Long-Term Outcomes in Dogs With Sinonasal Aspergillosis Treated With Intranasal Infusions of Enilconazole

Long-term outcomes (mean 38±17 months) were evaluated in 27 dogs with sinonasal aspergillosis after successful medical treatment using intranasal infusions of 1% or 2% enilconazole (1%, n=15; 2%, n=12). Long-term outcomes with both treatment protocols were good, with half of the dogs being asymptomatic throughout the follow-up period. The remaining dogs showed mild clinical signs compatible with chronic rhinitis/sinusitis. These clinical signs were interpreted as chronic lymphoplasmacytic rhinitis/sinusitis and episodes of bacterial rather than fungal infection. Three dogs had confirmed reinfection or relapse 2 to 36 months after clinical resolution. **J Am Anim Hosp Assoc 2007;43:33-38.**

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Introduction

Canine nasal aspergillosis is a relatively common disease affecting between 12% and 34% of dogs presented for chronic sinonasal signs.[1,2] *Aspergillus* (*A.*) *fumigatus* is the most common etiological agent, but other subspecies such as *A. niger* may also be involved.[3] Nasal aspergillosis can cause severe destruction of the nasal mucosa and underlying turbinates.[4] Clinical signs include chronic, profuse, mucopurulent to hemorrhagic nasal discharge; nasal pain; increased airflow through the nostril on the affected side; and ulceration, hyperkeratosis, and discoloration of the rhinarium.[4] Severely affected dogs may also show signs of systemic illness, such as depression and anorexia.[4]

Systemic treatment with oral antimycotic agents such as thiabendazole, ketoconazole, itraconazole, or fluconazole is costly and requires prolonged administration.[4] Efficacy has been reported as 40% to 50% for thiabendazole and ketoconazole and 60% to 70% for fluconazole and itraconazole.[5-8] Topical treatment with clotrimazole or enilconazole has been associated with higher success rates and has improved the management of this previously intractable condition.[9,10] Surgical implantation of infusion tubes and irrigation of the nasal cavities and frontal sinuses twice daily for 7 to 14 days with topical antifungal agents have been the standard treatment for many years.[9] More recently it has been shown that minimally invasive techniques using nonsurgically placed tubes provide better distribution of the drugs into the sinuses, are equally effective, and are associated with fewer complications.[10-12]

Several studies have evaluated different noninvasive infusion techniques for their ability to establish a cure; however, only a few studies have evaluated the long-term outcomes in dogs after confirmed resolution of the infection.[10,13-17] The aims of the present study were to evaluate and compare the long-term outcomes in dogs with sinonasal aspergillosis after successful medical treatment using topical administration of enilconazole by two noninvasive infusion techniques.

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Materials and Methods

Medical records of dogs presented for investigation of chronic nasal disease from January 1998 through May 2003 were reviewed. Dogs were included in the study if the following criteria were fulfilled: availability of a complete medical record; confirmed diagnosis of sinonasal aspergillosis based on clinical signs, radiography, or computed tomography (CT); direct visualization of fungal plaques on rhinoscopy; histopathology and fungal culture[a] of nasal biopsies compatible with aspergillosis; confirmed resolution of infection after medical treatment by follow-up rhinoscopy, culture, and histopathology; and availability of telephone follow-up information. Twenty-seven dogs met the inclusion criteria. Twenty-one of these dogs had participated in a clinical study comparing the effectiveness of two noninvasive infusion techniques using enilconazole.[16] Of the 27 dogs, 15 were treated with 1% enilconazole emulsion[b] infused via blindly placed intranasal catheters (Group A). Twelve dogs were treated with a 2% emulsion of enilconazole infused through catheters endoscopically placed into the frontal sinus (Group B). In all cases, bilateral treatment was performed regardless of whether the disease was unilateral or bilateral. Age, breed, sex, and weight of each dog were recorded, as well as the side(s) affected.

