and dimethyl sulfoxide (30 ml), was successfully used to treat pharyngeal
infection with *C. coronatus* in one horse. There are several other reports of successful treatment of nasopharyngeal infection with *C. coronatus* using topical or intralesional amphotericin B. It is important to remember that long-term therapy and reevaluation are essential because recurrence is possible.

A mare with *C. coronatus* granulomatous tracheitis was successfully treated with iodide therapy (44 mg/kg IV of 20% sodium iodide for 7 days; then 1.3 mg/kg PO of EDDI q12h for 4 months, then q24h for 1 year, then once per week). Excessive lacrimation was an occasional adverse effect of the iodide but resolved if therapy was discontinued for 1 day.

*C. coronatus* cultured from a nasal mass in one horse was found to be resistant in vitro to ketoconazole and itraconazole. Treatment with itraconazole (3 mg/kg PO q24h for 4½ months) was ineffective. Oral fluconazole was successful in treating two pregnant mares with nasal conidiobolomycosis. One mare was administered 2 mg/kg PO q12h for 8 weeks; the other mare was treated at currently recommended dosages (a loading dose of 14 mg/kg followed by 5 mg/kg q24h PO) for 6 weeks. The lesions in the second horse were more extensive but resolved more rapidly than those in the horse treated with the lower dose. Intralesional injection ofazole antifungals, such as miconazole or fluconazole, to treat conidiobolomycosis has not been reported but could be considered when parenteral treatment is not economically feasible. A vaccine using *C. coronatus* antigen from broth cultures was unsuccessful in treating seven horses with conidiobolomycosis. Similar immunotherapy has been very successful in treating horses with pythiosis.

**Cryptococcosis**

Cryptococcosis is commonly caused by *C. neoformans* (var *neoformans* and var *gattii*)—a ubiquitous, saprophytic, round, basidiomycetous yeast-like fungus (5 to 10 µm in diameter) with a large heteropolysaccharide capsule (1 to 30 µm in diameter) that does not take up common cytologic stains (Figure 5). The capsule, which forms a clear halo when stained with India ink, is immunosuppressive and antiphagocytic. Capsular antigens that are secreted into the host’s body fluids bind opsonizing antibodies before they reach the organism. Equine cryptococcosis occurs at a relatively high frequency in Western Australia, and there is an epidemiologic relationship between *C. neoformans* var *gattii* and the Australian river red gum tree (*Eucalyptus camaldulensis*) as well as between *C. neoformans* var *neoformans* and avian (particularly pigeon) excreta. Cytologic or histopathologic identification is very reliable for diagnosis because of the characteristic morphology of the yeast. Differentiation of various cryptococcal species is possible based on culture characteristics, serologic identification, DNA sequencing, or immunohistochemical
staining. Serologic testing with latex agglutination to identify cryptococcal capsular antigen has been useful in the diagnosis of equine cryptococcosis, with resolution of lesions being correlated with declining serum titers.

Cryptococcosis in horses is primarily associated with pneumonia, rhinitis (Figure 6), meningitis, and abortion. Reports of successful medical treatment are rare.

**Pseudallescheriosis**

*Pseudallescheria boydii* is a saprophytic ascomycete (the telomorph is *Scedosporium apiospermum*). Infection with *P. boydii* most commonly involves the extremities; in human patients, it is known as *Madura foot*. Hyphae of *Fusarium* or *Aspergillus* spp within tissue cannot be differentiated unless they are cultured. *P. boydii* cultured from the nasal cavity and the sinus of a horse with chronic, malodorous nasal discharge was susceptible in vitro to miconazole, ketoconazole, natamycin, and clotrimazole (Figure 7). After debridement and flushing of the plaque, 5 g of 2% miconazole cream was infused twice daily for 4 weeks through lavage tubing that had been passed into the nasal passage through a hole drilled in the frontal bone and sinuses. Sodium iodide was administered systemically for 4 days followed by potassium iodide for 14 days. The nasal cavity was free of infection 30 and 60 days after treatment had been initiated.

