

Effectiveness of an Otic Product Containing Miconazole, Polymyxin B and Prednisolone in the Treatment of Canine Otitis Externa: Multi-site Field Trial in the US and Canada

Marc Engelen, DVM¹

Manuelle De Bock, DVM, PhD^{1,3}

Jonathan Hare, DVM, PhD²

Lieve Goossens, MSc¹

¹Janssen Animal Health, Turnhoutseweg 30, B-2340 Beerse, Belgium

²Kingfisher International Inc., 67 Edward Street, Stouffville, Ontario, Canada L4A 1A4

³Corresponding author: mdebock@its.jnj.com

KEY WORDS: Dog, otitis externa, miconazole, polymyxin B, prednisolone

ABSTRACT

To evaluate the effectiveness of an otic suspension containing polymyxin B, miconazole, and prednisolone (Surolan[®] otic suspension) in the treatment of canine otitis externa, clinical cases were recruited from veterinary practices at four geographic sites in the United States and Canada, and randomly assigned to either the test product or a positive control product containing gentamicin, clotrimazole, and betamethasone. Before and after treatment, cases were scored on four clinical parameters pain/discomfort, erythema, swelling, and exudates. Ear swabs were taken for bacterial and yeast culture and susceptibility testing. The vast majority of all otitis externa cases in this study exhibited clinical improvement of the inflammatory signs in the ear, with 97% of cases given the test product and 95% of the cases treated with the positive control product improving clinically. Non-

inferiority of the test product compared to the positive control product in the treatment of canine otitis externa was shown for each of the four clinical parameters and for the total clinical score. The most frequently cultured pathogenic organisms were Gram-positives, with 56% of dogs harboring isolates identified as *Staphylococcus* spp, 17% *Streptococcus* spp, 44% infections with the yeast *M. pachydermatis* and 12.5 % cases infected with the Gram-negative *Pseudomonas* spp. Susceptibility testing demonstrated a high susceptibility of all these microorganisms to the active constituents of the test product. Results show that the combination of polymyxin, miconazole, and prednisolone is a good choice for first line treatment of otitis externa in dogs.

INTRODUCTION

Otitis externa is characterized by acute or chronic inflammation of the epithelium of the external auditory ear canal, and is a common cause of visits to the veterinary clinic.^{1,2} Affected dogs typically present with swelling and erythema of the epithelial tissue of

the ear canal, increased discharge from the ceruminous glands in the ear, head shaking and behavior suggesting otic pain and pruritus.^{1,3} Otitis externa may result from numerous causes; in most chronic cases, more than one cause is present. Primary causes of otitis externa include parasite infections, foreign bodies, neoplasia, hypersensitivity diseases, disorders of keratinisation, glandular diseases, and autoimmune diseases.^{1,2,4} Some dogs may be predisposed to otitis externa if they have abnormally small or restrictive ear canals, pendulous ears, excessive moisture in the ear, or suffer from trauma to the ear.⁵ Bacteria and yeasts are rarely primary causes, and are usually regarded as important perpetuating factors. *Staphylococcus pseudintermedius* (formerly known as *S. intermedius*⁶), *Pseudomonas aeruginosa*, *Proteus* spp, *Escherichia coli*, and *Klebsiella* spp are the most commonly isolated secondary pathogens. *Malassezia pachydermatis* is the most common yeast that contributes to otitis externa as a perpetuating factor.⁷ A diagnosis is easily made from the history and the physical examination. Cytologic examination and/or culture are valuable in determining which infectious agents, if any, are present. Therapy of otitis externa depends on identifying and controlling the predisposing and primary diseases whenever possible. In addition, cleaning the ear canals, applying topical therapies, and administering systemic medications may be necessary for the effective elimination and control of primary causes and perpetuating factors.