The two treatment protocols are described in detail elsewhere.[16] Briefly, after meticulous debridement of the fungal plaques and placement of the intranasal or intrasinusoidal catheters, the dogs were positioned in dorsal recumbency with the hard palate parallel to the table. A Foley catheter[c] (20-French, 30-cc balloon) was introduced per os (PO) into the nasopharynx. The balloon was inflated and placed at the junction of the hard and soft palate. The pharynx was packed with pre-counted laparotomy sponges to absorb infusate that might leak around the balloon. The nostrils were occluded with Foley catheters[c] (12-French, 5-cc balloon). Syringe pumps were used to infuse a total of 120 to 150 mL of the enilconazole emulsion into both nasal cavities over a 1-hour period. During this time, the dog's head was rotated longitudinally left and right for 3 minutes every 15 minutes to allow better distribution of the infusate. At the end of the treatment, the head of the dog was tilted downward, and all catheters and sponges were removed to allow the infusate to drain from the nostrils. At induction of the anesthesia, antimicrobial treatment was started with cefazolin[d] (20 mg/kg intravenously) and was continued with cephalexin[e] (20 mg/kg PO *q* 8 hours) for 5 days. The dogs were reevaluated rhinoscopically every 3 to 4 weeks, and the intranasal infusions were repeated for up to three times until all infection had resolved. A cure was established if there was resolution of clinical signs, absence of fungal plaques on follow-up rhinoscopy, and a negative fungal culture (n=24). In three cases, resolution of sinonasal aspergillosis was based only on the absence of clinical signs, because the owners declined reevaluation and repeated rhinoscopy.

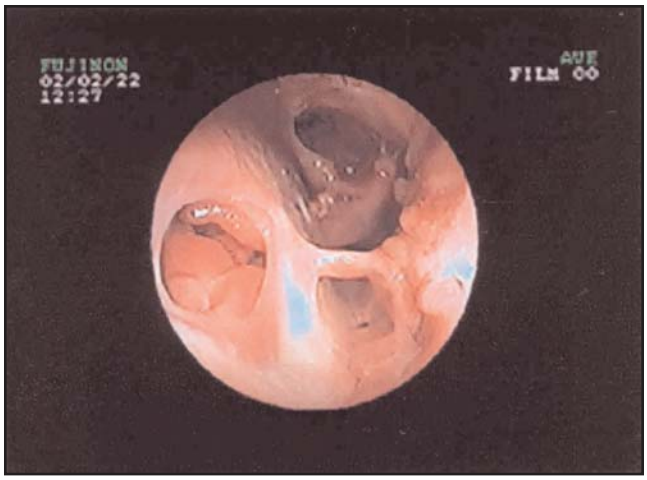
The owners of the 27 dogs were contacted via telephone in February and March of 2004 and asked to complete a questionnaire about the long-term treatment outcome. The questionnaire included questions about whether the animal was still alive and, if not, the cause of its death or euthanasia; the general condition of the animal; and the presence or absence of clinical signs of nasal disease. If clinical signs were present, the owners were asked to describe their severity and frequency. Nasal discharge was classified as serous if described as watery; mucoid if described as white; and mucopurulent if described as yellow or green. Other clinical signs such as sneezing, stertor, or abnormalities of the nares (e.g., hyperkeratosis, discoloration) were also recorded. The owners were also asked to report additional treatments. After completion of the survey, the dogs were classified as having very mild (i.e., occasional sneezing, serous discharge), mild (i.e., serous to mild mucopurulent discharge, sneezing <4 times per day, mild changes to nares), moderate (i.e., mucopurulent discharge, sneezing >4 times per day, stertor, moderate abnormalities of nares), or severe (i.e., severe mucopurulent discharge, sneezing >10 times per day, stertor, severe abnormalities of nares, nasal pain, affection of general condition) clinical signs. Frequencies of clinical signs were compared in both treatment groups by means of chi-square tests. A P value <0.05 was considered statistically significant.