Nasal mycosis caused by *P. boydii* has been reported in two other horses, both of which were euthanized. In one horse, an attempt was made to curette the nasal plaques, which was followed by topical treatment via a surgically placed drain that was flushed daily with dilute povidone-iodine for 10 days, followed by natamycin solution for 2 weeks. No improvement was noted, and the horse was euthanized. *P. boydii* has also been isolated from the pharynx of two of 60 healthy donkeys and uterine fluid from horses with chronic uterine infection. Miconazole, itraconazole, ketoconazole, and voriconazole are active in vitro against *P. boydii*, which generally responds poorly to amphotericin B. Topical miconazole is effective for superficial lesions.

**Rhinocryptococcosis**

*Rhinocryptococcus seeberi* rarely causes polypoid growths in the nasal, vaginal, and ocular mucous membranes of horses. On gross examination, mottled small white foci may be interspersed throughout the granuloma. We are not aware of any reports of treatment of *R. seeberi* in the literature.

**Coccidioidomycosis**

*Coccidioides immitis* is a soil saprophyte that grows in semiarid areas with sandy, alkaline soils. In the environment, *C. immitis* exists as a mycelium with thick-walled, barrel-shaped arthroconidia. Inhaled arthroconidia can enlarge to form nonbudding spherules, which incite an inflammatory reaction. Most infections are pulmonary or systemic and have been reviewed elsewhere. Localized, recurring nasal granulomas have also been reported. Nasal masses can be very slowly progressive. One horse developed a coccidioidal ethmoid mass 6 years after moving from Texas to a nonendemic area. The mass was surgically removed; 5 years later, the clinical signs recurred and the horse was euthanized because of the extensiveness of the lesions.
C. immittis is difficult to culture. However, serology is very useful in diagnosing infection, and decreasing titers are associated with clinical improvement. Oral itraconazole and fluconazole have been used to treat osseous and pulmonary coccidioidomycosis. Nasopharyngeal lesions can be treated surgically or medically, and long-term reevaluation is recommended.

Aspergillosis
Aspergillus in horses has been reviewed. Aspergillus spp have broad (2 to 4 µm in diameter), septate hyphae with parallel sides and acute right-angled branching. They have a propensity for vascular invasion. A definitive diagnosis can be made by culture or staining using immunohistochemistry or immunofluorescence (Fusarium spp and P. boydii appear similar on histologic examination). Serologic diagnosis has occasionally been useful but is often unreliable. Aspergillus spp are very common in the environment, especially in moldy feed and bedding. Aspergillus spp are the most common cause of guttural pouch mycosis (see below) and can also cause plaques in the nasopharynx.

In two horses, mycotic rhinitis was treated successfully with itraconazole (3 mg/kg PO q24h for 120 days, which achieved concentrations that exceeded the minimum inhibitory concentration for the organism). Additional successful treatments in two horses included topical nataamyacin (25 mg in 100 ml of saline) flushed via an endoscope as well as nystatin powder insufflated up the affected nostril. Another horse was treated successfully with nataamyacin solution via an indwelling facial catheter in the caudal maxillary sinus.

Guttural Pouch Mycosis
There are several excellent, detailed reviews of guttural pouch mycosis. Mycotic infection of the guttural pouch generally occurs on the dorsal wall of the medial compartment or on the lateral wall of the lateral compartment (Figure 8). Mycotic ulcerations are typi-
cally located over the internal carotid artery and less commonly located over the external carotid artery or maxillary artery. Plaques can vary in size and can expand to cover the entire roof of the pouch. Infection may erode through the median septum into the neighboring pouch, causing bilateral infection.

