

Multi-centre assessment of mycotic rhinosinusitis in dogs: a retrospective study of initial treatment success (1998 to 2008)

OBJECTIVES: To retrospectively review the first treatment response of dogs with mycotic rhinosinusitis to commonly utilised treatment techniques.

METHODS: Medical records of dogs treated for mycotic rhinosinusitis were obtained retrospectively via a manual review of the clinical databases of six veterinary referral centres for the period of January 1998 to June 2008, and first treatment outcome was evaluated. Historical and clinicopathological findings were also reviewed to evaluate their impact on treatment success or failure.

RESULTS: There was no significant difference in first treatment outcome between treatment groups ($P=0.21$). When all topical treatments were considered together ($n=85$), 39 dogs (45.8%) had a successful first treatment. Initial treatment success was associated with a younger age (56.3 versus 75.8 months; $P=0.02$) and was 2.7 times more likely in dogs with unilateral disease, although this was not significant ($P=0.07$). Adjunctive therapy with systemic antifungal agents was associated with treatment failure ($P\leq 0.01$). Fifty-nine dogs (69.4%) responded successfully following multiple treatments.

CLINICAL SIGNIFICANCE: Treatment of mycotic rhinosinusitis remains challenging, and multiple treatments are frequently required for adequate treatment. Reasons for first treatment failure are likely multifactorial in origin, making it difficult to predict those dogs that are likely to have a superior prognosis, regardless of the treatment type used.

M. SHARMAN, A. PAUL, D. DAVIES*, B. MACKAY†, G. SWINNEY‡, V. BARRS§, A. ARTEAGA§, I. D. ROBERTSON AND C. MANSFIELD

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Department of Veterinary Clinical Sciences, Murdoch University, South Street, Murdoch, Western Australia 6150, Australia

*Adelaide Veterinary Specialist and Referral Centre, 102 Magill Road, Norwood, South Australia 5067, Australia

†Veterinary Specialist Services, Hometown, Cnr Lexington and Logan Road, Underwood, Queensland 4119, Australia

‡Veterinary Specialist Centre, 14-20 Dehli Road, North Ryde, New South Wales 2113, Australia

§University of Sydney Veterinary Teaching Hospital, University of Sydney, 65 Parramatta Road, Camperdown, New South Wales 2050, Australia

Dr G. Swinney's current address is the University of Sydney Veterinary Teaching Hospital, University of Sydney, 65 Parramatta Road, Camperdown, New South Wales 2050, Australia

INTRODUCTION

Mycotic rhinosinusitis is an uncommon cause of chronic nasal disease in dogs with a frequency of seven to 34% reported (Sharp and others 1991b, Latge 1999, Tasker and others 1999, Peeters and Clercx 2007, Meler and others 2008). Environmental dissemination of ubiquitous soil saprophytes such as *Aspergillus* spp. via air currents allows exposure of human beings and animals through inhalation. These fungal elements are usually eliminated by a range of host defence mechanisms and disease does not occur (Latge 1999). It is unclear why only small numbers of dogs develop mycotic rhinosinusitis. Facial trauma, nasal foreign bodies and dental disease have been implicated in some cases (Sharp and others 1991b, Peeters and Clercx 2007),

Table 1. First and overall treatment success rates in previously published studies of mycotic rhinosinusitis

Treatment type	Number of dogs	First treatment success (%)	Overall treatment success (%)
Indwelling catheters – enilconazole			
Sullivan and Sharp (1986)			
Enilconazole (10mg/kg) + ketoconazole (10mg/kg)	5	100	NA
Sharp (1993)			
Enilconazole (10mg/kg) + ketoconazole (10mg/kg)	7*	85.7	100
Enilconazole (10mg/kg) only	24	50 (83) [†]	NA
Temporary trephination – 1% clotrimazole			
Matthews and others (1998)	37	62	83.7
Friend and others (2002)	23	76.9*	86.9
Non-invasive catheter soaks – 1% clotrimazole			
Matthews and others (1998)	23	69.5	91.3
Non-invasive catheter soaks – 1% enilconazole			
Zonderland and others (2002)	19	47.3	89.5
Saunders and others (2003)	36	55.5	94.4
Schuller and Clercx (2007)	15	46.6	93.3
Endoscopically inserted catheters – 2% enilconazole			
Zonderland and others (2002)	7	85.7	100
Schuller and Clercx (2007)	12	58.3	83.3
Depot clotrimazole therapy			
Sissener and others (2006)	14	86	86