The test product used in this study contains miconazole, polymyxin B, and prednisolone. Miconazole is a synthetic imidazole derivative with a high antifungal activity and a strong antibacterial activity against Gram-positive bacteria such as *S. aureus*^{8,9} Miconazole has demonstrated in vitro and in vivo effectiveness in dogs against several species of yeast including *M. pachydermatis* isolated from cases of canine otitis externa.^{8,10-12}

Polymyxin B is a broad-spectrum polypeptide antibiotic. Its spectrum of activity

consists predominantly of Gram-negative bacilli such as *E. coli*¹³ *Salmonella*, *Shigella*, and especially *P. aeruginosa*.^{14,15} It has a strong bactericidal effect, and development of resistance to it is rare. In human medicine, it is used in topical formulations because there is no systemic resorption.^{16,17} Furthermore, there is little or no systemic use in veterinary medicine, which reduces the chance of development of resistant strains. Therefore, polymyxin B is considered a first-line antibiotic in topical ear treatments.¹⁸ A unique feature of the combination of polymyxin B and miconazole is the synergistic effect that was demonstrated against *E. coli*, *S. aureus*, *P. aeruginosa* and *M. Pachydermatis*.^{13,19}

Prednisolone is a glucocorticoid with strong anti-inflammatory activity and minimal effects on carbohydrate and mineral metabolism. For many years, prednisolone has been widely used in both human and veterinary medicine for systemic and topical use. Within the test product, its anti-inflammatory and antipruriginous properties contribute to a rapid symptomatic relief and support a rapid clinical healing by decreasing edema formation and capillary dilatation.²⁰

The objective of this study was to confirm the effectiveness and safety of the test product compared to a positive control product when used under field conditions in North America at proposed label directions in the treatment of canine bacterial and/or fungal canine otitis externa.

MATERIALS AND METHODS

Investigational animals

Clinical canine cases of otitis externa were recruited from companion animal veterinary practices at four geographical areas in the United States and Canada. Forty-nine investigators from 31 animal clinics participated in the trial. Dogs in good general health were eligible for study participation regardless of breed, gender, or age if presented with defined clinical signs of unilateral or bilateral otitis externa and confirmed bacterial and/or yeast infection. In order to assess eligibility, a detailed history and clinical

examination was conducted. The investigator scored the severity of four signs of ear inflammation: pain/discomfort, erythema, swelling, and quantity of exudates of the ear. The following scoring system was used: 0 = normal, 1 = mild, 2 = moderate, and 3 = marked. Study inclusion and exclusion criteria are provided in Table 1. Prior to the first treatment, ear cleaning to remove waxy material, exudates and other debris from the patient's ear pinnae and the ear canals was performed in the veterinary clinic. Warmed saline was used as cleaning solution. No other cleaning product was permitted. Sedation of the animal in order to facilitate the cleaning procedure and minimize discomfort to the animal was permitted if needed.

Treatments

This multi-site field trial was conducted under the guidelines of Good Clinical Practice (VICH GL9) and was a randomized, double blinded study with a positive control. Dogs were randomly assigned to either the test product containing 23 mg miconazole nitrate, 0.5293 mg polymyxin B sulphate and 5 mg prednisolone acetate per ml (Surolan® otic suspension, Janssen Animal Health, Belgium) or to the positive control product containing 10 mg clotrimazole, 3 mg gentamicin sulphate and 1 mg betamethasone valerate per gram (Otomax®

Ointment, Schering-Plough Animal Health, USA). Dogs randomized in the test product group were treated twice daily for 7 days with five drops of the test product. Dogs randomized in the positive control group were treated twice daily for 7 days with four (dogs < 13.6 kg) or eight (dogs ≥ 13.6 kg) drops. The qualified hospital technician administered the initial treatment. Thereafter, all other treatments were applied by the animal owner. The investigator was therefore fully blinded to the treatment each dog had received.

Administration of any systemic or topical antibiotics and/or anti-inflammatory drug other than the test or positive control product during the study was not permitted.

Evaluation criteria

Prior to the start of treatment, and at 2 to 4 days after the end of treatment, the investigator conducted a physical examination of the dog, whereby the severity of the ear inflammation was scored (scoring system as described above) and any clinical abnormality in the animal was observed. This ear examination was performed prior to any swab collection or ear cleaning procedure. In case of bilateral otitis externa, the right ear was chosen, unless the total clinical score did not add up to 5, in which case the left ear was chosen. The investigator also assessed the

Table 1. Study inclusion and exclusion criteria

<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Unilateral or bilateral clinical otitis externa • Minimum overall clinical score of 5, assessed from four clinical parameters • Confirmed bacterial and/or yeast infection from an ear swab
<p>Exclusion criteria</p> <ul style="list-style-type: none"> • Treated with local or systemic anti-microbial and/or anti-inflammatory therapy in the last 30 days • Treated with a depo form of corticosteroids in the last 4 months • Displaying evidence of head tilt (inner/middle ear infection) • Verified ruptured tympanic membrane • Concurrent infection with <i>Otodectes cynotis</i> • Poor general health or high anesthetic risk • Pregnant

gross hearing of the dog. A high frequency audible dog whistle was used. The evaluation was performed prior to any physical manipulation or examination of the dog. The dog's hearing was categorized as normal, reduced, or absent. Any adverse events of the test and positive control product were monitored by the investigator in cooperation with the animal owner.