Horses generally have intermittent mucopurulent to serosanguineous nasal discharge or epistaxis. Erosion of the internal carotid artery or, less commonly, the external carotid artery or maxillary artery can result in fatal hemorrhage (Figure 9). If guttural pouch mycosis associated with epistaxis is untreated, 50% of affected horses will die. Bouts of epistaxis are unpredictable, but several usually occur before a fatal bleeding episode. Endoscopy or placement of lavage catheters carries a significant risk for dislodging fungal plaques or previously formed clots, which can result in further hemorrhage. Secondary neurologic abnormalities may result if thrombi from the internal carotid artery dislodge and embolize to the brain, causing subsequent cerebral dysfunction. Inflammation can affect cranial nerves that traverse the guttural pouch, leading to the development of laryngeal hemiplegia, dysphagia, facial paralysis, or Horner’s syndrome.

Guttural pouch mycosis is most often caused by...
Aspergillus spp, particularly A. nidulans (Figure 10). Infections with Mucor, Penicillium, Paecilomyces, Chrysosporium, Rhizopus, and Alternaria spp have also been reported. Surgical arterial occlusion by either balloon catheter technique or transarterial coil is the preferred treatment for guttural pouch mycosis; there is little evidence for the necessity of adjunctive medical therapy\(^8\). (e.g., oral or topical thiabendazole; topical nystatin, natamycin, miconazole, or enilconazole; oral or systemic iodosides).

If surgical options are not available, topical medications can be applied via an indwelling catheter (a temporary Chamber’s catheter or long-term commercial guttural pouch catheter) that is advanced through the guttural pouch opening. Medications may also be sprayed directly on the lesion through the biopsy portal of a flexible endoscope. The dorsal location of the lesions makes treatment difficult, and there is always the risk for fatal hemorrhage.

Intranasal 2% miconazole has been used in the resolution of four cases of guttural pouch mycosis.\(^23\) In two cases, 70 mg of injectable miconazole solution was diluted in 10 mL of normal saline; in two other cases, 400 mg of warmed gynecologic miconazole cream was infused into the guttural pouch once daily for 1 week, then every other day for 2 weeks. Treatment using the gynecologic cream was continued twice per week for an additional 3 weeks. All horses recovered uneventfully.\(^23\) Although enilconazole is not available in the United States, it has been used topically as a 0.9% or 1.7% solution to successfully treat four cases of guttural pouch mycosis.\(^23\) In two cases, 70 mg of injectable miconazole solution was diluted in 10 mL of normal saline; in two other cases, 400 mg of warmed gynecologic miconazole cream was infused into the guttural pouch once daily for 1 week, then every other day for 2 weeks. Treatment using the gynecologic cream was continued twice per week for an additional 3 weeks. All horses recovered uneventfully.\(^23\) Although enilconazole is not available in the United States, it has been used topically as a 0.9% or 1.7% solution to successfully treat four cases of guttural pouch mycosis caused by Rhizopus, Aspergillus, Penicillium, Mucor, Chrysosporium, and Alternaria spp.\(^25\,26\)

Systemic treatment of guttural pouch mycosis has also been successful using intraconazole and topical enilconazole.\(^24\) Itraconazole (5 mg/kg PO for 3 weeks) was administered, and topical enilconazole (60 mL) was later sprayed directly onto the mycotic lesion using endoscopic guidance for 2 weeks.\(^24\) Medical therapy may be a more economically feasible treatment option than surgical arterial occlusion and can be considered when neurologic deficits are present in the absence of epistaxis.

**CONCLUSION**

Conidiobolomycosis, aspergillosis, cryptococcosis, coccidioidomycosis, and pseudallescheriosis are the most commonly reported causes of fungal granulomas in the equine respiratory tract. Infection with other organisms is possible, and new etiologies will likely be reported in the future. Determination of the specific fungal agent influences the choice of the antifungal in medical management but may be irrelevant in surgical intervention. Drugs available for systemic therapy are becoming more affordable (especially fluconazole), but it has not been determined whether medical therapy with a sole agent is more or less efficacious or cost effective than are combinations of surgical debulking, intraluminal injection, and/or the use of systemic antifungals.