*Includes five dogs from Sullivan and Sharp (1986)

[†]Twelve dogs (50%) were considered cured based upon re-examination which included radiologic examination and rhinoscopy. A further eight dogs (33%) were possibly cured based upon the absence of clinical signs (n=7) or the absence of disease at post-mortem examination following death from unrelated disease (n=1). Two dogs failed treatment and did not receive further therapy

*A total of 23 dogs were included in the study. For group A dogs (n=13), 10 had a successful first treatment (76.9%) and 12 dogs were successful following multiple treatments. As group B dogs routinely received a second treatment regardless of whether disease was determined to be present upon reassessment, first treatment outcome in this group could not be assessed. Twenty dogs (86.9%) were reported as having successful outcomes when all treatments were considered

and localised immunodeficiency has also been proposed to be a predisposing factor, with no evidence of systemic immunodeficiency existing (Peeters and Clercx 2007, Day 2009).

Marked destruction of the nasal turbinates occurs and disease may extend into the periorbital structures and cranial vault causing structural deformity and neurological signs. Turbinate destruction occurs in the absence of tissue invasion as a result of host inflammatory response in conjunction with dermonecrotic fungal toxins (Peeters and others 2005, Peeters and Clercx 2007, Day 2009). *Aspergillus fumigatus* is the most frequently isolated organism, although a variety of species including *Aspergillus niger*, *Aspergillus nidulans* and *Aspergillus flavus* have also been implicated (Peeters and Clercx 2007). *Penicillium* spp. and other fungal organisms such as *Scedosporium* are rare causes (Harvey 1984, Cabañes and others 1998, Caro-Vadillo and others 2005, Coleman and Robson 2005, Paul and others 2009).

Treatment of canine mycotic rhinosinusitis remains challenging. Oral administration of antifungal agents such as thiabendazole and ketoconazole results in cure rates of approximately 50% (Harvey and O'Brien 1983, Harvey 1984, Sharp

and Sullivan 1989), whereas sole treatment with itraconazole and fluconazole has reported cure rates of 70% (Sharp and others 1991a, Peeters and Clercx 2007). Topical therapy is considered to provide better clinical outcome via direct effects on fungal plaques (Peeters and others 2005). A number of topical treatment techniques have been described and are reported to be associated with greater success rates than oral treatment, but multiple treatments are often required to achieve cures with these methodologies (Table 1) (Sharp and Sullivan 1986, Sharp and others 1993, Mathews and others 1998, Friend and others 2002, Zonderland and others 2002, Saunders and others 2003, Sissener and others 2006, Schuller and Clercx 2007).

This study retrospectively reviewed the treatment response of mycotic rhinosinusitis to commonly utilised techniques in multiple veterinary referral centres.

MATERIALS AND METHODS

Medical records of dogs treated for mycotic rhinosinusitis were obtained via a manual search of clinical databases from six veterinary referral centres [Murdoch University Veterinary Hospital (MUVH), Veterinary

Specialist Services (VSS), Veterinary Specialist Centre (VSC), Queensland Veterinary Specialists (QVS), University of Sydney Veterinary Centre (UVSC) and Adelaide Veterinary Specialist and Referral Centre (AVSRC)] for the time period January 1998 to June 2008.

Dogs with complete medical records and a confirmed diagnosis of mycotic rhinosinusitis that was treated with topical or systemic antifungal therapy were included. Mycotic rhinosinusitis was considered confirmed when more than two ancillary diagnostic tests were positive (diagnostic imaging, rhinoscopy, mycology, serology, cytology or histopathology).

The following information was recorded for each case: age, gender, breed, body-weight, clinical signs, duration of clinical signs, whether unilateral or bilateral nasal disease was present, diagnostic imaging findings, rhinoscopy findings, histopathological findings, fungal culture results, serology results, presence of a nasal foreign body, frontal sinus involvement, type of treatment administered, duration of therapy and treatment outcome.

