Intranasal infusion of clotrimazole for the treatment of nasal aspergillosis in two cats

Eva Furrow, VMD, and Reid P. Groman, DVM, DACVIM, DACVECC

Case Description—Two cats (13 and 11 years old) were evaluated to determine the cause of nasal discharge of varying duration (4 days and 5 months, respectively).

Clinical Findings—Computed tomography revealed marked turbinate destruction and soft tissue densities in the nasal passages. Histologic examination of nasal specimens revealed chronic active inflammation and branching fungal hyphae consistent with Aspergillus spp. Fungal culture of nasal specimens resulted in growth of Aspergillus spp. Testing yielded negative results for antibodies against Aspergillus spp.

Treatment and Outcome—Both cats were anesthetized and treated with a 1-hour intranasal infusion of clotrimazole. Recovery from the procedure was uncomplicated, and both cats had complete resolution of clinical signs.

Clinical Relevance—Little information is available on the treatment of nasal aspergillosis in cats, and the prognosis for affected animals is considered poor. The procedure for local intranasal infusion of clotrimazole in 2 cats was described here. Results and follow-up monitoring for both cats suggested that this may be a safe, effective, and durable treatment for cats with nasal aspergillosis. (J Am Vet Med Assoc 2009;235:1188–1193)

A 13-year-old spayed female Siamese cat was evaluated for bilateral nasal discharge and dyspnea of 4 days’ duration. The clinical signs had progressed despite treatment with amoxicillin-clavulanate (16 mg/kg [7.3 mg/lb], PO, q 12 h). The cat had a history of diabetes mellitus, chronic renal disease (International Renal Interest Society stage 1, substages nonproteinuria and high-risk hypertension with no complications), and inflammatory bowel disease. Chronic diseases of the cat were being managed by administration of glargine insulin (0.5 U/kg [0.23 U/lb], SC, q 12 h), amlodipine (0.625 mg, PO, q 24 h), famotidine (1 mg/kg [0.45 mg/lb], PO, q 24 h), and immunosuppressive doses of prednisone (2.5 mg/kg [1.14 mg/lb], PO, q 24 h; changed from administration of budesonide 2 months prior to evaluation for nasal disease).

Physical examination revealed bilateral mucopurulent nasal discharge, stertor, and bradycardia (heart rate, 120 beats/min). The cat had inspiratory dyspnea when breathing nasally; the respiratory effort improved during open-mouth breathing. Results of examination of the oral cavity were unremarkable. The cat was underweight, with a body condition score of 2 (scale of 1 to 9). Thoracic radiography revealed hyperinflation of the lungs and aerophagia consistent with the history of increased respiratory effort. No evidence of pulmonary parenchymal disease was evident.

Electrocardiography revealed a sinus bradycardia with periods of sinus arrest and escape beats. Echo-cardiography did not reveal evidence of underlying myocardial disease; the bradycardia was attributed to increased vagal tone associated with pronounced respiratory effort.

A CBC revealed mild normocytic normochromic anemia (Hct, 29%; reference range, 31.7% to 48%). Abnormalities on serum biochemical analysis included mild increases in the glucose concentration and activity of aspartate aminotransferase. Isosthenuria, glucosuria, proteinuria, and hematuria were detected during urinalysis of a sample obtained via cystocentesis. Microbial culture of a urine sample did not yield bacteria. The cat had negative results when tested by use of an ELISA for FeLV antigen and antibodies against FIV.

The following day, the cat was anesthetized for CT and retrograde rhinoscopy with collection of biopsy specimens. Marked bilateral destruction of the turbinates and retrograde rhinoscopy with collection of biopsy specimens were evaluated for FeLV antigen and antibodies against FIV.

Histologic examination revealed fungal rhinitis with extensive necrosis, fibrin deposition, and degeneration of the nasal mucosa. Aspergillus fumigatus was confirmed via culture of the nasal turbinate biopsy.