**REFERENCES**

Fungal Infections of the Upper Respiratory Tract


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I. Which statement about fungal cell structure is incorrect?
a. Fungal cell walls are composed of chitins, glucans, and mannan.
b. Fungal cell membranes contain ergosterol.
c. Fungi are prokaryotes, as are bacteria.
d. Dimorphic fungi can change between forms, depending on environmental conditions.
2. Which statement about guttural pouch mycosis is incorrect?
   a. Horses usually present with episodic mucopurulent to serosanguineous nasal discharge.
   b. Fatal epistaxis can occur if there is erosion into an artery.
   c. The most common cause is *Aspergillus* spp.
   d. Fungal plaques frequently involve the retropharyngeal lymph nodes on the ventral wall of the medial compartment of the guttural pouch.
   e. Cranial nerve dysfunction can lead to the development of laryngeal hemiplegia, dysphagia, facial paresis, or Horner syndrome.

3. Which statement about antifungals is correct?
   a. Amphotericin B is an azole antifungal.
   b. Intravenous amphotericin B can be nephrotoxic.
   c. The use of compounded itraconazole is recommended to reduce costs of therapy.
   d. Miconazole is an inexpensive, safe, and effective intravenous antifungal.
   e. Ketoconazole has good oral bioavailability.

4. Which statement about infection with *C. coronatus* is incorrect?
   a. *C. coronatus* is a round, basidiomycetous yeast-like fungus with a large heteropolysaccharide capsule.
   b. Hyphae of *C. coronatus* are thin-walled, highly septate, and irregularly branched.
   c. The lesions typically have large numbers of eosinophils and fewer macrophages, neutrophils, plasma cells, and lymphocytes surrounding the hyphae.
   d. Infection generally results in granulomatous lesions in the nasal passages, trachea, or soft palate.
   e. Successful resolution has been obtained with intraleisional amphotericin B, oral fluconazole, and oral itraconazole.

5. Which statement about *C. neoformans* is incorrect?
   a. Cytologic or histopathologic identification is very reliable for diagnosis because of characteristic morphology.
   b. Resolution of cryptococcal lesions is correlated with decreasing serum titers.
   c. Cryptococcosis in horses is primarily associated with pneumonia, rhinitis, meningitis, and abortion.
   d. Successful medical treatment of cryptococcosis has never been reported in horses.
   e. *C. neoformans* has a large heteropolysaccharide capsule that is immunosuppressive and antiphagocytic.

6. An epidemiologic association among the Australian river red gum tree, bird droppings, and ______ has been described.
   a. *Alternaria* spp
   b. *Aspergillus* spp
   c. *C. coronatus*
   d. *C. neoformans*
   e. *P. boydii*

7. Guttural pouch mycosis is most often caused by infection with
   a. *Aspergillus* spp.
   b. *C. neoformans*.
   c. *Alternaria* spp.
   d. *P. boydii*.
   e. *C. coronatus*.

8. The preferred surgical treatment of guttural pouch mycosis is
   a. arterial occlusion by balloon catheter or transarterial coil.
   b. curettage via Viborg’s triangle.
   c. stylohyoid ostectomy.
   d. jugular vein occlusion.
   e. trephination via the nasomaxillary sinus into the pouch as well as topical therapy.

9. *Aspergillus* spp typically have
   a. thin-walled, highly septate hyphae with irregular branching.
   b. broad, septate hyphae with parallel sides and acute, right-angled branching.
   c. narrow, nonseptate hyphae with tapering sides.
   d. round, yeast-like cells with a large heteropolysaccharide capsule.
   e. nonencapsulated cells with broad-based budding.

10. Which azole antifungal is toxic if administered systemically?
    a. itraconazole
    b. fluconazole
    c. ketoconazole
    d. miconazole
    e. voriconazole