Results

Among the 27 dogs, 14 breeds were represented. The most frequent breeds were the golden retriever (n=7), Labrador retriever (n=3), German shepherd dog (n=3), rottweiler (n=2), and bull terrier (n=2). Other breeds having one affected dog were the Afghan hound, dachshund, Groenendael, Pyrenean sheepdog, basset hound, Newfoundland, Hovawart, Great Dane, and German shorthaired pointer. One dog was a mixed-breed dog. Eleven dogs were females (four spayed), and 16 were intact males. Age at the time of the diagnosis ranged from 1 to 10 years (median 5.0±2.7 years, mean 5.1±2.5 years). Age at the time of final follow-up ranged from 1.7 to 14 years (median 8.8±3.2 years, mean 8.5±3.2 years). Body weight ranged between 5.7 and 53 kg (median 31.5±11.4 kg, mean 33.2±11.4 kg). Seventeen dogs had left unilateral disease, four dogs had right unilateral disease, and six dogs had bilateral disease at the time of initial presentation. Fourteen dogs required one course of therapy (n=7 Group A; n=7 Group B), eight dogs had two courses (n=4 Group A; n=4 Group B), and five dogs required three courses (n=4 Group A; n=1 Group B) of topical treatments to effect a cure. The figure is a rhinoscopic image of the nasal cavity of a dog at the time a cure was established.

Follow-up periods ranged from 5 to 64 months (median 39.0±17.3 months; mean 38.6±17.3 months). Of the 27 dogs, 20 were still alive in February/March of 2004. Five dogs were euthanized for unrelated diseases, namely, chronic diarrhea (n=1), congestive heart failure (n=1), chronic dermatitis (n=1), mammary tumors (n=1), and a bone tumor (n=1). Two dogs died suddenly without a diagnosis. None of the dogs died or were euthanized for nasal-related disorders.

One dog in Group A and two dogs in Group B had rhinoscopically confirmed recurrence of sinonasal



Figure—Rhinoscopic image (angled dorsally 30˚) of the right frontal sinus of a 3-year-old, female Labrador retriever, obtained 3 weeks after treatment of sinonasal aspergillosis with 2% enilconazole infusion administered via endoscopically placed tubes.

aspergillosis at 23 months, 36 months, and 2 months respectively. The three dogs were asymptomatic until relapse. When relapse was confirmed, the first dog was treated with ketoconazolef (10 mg/kg PO *q* 12 hours for 6 weeks) and local thiamphenicol/acetylcysteine nasal drops[g] (*q* 6 hours for 10 days) with good response, and this dog remained asymptomatic for another 28 months. In the second dog, sinonasal flush using 2% enilconazole was repeated, and itraconazole[h] (5 mg/kg PO *q* 12 hours) was given for several weeks. The dog improved, but mild clinical signs persisted. On relapse, the third dog was treated with several weeks of itraconazole (5 mg/kg PO *q* 12 hours), but moderate nasal signs persisted.

Eight of 15 dogs in Group A and five of 12 dogs in Group B (total of 13 dogs) were asymptomatic throughout the whole follow-up period. The remaining 14 dogs (n=7 Group A; n=7 Group B) had persistent clinical signs of nasal disease. The Table summarizes the nasal signs that occurred within the different treatment groups. Nasal signs were episodic in five dogs (n=3 Group A; n=2 Group B) and continuous in nine dogs (n=4 Group A; n=5 Group B). The frequency of clinical signs was not significantly different between groups. Nasal signs were very mild in three dogs, mild in seven dogs, and moderate in four dogs. None of the dogs had severe signs. There was no statistical difference in the severity of clinical signs between the two treatment groups. No changes in the general condition of the dogs occurred in either group.

The most common clinical signs in symptomatic dogs were mucopurulent nasal discharge and sneezing. Three dogs in Group B sneezed a few times in the morning, and after they had expelled some plugs of mucopurulent material, no sneezing or nasal discharge occurred throughout the rest of the day.