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The cat recovered well from the procedures, and the nasal discharge and respiratory distress resolved during the subsequent 3 days. The cat was discharged to the owner, who was instructed to administer metronidazole (10 mg/kg [4.5 mg/lb], PO, q 24 h), prednisone (2.5 mg/kg, PO, q 24 h), and famotidine (1 mg/kg, PO, q 24 h) for management of the cat’s inflammatory bowel disease and glargine insulin (0.25 U/kg [0.11 U/lb], SC, q 12 h) for management of diabetes mellitus. Hypertension was not detected at any time during hospitalization, despite discontinuation of amlodipine. Therefore, it was recommended that the owner not administer this medication.

The esophagostomy tube was removed 5 weeks later. At that time, the cat’s appetite had returned, and it was eating appropriate amounts of food. At 2 years after treatment, the cat was doing well with no evidence of rhinitis.

An 11-year-old spayed female domestic short-haired cat was evaluated because of a 5-month history of sneezing, nasal congestion, and discharge from the right naris; prior to examination, the cat had been receiving antimicrobials (amoxicillin-clavulanate, sulfadimethoxine-ormetoprim, and sulfamethoxazole-triamethoprim; dosages unknown), but no improvement was evident. Results of a CBC and serum biochemical analysis were within reference limits. Evaluation of skull radiographs taken by the referring veterinarian revealed an increased opacity in the right nasal passage and right frontal sinus; results for thoracic radiographs were unremarkable. The referring veterinarian had performed nasal flushes and normograde biopsy to obtain specimens of nasal mucosa from the cat; histologic examination revealed severe rhinitis and fungal hyphae consistent with Aspergillus spp. Bacterial culture of the nasal mucosa yielded growths of Pasteurella spp and α-hemolytic Streptococcus spp. The cat had access to the indoors and outdoors and had been vaccinated annually against FeLV.

Figure 1—Transverse plane, precontrast, CT image of a 13-year-old Siamese cat with bilateral nasal discharge and dyspnea of 4 days’ duration. Turbinate destruction is evident bilaterally. Notice the soft tissue densities throughout the right nasal cavity and in the ventral portion of the left nasal cavity.
Mucopurulent discharge from the right naris was the only abnormality detected during physical examination. The cat was anesthetized for CT and rhinoscopy with collection of biopsy specimens. The CT revealed bilateral destruction of turbinates and mild bony lysis. Soft tissue densities were evident throughout the right nasal cavity and frontal sinus. The cribriform plate appeared to be intact. Rhinoscopy did not reveal any gross abnormalities. Retrograde and antegrade biopsies of the nasal passages were performed, followed by flushing of the nasal passages with sterile saline solution. Histologic examination of the nasal biopsy specimens identified chronic active rhinitis. Serologic testing with an ELISA to detect antibodies against Aspergillus spp yielded negative results. The cat was discharged to the owner, who was instructed to administer clindamycin to empirically treat and prevent secondary bacterial infection.

Five months later, the cat was returned to our facility because of persistent discharge from the right naris. A second CT examination was performed. The CT findings were unchanged, compared with the findings for the first CT examination. A flush of the nasal passages was performed. Thick brown material was removed during the flushing and submitted for cytologic examination. The cytologic examination revealed abundant necrotic cellular debris and branching fungal hyphae. Fungal culture resulted in growth of unspecified Aspergillus spp. The cat's clinical signs improved after the nasal flush, and the owner declined further treatment at that time.

Three months later, the cat was admitted because of recurrence of nasal discharge. No abnormalities were evident in results of a CBC and serum biochemistry analysis. Thoracic radiography was repeated, but no abnormalities were detected. A third CT examination was performed to assess progression of disease and integrity of the cribriform plate. The cribriform plate was intact. The degree of turbinate destruction was unchanged, and there was less soft tissue density in the right frontal sinus, compared with results of previous CT examinations. At this time, the owner elected to proceed with antifungal treatment. Intranasal infusion of clotrimazole was performed as described previously. The cat had an uncomplicated recovery after the procedure, and it did not require a feeding tube. Four years after the clotrimazole infusion, the cat was doing well and had no clinical signs of nasal disease.