On the initial visit, the ear under investigation was swabbed and the specimen examined microscopically in the clinic for ear mites. A second swab was taken for laboratory analyses, including bacterial and yeast culture, identification, and antimicrobial susceptibility. Samples were cultured to identify bacteria to the level of species and yeast to the level of genus. Yeast identification was based on direct morphological characterization and by culture. Colony counts were made for each organism identified.

Identified pathogens, as per the assessment of the laboratory, were susceptibility tested. Bacterial cultures were tested in a susceptibility panel including polymyxin B sulphate, gentamicin sulphate and miconazole nitrate. Yeast cultures were tested for susceptibility to miconazole nitrate. Bacterial susceptibility to drugs was tested with the agar-disk-diffusion test also known as the Kirby-Bauer test.²¹ For miconazole, susceptibility of the organisms to the antimicrobial was tested with the minimum inhibitory concentration (MIC) in a dilution test. The test was performed by inoculating the wells of a plate with the bacterial or yeast culture and dilutions of the antimicrobial arranged across the rows. The MIC was directly determined by observing the exact concentration required to inhibit bacterial or yeast growth. Although synergistic effects of the combination miconazole - polymyxin B against *E. coli*, *S. aureus*, *P. aeruginosa* and *M. pachydermatis* have been described in literature,^{13,19} susceptibility to the combination miconazole - polymyxin B was not evaluated in this study.

Statistical analysis

All analyses were performed using the Sta-

tistical Analysis System for Personal Computers (SAS) Version 9.1.3 (SAS Institute, Cary, NC, USA). The experimental unit for the effectiveness evaluation was one ear of an individual dog and for the safety evaluation one individual dog.

Two outcomes of the four clinical parameters and the overall clinical parameter were analyzed: the binary outcome "improvement vs no-improvement" and the continuous outcome "change in clinical score after treatment." Improvement was defined as a decrease of at least one level on the scale between the pre- and post-treatment period. Otherwise, it was classified as no-improvement. For the binary outcome, a generalized linear model with the logit link was fitted (treatment and *Staphylococcus* spp infection included as fixed effects and clinic and treatment-by-clinic as random effects) to perform the non-inferiority testing. Non-inferiority was concluded if the lower limit of the one-sided 95 % confidence interval for the difference in chance of improvement (test product – positive control product) was no more negative than -10 %. For the continuous outcome, a multivariate random effect linear model was fitted which includes treatment and *Staphylococcus* spp infection as fixed effects and clinic and treatment-by-clinic as random effects. Each confirmed pathogen from each individual case was categorized into one of the following multi-levels variables: test product-sensitive, test product-resistant, positive control-sensitive, or positive control-resistant. Descriptive analysis was conducted to determine the distribution of the data.

RESULTS

Three hundred and thirty-seven (337) clinical cases were enrolled in the study and initiated on treatment. Elimination of cases due to violation of inclusion/exclusion criteria, failure of the microbial growth requirement, or other protocol violations, resulted in 176 cases (91 test product and 85 positive controls) strictly complying to the protocol and, therefore, considered valid for the effectiveness analyses. Three hundred and twenty-

two (322) cases remained for the safety evaluation. Table 2 lists descriptive data of the 91 dogs treated with the test product and the 85 dogs treated with the positive control product with regard to sex, age, and weight. An overview of the microorganisms isolated prior to treatment is shown in Table 3.

The vast majority of all otitis externa cases in this study exhibited clinical improvement of the inflammatory symptoms in the ear, with 97 % of the cases given the test product and 95 % of the cases treated with the positive control product improving clinically (Table 4).

