Increased Resistance of *Staphylococcus pseudintermedius* to the Commonly Used Antibiotics in Canine Dermatology

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ABSTRACT

Increased resistance of *Staphylococcus spp*. is a growing problem in veterinary medicine. This study was performed to examine antimicrobial susceptibility of *Staphylococcus pseudintermedius* and other bacteria isolated from canine skin and ear infections over a 7 year period: 2000-2006. Eighty-six dogs which met predetermined inclusion criteria were examined. Bacterial isolates were examined for susceptibility to four commonly used antibiotics: cephalothin (first generation cephalosporin), amoxicillin-clavulanate, potentiated sulfonamide and enrofloxacin. The degree of susceptibility and the percentage of resistant strains of the bacteria to the antibiotics were compared between two periods: 2000-2002 and 2003-2006. Comparison between sample sites and association between susceptibility and signalment were examined. Resistance of *S. pseudintermedius* and *Proteus spp*. to cephalosporins and amoxicillin-clavulanate increased over the years and it was statistically significant for *S. pseudintermedius* (P=0.018). Susceptibility of *S. pseudintermedius* to cephalosporins and amoxicillin-clavulanate decreased over the years (P= 0.009). Susceptibility of *Proteus spp*. to amoxicillin-clavulanate and fluoroquinolones decreased as well (P=0.037, P=0.055 respectively). More skin than ear isolates of *S. pseudintermedius* and *Proteus* were resistant to cephalosporins and amoxicillin-clavulanate. More ear isolates of *Proteus* were resistant to potentiated sulfonamides (P= 0.039). All isolates of *Proteus* from mix breed dogs, but not from German shepherds were resistant to cephalosporins (P=0.032). This study showed an increased resistance and decreased susceptibility of two common bacteria found in dogs' skin and ear infections. These findings should encourage clinicians to submit samples for culture and susceptibility before commencing antibacterial therapy, so as to provide a more accurate therapeutic decision and avoid unnecessary antibiotic use.

Key words: dogs, bacteria, *Staphylococcus pseudintermedius*, antibiotics

INTRODUCTION

Bacterial skin and ear infections are very common in dogs. In most of the cases the proliferation of bacteria is secondary to another dermatological problem such as allergy, ectoparasites or systemic diseases such as hypothyroidism, hyperadrenocorticism and others. *Staphylococcus pseudintermedius* (formerly *S. intermedius*) is the most common microorganism isolated from skin and ear infections (1, 2). It is also the most common commensal isolate from healthy skin and ears (3, 4, 5). Treatment of canine pyoderma and otitis externa are usually empirical and are based on clinical experience. Samples are sent for culture and susceptibility tests usually when more than one type of microorganism is identified in a cytological examination, or when there is a failure in response to the commonly used antibiotics (1, 5). Bacteria can easily acquire and transfer multiple resistant genes which accelerate the emergence of antibacterial resistance. It occurs par-

ticularly in animal species and increases the risk of spread of resistance to other species, including humans (6).

The emerging problem of methicillin resistant *Staphylococcus aureus* (MRSA) also affects veterinary medicine and pet dogs have been found to be carriers (7). Furthermore, an increased resistance of some other types of *Staphylococci* has been found over the last few years (8). Although the occurrence of *S. pseudintermedius* in humans is uncommon, it is considered as a zoonotic microorganism and its resistance can cause a serious problem to dog owners (7). The increased resistance of *S. pseudintermedius* isolates from pyoderma and otitis externa to multiple antimicrobials has been previously reported (9). The aim of this study was to examine the antimicrobial susceptibility of *S. pseudintermedius* and other bacteria isolated from skin and ear infections in dogs in Israel, and to examine whether the susceptibility to commonly used antibiotics has changed over a period of 7 years. The different isolates from skin and ears were compared and the susceptibility to antimicrobials checked for their possible correlation with epidemiological parameters.

MATERIALS AND METHODS

Data collection

Medical records of dogs diagnosed with pyoderma and/or otitis externa that were examined at the dermatology department of the Veterinary Teaching Hospital, Koret School of Veterinary Medicine, The Hebrew University of Jerusalem (D-K-VMTH) between the years 2000-2006 were examined retrospectively. Inclusion criteria were the presence of data of bacterial culture in which *S. pseudintermedius* was isolated; signalment; the site from which the sample was obtained for bacteriology; results of susceptibility tests and results of cytological examinations. The absence of any of the above data was considered as exclusion criterion. Dogs that were treated with antibiotics for up to a week prior to obtaining the samples for culture and susceptibility were excluded. Furthermore where any other bacterial isolates were made their susceptibility test results were recorded and included in this study.

Samples collection

Samples from skin were obtained from intact pustules and/or epidermal collarettes in cases of superficial pyoderma of various etiologies using sterile cotton-tipped applicators. Samples from ears were collected from the distal horizontal canals from cases of otitis externa by using sterile cotton-tipped applicators.