**Discussion**

Aspergillus spp are saprophytic fungi that are ubiquitous in the environment and have been isolated from the coat of healthy cats and dogs. Aspergillus spp are considered opportunistic pathogens that induce systemic disease in immunocompromised humans and other animals. In cats with systemic aspergillosis, 70% have underlying diseases, such as feline panleukopenia, FeLV, feline infectious peritonitis, and endoparasites. In dogs, systemic aspergillosis is most often reported in German Shepherd Dogs that have been suggested to have a hereditary immune defect. The most commonly infiltrated organs in cats and dogs with systemic aspergillosis include the lungs, kidneys, intestines, liver, spleen, lymph nodes, and CNS. In contrast to systemic infection, nasal infection is considered a local disease that can develop in immunocompetent animals.

Nasal aspergillosis is a rare disease in cats. Other than the 2 cats reported here, there are only 13 previously described cases of aspergillosis or penicilliosis in cats affecting the nasal cavity, sinuses, or orbits. Those 13 cats ranged from 1 to 12 years of age. The cats reported here were 13 and 11 years old. Seven of the 13 previously reported cats were Persians or Himalayans, which suggests a possible breed predisposition. The cats reported here were a Siamese and a domestic shorthair cat.

As stated previously, incompetence of the immune system is not believed to be required for nasal infection with aspergillosis. Only 1 of the 13 previously reported cats with sinonasal or orbital aspergillosis had a confirmed immunosuppressive condition (ie, FeLV). In the cats reported here, one had diabetes mellitus and was receiving corticosteroids, either of which could have contributed to an immunosuppressive state; the other cat appeared healthy.

In the 2 cats described here, signs of nasal disease were evident with no ocular abnormalities. In the 13 previously reported cats, 6 exclusively had nasal signs, 3 exclusively had orbital signs, and 4 had both nasal and orbital signs. Signs of orbital involvement included exophthalmos, epiphora, resistance to retropulsion, anterior uveitis, and prolapse of the nictitating membrane.

It can be difficult to diagnose nasal aspergillosis because no single test result is deemed definitive. In dogs, 2 or more criteria must be fulfilled to reach a diagnosis. These criteria include characteristic imaging findings, direct observation of fungal plaques, identification of organisms via cytologic or histologic examinations, positive results for fungal culture, and positive results for serologic tests.

Turbinate destruction, thickened nasal mucosa, hyperostosis, and soft tissue densities or masses are the most common lesions detected during imaging in dogs with nasal aspergillosis. These findings have high sensitivity but low specificity because they can also be found in dogs and cats with neoplastic and even inflammatory rhinitis. Nasal imaging via CT of the cats described here revealed marked turbinate destruction and soft tissue densities in both cats and thickened nasal mucosa in 1 cat. One of the cats had visible fungal plaques detected during rhinoscopy. This appears to be a common finding in cats with nasal aspergillosis because 11 of the previously reported 13 cats had grossly visible white, gray, or yellow plaques or granulomas detected during rhinoscopy, surgery, or necropsy.

The sensitivity of histologic examination of nasal specimens for the diagnosis of aspergillosis is variable. In 1 study of dogs with nasal aspergillosis, fungal hyphae were detected in only 17 of 41 (41%) dogs from which nasal biopsy specimens were obtained. In another study in dogs, investigators reported a higher detection rate, with fungal elements visible in 17 of 21 (81%) dogs. In the cats reported here, identification of fungal elements via histologic examination was inconsistent. In the first cat, examination revealed that 3 of 5 biopsy specimens had fungal elements visible white, gray, or yellow plaques or granulomas detected during rhinoscopy, surgery, or necropsy.
rhinitis, whereas the other 2 were interpreted as chronic active rhinitis. In the second cat, histologic and cytologic findings from samples obtained on 2 separate dates were consistent with fungal rhinitis, whereas examination of biopsy specimens collected between those 2 dates failed to reveal fungal elements. In the previous reports of cats with nasal aspergillosis, detection of fungal rhinitis via histologic examination was similarly complicated. Of 6 cats that had specimens obtained via rhinoscopy, 3 were identified with fungal rhinitis, whereas the other 3 were interpreted to have lymphocytic-plasmacytic or mixed-cell rhinitis. In these latter cats, additional biopsy specimens obtained from the frontal sinus (via trephination or rhinoscopy) revealed *Aspergillus* infection.\(^3,25\) The low sensitivity of histologic examination may be attributable to the distribution of the fungi; *Aspergillus* spp are found primarily on the mucosal surface without invasion into deeper tissues.\(^26\) Cytologic examination may yield more favorable results; one study\(^26\) in dogs with nasal aspergillosis revealed that cytologic review of samples obtained via brushing of lesions or squash preparation of biopsy specimens had an excellent sensitivity of 93% to 100%.