For the overall clinical parameter, which considered all four clinical parameters (pain/discomfort, erythema, swelling, and exudates), and for three out of the four clinical parameters separately (pain/discomfort, erythema, and exudates), the mean improvement proportion for the test product was greater than that for the positive control product. The lower one-sided 95% confidence interval of the improvement proportion difference (test product – positive control product) was not less negative than –10 % for all four clinical parameters and the overall clinical parameter. The test product was thus demonstrated to be non-inferior to the positive control product. Moreover, the test product was found to be superior to the positive control product for the param-

eters pain/discomfort, erythema, exudates, and the overall clinical parameter.

Regarding the degree of clinical improvement, on average, the overall clinical score (pain, erythema, swelling, and exudates; each parameter graded 0 – 3 in severity) had decreased 5.6 points for the test product and 5.5 points for the positive control product at the time of the final visit compared to the initial visit. There was no statistically significant difference between the treatment groups. In more than 80 % of the animals, the total clinical score decreased by 4 points or more.

Ear swab results (Table 3) often demonstrated more than one pathogenic organism growing in each specimen. The most commonly isolated species were *S. pseudintermedius* and *M. pachydermatis*. Table 3 also shows the number of responsive cases (figures between brackets). From these data, it is clear that the test product is highly effective against all of the isolated organisms, including *Staphylococcus* spp, *Streptococcus* spp, *Malassezia* spp, and *Pseudomonas* spp.

Bacterial and *Malassezia* isolates were tested for resistance/sensitivity to polymyxin B, miconazole, and gentamicin. The results of the susceptibility testing (Table 5) demonstrated a high susceptibility of *M. pachydermatis*, *S. pseudintermedius*,

Table 2. Descriptive Data for the Baseline Covariates by Treatment Group

Covariates	Test product % (# dogs)	Positive control % (# dogs)
Sex		
Female	49.5 % (45)	38.8 % (33)
Male	50.5 % (46)	61.2 % (52)
Age group		
≤ 2 years	30.8 % (28)	31.8 % (27)
> 2 years to < 9 years	49.5 % (45)	45.9 % (39)
≥ 9 years	19.7 % (18)	22.3 % (19)
Weight (kg)		
Mean	26.0	24.9
Standard deviation	15.0	14.1

Table 3. Frequency of isolation of potential otitis externa pathogens

Organism	Frequency of pre-treatment isolation (# of responsive cases)	
	Test product (n=91)	Positive control (n=85)
<i>S. pseudintermedius</i> †	47 (45*)	46 (44)
<i>M. pachydermatis</i>	40 (38*)	38 (36)
γ-non-hemolytic streptococci	14 (13)	5 (5)
<i>P. aeruginosa</i>	9 (9)	10 (9)
<i>Pseudomonas</i> spp.	2 (2)	1 (1)
Yeast (unidentified)	6 (6)	7 (7)
<i>Proteus mirabilis</i>	6 (6)	5 (4)
β-hemolytic streptococci	6 (5)	0 (0)
α-hemolytic streptococci	4 (4)	1 (1)
Other staphylococci	1 (1)	5 (5)

† formerly *S. intermedius*

*denotes a pathogenic otitis externa species for which there were a minimum of 10 evaluable, responsive cases with pre-treatment isolation and identification down to the genus level (required by CVM-FDA for inclusion of a species in the product claim).

Table 4. For each clinical parameter and the overall clinical parameter, frequency distribution of improvement vs no-improvement and mean difference in improvement probability together with the lower limit of a one-sided 95 % confidence interval by treatment group

Clinical parameter	Treatment group	No adjusting for confounders				Adjusting for confounders	
		Improvement		No-improvement		Improvement	
		No.	%	No.	%	Mean	95 % LL*
Pain/Discomfort	Test product	84	94.4	5	5.6	94.4	-0.04
	Positive control	77	91.7	7	8.3	91.7	
Swelling	Test product	76	87.4	11	12.6	89.1	-0.10
	Positive control	72	90.0	8	10.0	90.5	
Erythema	Test product	82	90.1	9	9.9	91.2	-0.04
	Positive control	73	85.9	12	14.1	86.1	
Exudate	Test product	75	82.4	16	17.6	83.1	-0.09
	Positive control	70	82.3	15	17.7	82.1	
Overall	Test product	88	<u>96.7</u>	3	3.3	<u>96.7</u>	-0.03
	Positive control	81	<u>95.3</u>	4	4.7	<u>95.3</u>	