Treatment success was defined as complete resolution of nasal disease as determined by physical examination and clinical history for at least a 6-month

period following treatment. Any dog that had recurrent signs of nasal disease in which fungal organisms were not identified and therapy for lymphoplasmacytic rhinitis or secondary bacterial rhinitis was successful were classified as treatment successes. Treatment failure was defined as any dog with continued signs of nasal disease where mycotic rhinosinusitis was confirmed or could not be ruled out.

Data were analysed using the Statistical Package for Social Scientists (SPSS Version 16.0, Inc. Chicago, IL, USA). Chi-squared tests for independence or Fisher's exact tests were used to determine the significance of first treatment success and categorical variables. Odds ratios and their 95% confidence intervals were also calculated. For continuous variables the homogeneity of variances was initially assessed. For those with significantly different variances, a Mann-Whitney U test was conducted, and where variances were similar an analysis of variance was calculated and means compared. Significance was defined as *P* less than or equal to 0.05.

RESULTS

In all, 116 dogs were initially identified in which diagnosis of mycotic rhinosinusitis and/or treatment with antifungal agents had been administered and these were reviewed. Thirty-one dogs were excluded from the analysis as they did not match the inclusion criteria. The remaining 85 cases were included in the assessment of treatment outcome. The most common breeds were Rottweilers (*n*=10), golden retrievers (*n*=7), Australian cattle dogs (*n*=6), Staffordshire bull terriers (*n*=6), miniature schnauzers (*n*=5), bull terriers (*n*=4), German shepherd dogs (*n*=4), Malamutes (*n*=4), Labradors (*n*=3) and Australian kelpies (*n*=2). Twenty-two were crossbred dogs and 12 other breeds were represented, all of which were mesocephalic or dolicocephalic breeds. Twenty-six (30.6%) dogs were neutered females and 59 (69.4%) were males (13 in total). The mean age at presentation was 5.57 years (median 4.5 years; range 1 to 14 years). Mean bodyweight was 29.2 kg (range 6.6 to 70.4 kg). Twenty-one cases were included from VSS, 23 from VSC,

16 from MUVH, 10 from UVSC, 8 from QVS and 7 from AVSRC.

Treatment

Ten dogs were treated with a short 5-minute clotrimazole soak (1% clotrimazole in polyethylene glycol) followed by administration of clotrimazole cream (clotrimazole 1% cream; Canesten®, Bayer) as a depot therapy into the trephined frontal sinuses (Sissener and others 2006). Seven (70%) of these dogs were considered cured after first treatment.

Forty-five dogs were treated with a 1-hour non-invasive soak, via tubes inserted into the external nares, with clotrimazole (clotrimazole 1% solution as Canesten®, Bayer; clotrimazole 1% solution compounded in polyethylene glycol), as described by Matthews (Mathews and others 1998, Zonderland and others 2002). Eighteen (40.0%) of these dogs were considered cured after their first treatment.

Frontal sinus trephination for temporary catheter placement and a 1-hour soak was performed in 24 dogs given clotrimazole (clotrimazole 1% solution as Canesten®, Bayer; clotrimazole 1% solution compounded in polyethylene glycol) and in two dogs given enilconazole (Imaverol®; Austrichter) (Mathews and others 1998, Friend and others 2002). Thirteen (50%) of these dogs were considered treatment successes after the first treatment.

There was no statistical difference in first treatment outcome between these treatment groups (*P*=0.21) (Table 2). Four dogs received modified treatment

protocols or other topical treatments, and outcome was not compared due to low numbers. Dogs requiring multiple treatments to obtain a cure received a range of topical treatments often different from the initial protocol.

When all topical treatment cases were considered together (*n*=85), 39 (45.8%) were successful after the first treatment and 59 (69.4%) were successful following multiple treatments (Table 2). The number of topical treatments given ranged from 1 to 6 (mean 1.5; median 1). Eleven (12.9%) dogs were euthanased or died due to failure of treatment or due to progressive neurological signs. Fifteen (17.6%) dogs that failed first treatment were lost to follow-up following multiple treatments, or based upon their available follow-up were categorised as treatment failures.