Fungal culture is another diagnostic test that has high specificity but poor sensitivity in dogs with nasal aspergillosis.\(^36,37,39\) The most common species cultured in dogs is *Aspergillus fumigatus*.\(^3,37\) Both of the cats reported here had fungal cultures that yielded *Aspergillus* spp (one yielded growth of *A. niger*, and the other yielded growth of an unspecified *Aspergillus* spp). Of the previously reported cats, fungal cultures were performed for 8, 5 of which yielded *Aspergillus* organisms (1 *A. niger*, 1 *A. fumigatus*, 1 *Aspergillus udaquaeae*, and 2 unspecified *Aspergillus* spp).\(^3,21-27\)

Serologic testing for *Aspergillus* spp may also have a high rate of false-negative results. In dogs, sensitivity and specificity of serologic testing are reported to be 67% to 76.5% and 98% to 100%, respectively, for agar-gel double immunodiffusion and 88.2% and 96.8%, respectively, for ELISA.\(^37,40\) Seven of the previously reported cats were serologically tested for *Aspergillus* spp, but only 4 had positive results.\(^3,21-23,27\) Both of the cats reported here had negative results for serologic tests to detect *Aspergillus* spp. We can infer on the basis of this information that the sensitivity for serologic testing in cats is low. However, the specificity for serologic testing to detect *Aspergillus* spp has not been established in cats.

Information regarding effective treatment of cats with nasal aspergillosis is extremely limited. There is no standard of care, and prognosis is considered poor.\(^5,18,21-25\) Of the 13 previously reported cats, 6 had resolution of clinical signs at follow-up examinations. However, no 2 cats had resolution of clinical signs after receiving the same treatment. The successful treatments included nasal lavage, rhinotomy with application of iodoform paste, oral administration of itraconazole, oral administration of fluconazole, oral administration of posaconazole, and intranasal infusion of clotrimazole.\(^5,21,23,24\) The majority (8/13) of the cats were initially treated with itraconazole; 3 cats developed adverse effects (hepatotoxicosis), another 3 cats failed to respond or relapsed, 1 cat was lost to follow-up monitoring, and only 1 cat had long-term resolution of clinical signs.\(^3,24-27\) Solely on the basis of these reports, it is difficult to make a recommendation for the treatment of cats with nasal aspergillosis.

In contrast to treatments in cats, treatments for dogs with nasal aspergillosis have been clearly described. The treatment of choice is intranasal infusion of clotrimazole or enilconazole. The antifungal agent is infused via nonsurgically placed catheters. The procedure is performed in anesthetized dogs, with a treatment time of 1 hour. Prognosis is good, with resolution of clinical signs in 47% to 65% of dogs after 1 treatment and 80% to 90% of dogs after additional treatments.\(^41-42\) Rhinoscopic debridement is recommended prior to infusion of an antifungal agent.\(^41-44\) In 1 study,\(^43\) investigators found that a similarly high success rate can be achieved with deposition of clotrimazole cream into the frontal sinus via trephination. This procedure allows a shorter anesthetic period with a potentially prolonged period of antifungal contact. Lower success rates (60% to 70%) are seen with orally administered systemic treatments such as itraconazole or fluconazole.\(^42\)

The 2 cats in this report, combined with 1 cat from a previous report,\(^1\) offer evidence that nasal aspergillosis can resolve in cats after intranasal infusion of clotrimazole via a technique similar to that described for dogs. The 3 cats each received a 1-hour nasal infusion of clotrimazole administered via nonsurgically inserted catheters. All of the cats had resolution of clinical signs after a single treatment. No adverse effects were reported as a result of this treatment. It is important to mention that 2 additional cats in the previous reports\(^43,45\) were treated with an infusion of clotrimazole. One had no response to this treatment. The other cat responded but was euthanized several months later because of development of new clinical signs (dysphagia and anorexia); it was not determined whether the signs were attributable to recurrence of fungal disease. Both of those cats were unusual in that they had substantial fungal disease of the orbit, and the clotrimazole was administered via trephination of the frontal sinus. In contrast, the 3 cats that responded successfully to clotrimazole had only sinonasal disease and received the drug via intranasal infusion.