* Lower confidence limit

Table 5. Frequency distribution of the resistance and sensitivity to the test product and the positive control for pathogens cultured from each dog by treatment group

Bacterial/yeast species infection and sensitivity results ^a	Test product ^b	Positive control ^c
<i>Staphylococcus</i> spp. positive dog		
No. of dogs with pathogen sensitive to treatment given	39 (100.0 %)	47 (97.9 %)
No. of dogs with pathogen resistant to treatment given	0 (0.0 %)	1 (2.1 %)
<i>Pseudomonas</i> spp. positive dog		
No. of dogs with pathogen sensitive to treatment given	10 (90.9 %)	7 (70.0 %)
No. of dogs with pathogen resistant to treatment given	1 (9.1 %)	3 (30.0 %)
<i>Escherichia coli</i> positive dog		
No. of dogs with pathogen sensitive to treatment given	0 (0.0 %)	1 (100.0 %)
No. of dogs with pathogen resistant to treatment given	1 (100.0 %)	0 (0.0 %)
<i>Malassezia</i> positive dog		
No. of dogs with pathogen sensitive to treatment given	8 (100.0 %)	not tested
No. of dogs with pathogen resistant to treatment given	0 (0.0 %)	not tested
<i>Streptococcus</i> spp. positive dog		
No. of dogs with pathogen sensitive to treatment given	8 (88.9 %)	2 (40.0 %)
No. of dogs with pathogen resistant to treatment given	1 (11.1 %)	3 (60.0 %)

^aIf a dog's ear had more than one species of the same pathogen and if one pathogen was classified as resistant, the dog was classified as resistant regardless of the status of the other pathogen.

^bSensitive to test product = treatment with test product + sensitive to polymyxin B or miconazole; resistant to test product = treatment with test product + resistant to polymyxin B and miconazole

^cSensitive to positive control = treatment with positive control + sensitive to gentamicin; resistant to positive control = treatment with positive control + resistant to gentamicin.

and *P. aeruginosa* to the active constituents of the test product. No dogs harboured *Staphylococcus* isolates that were resistant to polymyxin B and miconazole or *Malassezia* isolates resistant to miconazole. Sixty (60%) percent of the dogs treated with the positive control product had *Streptococcus* isolates that were resistant to gentamicin, whereas only 11% of the dogs treated with the test product had *Streptococcus* isolates that were resistant to polymyxin B and miconazole. Thirty (30%) percent of the dogs treated with the positive control product harboured *Pseudomonas* isolates that were resistant to gentamicin, whereas only 9% of the dogs treated with the test product had *Pseudomonas* isolates that were resistant to polymyxin B and miconazole.

Few adverse events were reported in

either treatment group. In the test product group, adverse reactions were noted in five dogs. Two dogs experienced reduced hearing at the end of treatment; on follow-up one dog had normal hearing capacity while the other case was lost for follow-up. Residue build-up was reported in two dogs and pain upon drug application in another dog. In the group treated with the positive control product, adverse reactions were reported in eight dogs. Residue build-up was noted in one dog. Four dogs vomited during treatment, one dog showed red pustules on the pinna and head shaking was observed in another dog. One dog experienced reduced hearing at the final visit. At the follow-up enquiry, the dog was reported having reversed the hearing capacity to normal.

DISCUSSION

Canine patients with inflammation of the epithelium of the external ear canal are commonly seen in veterinary practice.¹ Most cases of otitis externa in dogs respond well to treatment with topical medication. Otic combination products contain antibiotic, anti-fungal, and anti-inflammatory components to relieve discomfort, lessen inflammation, and concurrently eliminate infection in the ear canal.

This extensive US field study with 337 enrolled clinical cases of canine otitis externa demonstrated clinical improvement after aural treatment with the test product in a cleaned ear and at the recommended dose applied twice daily for 7 consecutive days. The test product was shown to be effective in 97% of all clinical ear cases presented, with improvement independent of animal weight (breed), gender, age, and geographical location. The clinical improvement of the otitis externa was better for the test product compared to the positive control product in this study. The test product was non-inferior to the positive control product for all of the four clinical parameters (pain/discomfort, swelling, erythema, exudate) and the overall clinical parameter.