Analysis of age, gender and bodyweight data indicated that treatment success was associated with a younger age (56.3 versus 75.8 months; *P*=0.02), with no difference in the distribution of gender (females=28.2% failure group (13 of 46) versus 33.3% success group (13 of 38); *P*=0.352) or bodyweight (28.9 kg failures versus 29 kg successes; *P*=0.96) of dogs between treatment outcome groups.

Successful first treatment was 2.7 times more likely in dogs with unilateral nasal discharge compared with those with bilateral discharge, but this was not significant (*P*=0.07). Although prior duration of clinical signs was longer in the failure group, this also was not significant (failures: median=15.3 weeks, mean=8 weeks;

Table 2. First treatment response of mycotic rhinosinusitis to commonly utilised techniques in multiple veterinary referral centres (1998 to 2008)

Treatment type	Number of dogs	Referral centre case breakdown	First treatment success (%)
Depot clotrimazole therapy	10	AVSARC=4; MUVH=1; UVSC=5	60
Non-invasive catheter soaks – 1% clotrimazole	45	AVSARC=3; MUVH=7; QVS=6; UVSC=2; VSC=18; VSS=9	40
Temporary trephination – 1% clotrimazole (<i>n</i> =24) enilconazole (<i>n</i> =2)	26	MUVH=8; QVS=1; VSC=5; VSS=12	50
All topical treatments combined	85		43.5
Depot therapy (10)			
Non-invasive soak (45)			
Temporary trephination (26)			
Indwelling catheters (2)			
Rhinotomy and soak (1)			
Topical nasal cream (1)			

successes: median=8.85 weeks, mean=6 weeks; $P=0.11$).

Adjunctive treatment with oral systemic antifungal agents was associated with treatment failure [41.3% (19 of 46) of treatment failures received systemic antifungals *versus* 10.2% (4 of 39) successes; $P\leq 0.01$] and was implemented at the time of diagnosis in 18 of 23 cases. Dogs in the treatment failure group received a longer course of adjunctive systemic antifungal therapy than those in the treatment success group [median=19.5 weeks (mean=8.5) failures *versus* median=4.87 weeks (mean=4) successes]. One dog in the treatment failure group was still receiving fluconazole for *Curvularia* spp. infection at the time of data collection, 13 months after diagnosis.

Treatment outcome was not associated with frontal sinus involvement ($P=0.76$), the presence of a nasal foreign body ($P=0.37$), results of serological testing ($P=0.59$), fungal culture ($P=0.62$) or histopathological demonstration of fungal elements ($P=0.92$). Although considered important for treatment outcome, the extent of debridement of fungal disease in each individual case was not able to be assessed retrospectively.

DISCUSSION

Young to middle-aged, mesocephalic and dolicocephalic dogs were diagnosed with mycotic rhinosinusitis in this study, similar to that which has been reported previously in other studies (Zonderland and others 2002, De Lorenzi and others 2006, Sissener and others 2006). A distinct male predisposition has also been reported, and this was observed in the overall population of dogs diagnosed in this study (69.6%) but cannot be conclusively proven due to the different hospital populations studied (Sharp and others 1991b, Zonderland and others 2002, Johnson and others 2006).

Although previous studies have reported encouraging first treatment success in 69 to 86% of dogs, the reports often only include small case numbers (Mathews and others 1998, Zonderland and others 2002, Sissener and others 2006). No significant difference in first treatment outcome between treatment methodologies

was observed in the current study. Two or more treatments were required in 54.2% of cases, and two dogs required six treatments before a cure was obtained. Treatment success following multiple treatments in the current study was 69.4%, less than previously reported (Sharp and Sullivan 1986, Sharp and others 1993, Mathews and others 1998, Friend and others 2002, Zonderland and others 2002, Saunders and others 2003, Sissener and others 2006, Schuller and Clercx 2007). Given the multi-institutional design of the current report, the authors feel this is likely a more realistic indication of clinical outcome. This may be an overestimation of treatment success given that recurrence beyond 6 months has been recorded (Schuller and Clercx 2007). Conversely treatment success could also be underestimated in this study as some dogs with persistent nasal signs may have actually been free of fungal infection. The authors would suggest, however, that the severity and persistence of the signs reported in these cases would constitute treatment failure in the opinion of the owner regardless of whether the presence or absence of fungal infection was confirmed.