Clotrimazole infusion is not without disadvantages. It requires that an animal be anesthetized for a minimum of 1 hour. The clotrimazole solution contains isopropanol and propylene glycol, which are irritants that can cause pharyngeal edema and inflammation. Enilconazole infusion should be investigated as an alternative to clotrimazole for the treatment of cats with nasal aspergillosis. Topically administered enilconazole (1% or 2%) is less systemically toxic and locally irritant than clotrimazole and may have sporocidal activity in the vapor phase at distances of up to 1 cm.\(^41,42,44\)

Topical infusion of clotrimazole is generally contraindicated in animals in which the cribiform plate is damaged.\(^2,3\) And, as mentioned previously, clotrimazole infusion may not be successful in animals with aspergillosis that involves the orbit.\(^24,25\) Finally, it has been suggested that debridement of fungal plaques is critical prior to treatment of nasal aspergillosis in dogs. Debridement may be difficult in cats because of the small size of their nasal passages. None of the 3 cats that have been treated successfully with clotrimazole underwent

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debridement prior to intranasal treatment, and it is un-
known whether debridement would improve the effi-
cacy of treatment in this species. Although information for dogs has been incorpor-
ated into the discussion, the authors recognize that there are anatomic and physiologic differences between these species; thus, the canine data cannot be directly applied to cats. The current recommendation for the treatment of nasal aspergillosis in dogs via intranasal infusion of clotrimazole or enilconazole was reached after years of extensive research. In the present report, the procedure for safe intranasal administration of clotrima-
zione in 2 cats is described. Results suggest that intranasal infusion of clotrimazole is an effective treatment without concurrent or subsequent oral administration of antifun-
gal agents, but the conclusion is greatly limited by the small number of cases. Future prospective studies are needed to determine whether intranasal administration of clotrimazole should be recommended as the standard of care in cats with nasal aspergillosis.

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Selected abstract for JAVMA readers from the American Journal of Veterinary Research

Plasma amino acid and whole blood taurine concentrations in cats eating commercially prepared diets
Cailin R. Heinze et al

Objective—to establish comprehensive reference ranges for plasma amino acid and whole blood taurine concentrations in healthy adult cats eating commercial diets and to evaluate the relationships of age, sex, body weight, body condition score (BCS), dietary protein concentration, and dietary ingredients with plasma amino acid and whole blood taurine concentrations.

Animals—120 healthy adult cats.

Procedures—Blood samples and a complete health and diet history were obtained for each cat, and reference intervals for plasma amino acid and whole blood taurine concentrations were determined. Results were analyzed for associations of age, breed, sex, body weight, BCS, use of heparin, sample hemolysis and lipemia, dietary protein concentrations, and dietary ingredients with amino acid concentrations.

Results—95% reference intervals were determined for plasma amino acid and whole blood taurine concentrations. A significant difference in amino acid concentrations on the basis of sex was apparent for multiple amino acids. There was no clear relationship between age, BCS, body weight, and dietary protein concentration and amino acid concentrations. Differences in amino acid concentrations were detected for various dietary ingredients, but the relationships were difficult to interpret.

Conclusions and Clinical Relevance—This study provided data on plasma amino acid and whole blood taurine concentrations for a large population of adult cats eating commercial diets. Plasma amino acid and whole blood taurine concentrations were not affected by age, BCS, or body weight but were affected by sex and neuter status. Dietary protein concentration and dietary ingredients were not directly associated with plasma amino acid or whole blood taurine concentrations. (Am J Vet Res 2009;70:1374–1382)