A previous clinical study conducted in Australia²² comparing the test product with an otic product containing neomycin, thioestrepton, nystatin, and triamcinolone and another otic product containing neomycin, monosulfiram, and betamethasone showed that the test product gave better results in the treatment of canine otitis externa than both positive control products. With the test product, a shorter course of treatment was required to achieve clinical recovery, and there was a lower rate of relapse in comparison with the other two products.

In this US study, ear swabs were collected from clinical cases independent of previous history of ear problems. The isolates exemplified the pathogen flora of dogs with otitis externa as seen in general practice.²³ Mixed infections were common. The most frequently

cultured pathogenic organisms were Gram-positives, with 56% of dogs harboring isolates identified as *Staphylococcus* spp and 17% *Streptococcus* spp. The second largest group of cases showed yeast infections with *M. pachydermatis* (44%). Otitis externa due to *Pseudomonas* infection represented a smaller proportion of the cases (12.5%). The infections seen represent a cross section of otitis externa seen in practice where treatment may be initiated without the backing of available microbiology culture diagnostics.

When administered in the ear canal, high concentrations of an ear medication are achieved locally at the infection site. The development of antimicrobial resistant bacteria is always a possibility when treating a bacterial infection site. There is also a potential to create resistant microorganisms at other sites of the body when commonly used topical drugs cross over the skin barrier and are absorbed into the blood stream leading to a low level of systemic concentrations. The polypeptide antibiotic polymyxin B is rarely used in parenteral application in humans and animals, but has its major usage topically with no systemic resorption.^{16,17} Many other antimicrobial agents commonly used both topically and systemically in companion animals, such as fluoroquinolones, may not constitute appropriate therapy for canine *Pseudomonas* infections as resistance is frequently encountered.²⁴ Gentamicin, fluoroquinolones, and other aminoglycosides with fast bactericidal action remain valuable agents in the combat of serious systemic infections in people.²⁵ Whenever possible, it is therefore preferable for the veterinarian to choose an effective drug for the canine patient less important in human medicine and not systemically used in veterinary medicine. The test product with polymyxin B may represent a lower risk for the development of clinically important antimicrobial resistance. A recently published study reported a bactericidal and fungicidal synergistic effect for the combination of polymyxin B and miconazole.¹⁹ The clear synergistic tendencies displayed by the two drug combination allows for the reduction of

the antibiotic concentrations and minimizes the probability of formation of resistances to these drugs.

The test product contains prednisolone, which is a mild glucocorticosteroid with a good safety profile. Stronger steroids used in other topical otitis products may induce adrenocortical suppression^{26,27} and other side effects.²⁸

Based on the excellent clinical response to the test product in this study, the majority of otitis externa cases presented in canine veterinary practice will successfully respond to the treatment with the test product, which was shown to be an effective and safe product.

Therefore, the combination of polymyxin, miconazole, and prednisolone is a good choice for first line treatment of otitis externa in dogs.

ACKNOWLEDGEMENTS

The authors are grateful to the American and Canadian veterinarians and their staff who participated in this extensive field trial.