Stertor was a relatively uncommon sign, but abnormalities of the nares were reported in more than half of the symptomatic dogs. Only a few dogs (n=6) were considered by the owners to need any treatment. Treatments were prescribed by the referring veterinarians in most cases. One dog in Group A received methylprednisolone[i] (0.5 mg/kg PO *q* 24 hours) continuously to control nasal signs. Two other dogs in Group A were treated one to three times with oral ketoconazole or itraconazole and saline nasal drops. Both dogs appeared to respond and were only very mildly and episodically symptomatic. One dog in Group A and two dogs in Group B occasionally received topical treatment with thiamphenicol/acetylcysteine nasal drops, but they still had mild nasal clinical signs.

Discussion

Although not compared with a standard hospital-based control population, the signalments of the dogs included in this study were similar to previous reports in that canine nasal aspergillosis mainly affected young to middle-aged dogs of mesocephalic or dolichocephalic breeds.[4] Initial comparison of the two topical treatment protocols described in this report suggested that the latter technique required fewer infusions to reach a cure.[16] The results of the current study, however, did not reveal any statistically significant differences in the long-term outcomes between the two treatment groups.

In two studies that evaluated the long-term outcomes in dogs after topical treatment with either clotrimazole or enilconazole, a single episode of nasal discharge occurred in seven of 57 and in five of 31 dogs, respectively.[10,17] No permanent nasal signs were reported. The follow-up periods in these two studies ranged from five to 61 months.[10,17] In contrast to these findings, about half of the dogs in the present study showed mild nasal signs after successful treatment of nasal aspergillosis. The general condition was not affected, however. The persistent nasal signs noted in dogs of this report might be explained by several factors. First, nasal aspergillosis is associated with extensive and irreversible turbinate destruction, which may have predisposed these dogs to bacterial rhinitis and sinusitis.[10,16] In this study, six dogs received treatments for persistent signs despite resolution of the nasal aspergillosis. Three responded to topical thiamphenicol and acetylcysteine nasal drops, which may have indicated the presence of bacterial rhinitis. No nasal cultures were performed in these dogs, however. Second, rhinosinusitis from aspergillosis is characterized histopathologically by a predominantly lymphoplasmacytic infiltrate of the nasal mucosa.[18] Lymphoplasmacytic rhinitis may persist even after resolution of the fungal infection and can cause severe turbinate destruction.[19] Given the suspected immune-mediated origin of lymphoplasmacytic rhinitis, oral corticosteroids have often been used as treatments.[19,21] During the follow-up period, one of the dogs in the present study was treated with anti-inflammatory doses of methylprednisolone, and the apparent response to treatment may have been consistent with lymphoplasmacytic rhinitis.

A third possible explanation for the persistence of mild nasal signs was either ongoing sinonasal aspergillosis (i.e.,

Table

Frequency and Nature of Persistent Clinical Signs in Dogs With Nasal Aspergillosis Treated With Enilconazole Infusions

	All Dogs	Treatment Groups	
Clinical Signs	**No. of Dogs (%)**	**Group A* No. of Dogs**	**Group B† No. of Dogs**
No nasal signs	13 (48)	8	5
Nasal signs present	14 (52)	7	7
Frequency			
Episodic	5 (19)	3	2
Permanent	9 (33)	4	5
Severity‡			
Very mild	3 (11)	1	2
Mild	7 (26)	4	3
Moderate	4 (15)	2	2
Nasal discharge	13 (48)		
Serous	3 (11)	1	2
Mucous	3 (11)	1	2
Mucopurulent	7 (26)	5	2
Sneezing	11 (41)		
Occasionally	6 (22)	4	2
Regularly (<4 x/d)	3 (11)	0	3
Frequently (>4 x/d)	2 (7)	1	1
Nares	10 (37)		
Dryness	6 (22)	4	2
Hyperkeratosis	1 (4)	1	0
Discoloration	3 (11)	1	2
Stertor	3 (11)	1	2
Recurrent disease	3 (11)	1	2
Total dogs	27 (100)	15	12