The lack of treatment response at first attempt is likely to be multifactorial in origin, making it difficult to predict which dogs are likely to have a superior prognosis regardless of the treatment type chosen. Despite comparable treatment protocols, the rate of first treatment success varies in previous reports (Table 1). Minor modification of the technique alone between these studies is less likely to contribute significantly, than the experience of the treating clinician and the degree to which fungal plaques are debrided may (Mathews and others 1998, Friend and others 2002, Zonderland and others 2002, Schuller and Clercx 2007).

In the current study, failure was significantly associated with age, but was not associated with a longer duration of clinical signs. Intuitively it would be reasonable to assume that dogs failing treatment had more extensive disease. Although the retrospective nature limits conclusive assessment duration of disease, the presence of large amounts of fungal plaques and frontal sinus involvement failed to have a statistical impact on treatment success or failure.

However, bilateral changes identified on rhinoscopy and prescription of adjunctive systemic antifungal therapy, both of which might suggest clinically worse disease, were more frequently recorded in the failure group. Objective stratification of disease severity was not possible because not all dogs had rhinoscopic or computed tomography (CT) images available for review. CT severity scoring may not have been helpful in assessing response, as studies assessing the value of CT in predicting outcome have produced conflicting results (Mathews and others 1998, Saunders and others 2003).

Outcome may also be influenced by the distribution and retention of antifungal agents used. It has been suggested that more effective penetration of affected areas may be achieved by physical debridement of fungal plaques to reduce extent of disease (Mathews and Sharp 2006). Variation in ability to perform this rhinoscopically and the degree to which debridement is performed is a very likely explanation for the differences observed. The retrospective nature of the current report makes it difficult to assess the degree to which debridement of fungal plaques occurred in each of the current cases, but this remains a potential factor. There was no difference in outcome between institutions, making specific techniques less likely contributors to overall success rates. In one study, however, meticulous removal of fungal plaques did not significantly improve outcome, regardless of the treatment type utilised (Schuller and Clercx 2007). Distribution and retention of antifungal agents may also be influenced by the viscosity of the drug and this has previously been demonstrated in experimental models (Richardson and Mathews 1995, Mathews and others 2009). Whether longer retention times are required for improved efficacy is not clear although reasonable distribution of agents is likely to be imperative for successful outcome. Two described techniques of deposition of clotrimazole cream and administration of 2% enilconazole via endoscopically inserted catheters originally have reported high first treatment success rates, albeit in small numbers of dogs, compared with less viscous agents, but this rate of success was not perpetuated in this study (Zonderland and others 2002, Sissener and others 2006).

Where local penetration of fungal plaques is adequate, antifungal drug resistance could also contribute to treatment failure, but this has not been documented apart from the poor activity of fluconazole against *Aspergillus* spp. (Hector 2005). Although *in vitro* susceptibility testing can easily be performed for fungal isolates, controversy remains as to what this means *in vivo* (Hector 2005, Wiebe and Karriker 2005). Pharmacokinetic studies of systemically administered antifungal agents are lacking in domestic animals, however, given that mycotic rhinosinusitis is considered a non-invasive disease for which topical drug administration is preferred, this is likely to be irrelevant (Peeters and others 2005). Newer antifungal agents such as posaconazole or voriconazole may prove to be more efficacious; however, both are administered orally and have not been evaluated in this disease to date.

Although every effort was made to include only dogs that satisfied sufficient criteria for the diagnosis of mycotic rhinosinusitis, it is not possible to completely rule out the probability that some of the dogs for which there was treatment failure were misdiagnosed or had underlying or pre-existing disease.

In conclusion, mycotic rhinosinusitis is an uncommon cause of chronic nasal disease that is usually the result of infection with *Aspergillus* spp. Although previous studies may report promising first treatment results, the inclusion of low case numbers is likely to be a confounding factor. First and overall treatment successes in this study were less than previously reported, particularly when compared with controlled prospective studies and over half of the dogs in this study required more than one treatment in order to achieve a cure. Reasons for treatment failure are likely numerous and multifactorial. Although difficult to prove definitively, duration and severity of disease, inadequate debridement of fungal plaques and poor

distribution of antifungal agents are likely to be major factors.

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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