REFERENCES

1. McKeever PJ and Torres S (1988) Otitis externa, part 1: The ear and predisposing factors to otitis externa. *Companion Animal Practice* 2:7.
2. Scott DW, Miller WH, Griffin CE (2000) External ear diseases. In: Scott D.W., Miller W.H., Griffin C.E., eds *Muller and Kirk's Small Animal Dermatology*. Philadelphia: WB Saunders Co, 1203-1232.
3. Gotthelf L (2000) Small animal ear diseases an illustrated guide. Philadelphia: WB Saunders Co, 45-119.
4. Hendricks A, Brooks H, Pocknell A, Bond R (2002) Ulcerative otitis externa responsive to immunosuppressive therapy in to dogs. *Journal of Small Animal practice* 43:350-354.
5. Harvey RG, Harari J, Delauche AJ (2001) Ethio-pathogenesis and classification of otitis externa. In: ear diseases of the dog and cat. Ames: Iowa State University Press, 81-122.
6. Devriese LA, Hermans K, Baele M, Haesebrouck F (2009) Staphylococcus pseudintermedius versus Staphylococcus intermedius. *Veterinary Microbiology* 133(1-2):206-207.
7. Grono LR (1980) Otitis externa In: Kirk R.W. (ed.) *Current Veterinary Therapy* VII. W.B. Saunders Co., Philadelphia.
8. Van Cutsem JM and Thienpont D (1972) Miconazole, a broad spectrum antimycotic agent with antibacterial activity. *Chemotherapy* 17:392-404.
9. Sud IJ and Feingold DS (1982) Action of antifungal imidazoles on Staphylococcus aureus. *Antimicrobial Agents and Chemotherapy* 22(3):470-474.
10. Uchida Y, Nakade T, Kitazawa K (1990) In vitro activity of five antifungal agents against Malassezia pachydermatis. *Japanese Journal of Veterinary Science* 52(4):851-853.
11. Bond R, Rose JF, Ellis JW, Lloyd DH (1995) Comparison of two shampoos for treatment of Malassezia pachydermatis-associated seborrhoeic dermatitis in Basset hounds. *Journal of Small Animal Practice* 36(3):99-104.
12. Guillot J and Bond R (1999) Malassezia pachydermatis: a review. *Medical Mycology* 37:295-306.
13. Cornelissen F and Van den Bossche H (1983) Synergism of the antimicrobial agents miconazole, bacitracin and polymyxin B. *Chemotherapy* 29:419-427.
14. Hariharan H, McPhee L, Heaney S, Bryenton J (1995) Antimicrobial drug susceptibility of clinical isolates of Pseudomonas aeruginosa. *Canadian Veterinary Journal* 36:166-167.
15. Hariharan H, Coles M, Poole D, Lund L, Page R (2006) Update on antimicrobial susceptibilities of bacterial isolates from canine and feline otitis externa. *Canadian Veterinary Journal* 47:253-255.
16. Bergan T and Fuglesang J (1982) Polymyxin antibiotics: chemical and pharmacokinetic properties. *Antibiotics & Chemotherapy* 31:119-144.
17. Evans ME, Feola DJ, Rapp RP (1999) Polymyxin B sulfate and colistin: old antibiotics for emerging multiresistant Gram-negative bacteria. *Annals of Pharmacotherapy* 33(9):960-967.
18. Griffin GE (2006) Topical ear treatments. Abstract taken from the proceedings of The North American Veterinary Conference, Orlando, FL, USA, 960-963.
19. Pietschmann S, Hoffmann K, Voget M, Pison U (2009) Synergistic effects of miconazole and polymyxin B on microbial pathogens. *Veterinary Research Communications* 33(6):489-505.
20. Bolinder A, Cameron K, Faubert L, Wilson J, Aramini J, Hare J (2006) In vivo efficacy study of the anti-inflammatory properties of Surolan® Suspension. *Canadian Journal of Veterinary Research* 70:234-236.
21. Bauer AW, Kirby WM, Sherris JC, Turck M (1966) Antibiotic susceptibility testing by a standardized single disk method. *American Journal of Clinical Pathology* 45(4):493-496.
22. Studdert VP and Hughes KLA (1991) Clinical trial of a topical preparation of miconazole, polymyxin and prednisolone in the treatment of otitis externa in dogs. *Australian Veterinary Journal* 58:192-195.
23. Oliveira LC, Leite CA, Brilhante RS, Carvalho CB (2008) Comparative study of the microbial profile from bilateral canine otitis externa. *Canadian Veterinary Journal* 49(8):785-788.
24. Rubin J, Walker RD, Blickestaff K, Bodeis-Jones S, Zhao S (2008) Antimicrobial resistance and genetic characterization of fluoroquinolone resistance of Pseudomonas aeruginosa isolated from canine infections. *Veterinary Microbiology* 131:164-172.
25. Martinez M, McDermott P, Walker R (2006) Phar-

- macology of the fluoroquinolones: a perspective for the use in domestic animals. *The Veterinary Journal* 172(1):10-28.
26. Reeder CJ, Griffin CE, Polissar NL, Neradilek B, Armstrong RD (2008) Comparative adrenocortical suppression in dogs with otitis externa following topical otic administration of four different glucocorticoid-containing medications. *Veterinary Therapeutics* 9(2):111-121.
27. Gubash R, Marsella R, Kunkle G (2004) Evaluation of adrenal function in small breed dogs receiving otic glucocorticoids. *Veterinary Dermatology* 15(6):363-368.
28. Ginel PJ, Garrido C, Lucena R (2007) Effects of otic betamethasone on intradermal testing in normal dogs. *Veterinary dermatology* 18(4):205-210.