* Group A=Frontal sinus infusion of 1% enilconazole via blindly placed intranasal tubes
† Group B=Frontal sinus infusion of 2% enilconazole via endoscopically placed intrasinus tubes
‡ See text for definitions

persistent infection) or reinfection (i.e., recurrence). It seemed unlikely that the presence of nasal signs in half of the dogs of this study was secondary to persistent nasal aspergillosis, because there was no evidence of fungal infection at the time a cure was established. Recurrence was unlikely given that none of the dogs showed signs of systemic illness or nasal pain, and clinical signs were nonprogressive and mild in nature. However, the absence of fungal rhinitis was not confirmed by rhinoscopic or microbiological examination at the time of the owner survey. An attenuated form of nasal aspergillosis or a form of allergic fungal sinusitis, as described in humans, may have been present in these dogs.[24]

Acute, severe clinical signs of nasal disease recurred in three dogs, and a second episode of sinonasal aspergillosis was confirmed rhinoscopically. The three dogs were asymptomatic until relapse. Relapse could be explained by either persistence of fungal agents or reinfection. Persistence of

fungi seemed possible in the case that recurred 2 months after treatment, but it appeared unlikely in the two cases that were diagnosed 36 months and 23 months later. Whether or not fungi can persist within sinus mucus without causing disease is unclear at present.[22] Persistence of fungi within the nasal mucosa may have been possible, despite the absence of fungal hyphae on histopathological and microbiological examination of tissue biopsies at the time a cure was established. Current evidence suggests, however, that canine sinonasal aspergillosis is not associated with significant tissue invasion of either mucosa or bone, so the disease in dogs may be similar to chronic, erosive, noninvasive fungal sinusitis of humans.[18,22]

Another possible explanation for a second episode of sinonasal aspergillosis was reinfection. Dogs with sinonasal aspergillosis are usually considered immunocompetent and show an active Th-1-dominated immunological response, which prevents generalized dissemination of the fungal infection.[18] However, some dogs with nasal aspergillosis have been reported to be immunosuppressed.[23] *Aspergillus fumigatus* may prevent transformation of B- and T-lymphocytes and inhibit mucociliary function of the nasal epithelial cells in humans *in vitro*, so it remains unclear whether immunosuppression is a primary abnormality or is caused by the disease.[24,25] Given that one dog was asymptomatic for 36 months, it is possible that other dogs in this study may relapse in the future.

This study had several limitations. Follow-up information was obtained by telephone conversations with the owners of the dogs, and the owners may have over- or underreported clinical signs. In most symptomatic dogs, clinical signs were not severe enough to justify rhinoscopic reexamination; however, from a scientific point of view, rhinoscopy would have been necessary to rule out ongoing fungal disease and to determine the exact cause of the nasal signs.

Conclusion

Long-term outcomes in 27 dogs after treatment of sinonasal aspergillosis with topical infusions of 1% and 2% enilconazole were considered good in that 13 of the dogs became asymptomatic. Symptomatic dogs had generally mild signs that only occasionally required treatment. Recurrence of sinonasal aspergillosis was rare (n=3) and may have occurred from persistence of infection or reinfection.

[a] Sabouraud Chloramphenicol Gentamicin Agar; Becton-Dickinson Microbiology Systems, Meylan, France
[b] Imaverol; Janssen-Cilag SA, Beerse, Belgium
[c] Foley silicone-coated latex urinary catheter; Mentor, Porgès S.A.S., France
[d] Cefacidal; Bristol-Myers Squibb Belgium SA, Brussels, Belgium
[e] Keforal; Eli Lilly Benelux SA, Brussels, Belgium
[f] Nizoral; Jansen-Cilag, Antwerp, Belgium
[g] Fluimucil nasal drops; Zambon, Brussels, Belgium
[h] Sporanox; Jansen-Cilag, Antwerp, Belgium
[i] Medrol; Upjohn, Puurs, Belgium

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