Method of culture and susceptibility

Samples were inoculated directly onto sheep blood agar (Columbia agar base supplemented with 5% sheep blood), and onto MacConkey agar in order to detect any gram negative bacteria. Identification of the bacteria was carried out based on colony and microscopic morphology, plasma coagulase and biochemical characteristics by standard methods (10). Antimicrobial susceptibility to cephalothin, amoxicillin-clavulanate, potentiated sulfonamides and enrofloxacin was assessed by disk-diffusion, performed and interpreted according to CLSI standards (11). Quantitative results of susceptibility were assessed by the sensitivity index as described by Elad (12).

Statistical analysis

Data collected from the 7 year period were divided to two segments: 2000-2002 and 2003-2006, and resistance was compared between the 2 periods (the years were divided in such a way as to obtain equal number of cases in each group).

The following parameters were examined from the collected data:

- Association between the resistance of *S. pseudintermedius* to the signalment.
- Association between the resistance of *S. pseudintermedius* to the site from which samples were obtained.
- Association between cytology results and those of the culture
- Association between resistances of *S. pseudintermedius* to those of other bacteria to the same antibiotics.
- Association between the resistance of *S. pseudintermedius* to one antibiotic and its resistance to other antibiotics.

All statistical tests were conducted using Statistical Package for the Social Sciences (SPSS), version 14. In order to assess the association between two qualitative variables, the Chi-square and the Fisher's exact tests were applied. The paired association between qualitative variables was analyzed using the McNemar test. The comparison of quantitative variables between two independent groups was

Table 1: Percentages of resistances of various bacteria to the commonly used antibiotics

Antibiotic: Bacteria:	Cephalosporin	Amoxicillin-clavulanate	Potentiated sulfonamide	Fluoroquinolone
S. pseudintermedius	7	12	15	7
Proteus spp	33	29	67	0
Pseudomonas aeruginosa	NP	NP	NP	11
E.coli	14	29	0	0
Streptococcus α-haemolytica	14	0	0	0
Streptococcus β-haemolytica	14	0	14	0
Corynebacterium spp	0	0	80	0
Pasteurella multocida	0	0	0	0
Klebsiella[a]	100	100	100	100
Bacillus spp[a]	100	100	0	0

NP – not performed
[a]only one isolate

carried out using the independent samples t-test, as well as the non-parametric Mann-Whitney test. When comparing quantitative variables between three or more independent groups, ANOVA and the non-parametric Kruskal-Wallis tests were applied. The strength of the linear association between two quantitative variables was estimated by calculating the Pearson correlation coefficient. All tests applied were two-tailed, and a p-value of 5% or less was considered statistically significant.

RESULTS

Eighty six dogs met the inclusion criteria and entered into the study.

Signalment

Out of the 86 dogs, 64% were males and 36% were females, 74.4% were intact. Age of onset of skin or ear infections ranged between 2 months and 10.5 years, with a mean of 3.28 years, standard deviation (SD) of 2.98 and median of 2 years. Breeds: 25 dogs (29.1%) were mix breeds, 12 (14%) were German shepherd dogs, 7 (8.1%) – Shar pei, 7 (8.1%) Labrador retriever and the rest were other breeds with 3 or less dogs in each breed.

Bacteriology data

Cocci were detected in 97% of cytology samples and rods in 78%. Rods in general were isolated in 47% of the cultures. There were 24.1% isolates from skin and 75.9% isolates from ears. In 41% of cases an additional type of bacteria was isolated and in 12% of cases two more additional species of bacteria were isolated. *Proteus spp*. were most frequently isolated in addition to *S. pseudintermedius* followed by *Pseudomonas aeruginosa*. The latter were isolated only from ear samples. Other bacteria that were isolated appear in the following order: *E.coli*, α-haemolytic *Streptococcus spp*., β-haemolytic *Streptococcus spp*., *Corynebacterium spp*., *Pasteurella multocida*, *Klebsiella spp*. and *Bacillus spp*. The latter 7 types of bacteria were not statistically analyzed for susceptibility due to small numbers in each group.

Resistance of the bacterial isolates to the different antibiotics

Four commonly used antibiotics were analyzed: cephalothin, amoxicillin-clavulanate, potentiated sulfonamides and enrofloxacin. The resistance of the various bacteria isolates to the four common antibiotics is presented in Table 1.

Resistance to more than one antibiotic

S. pseudintermedius: seven isolates (8%) were resistant to more than one antibiotic. one isolate (1.2%) was resistant to all 4 antibiotics, 2 isolates (2.3%) were resistant to 3 antibiotics and 4 isolates (4.6%) were resistant to two antibiotics.

Proteus spp: two isolates (13%) were resistant to 2 antibiotics and 3 isolates (20%) were resistant to 3 different antibiotics. One isolate of *E. coli* and one of *Bacillus spp*. were resistant to 2 antibiotics. One isolate of *Klebsiella* was resistant to all 4 antibiotics.

Comparison of antibiotic resistance between two periods: 2000-2002 and 2003-2006

The results of a comparison between the two periods are presented in Table 2.

Resistance of *S. pseudintermedius* to cephalothin and to amoxicillin-clavulanate was statistically significantly higher in the latter years (P=0.018). Between 2000-2002 none of the

Table 2: Percentages of resistances of the common bacteria: comparison between two periods 2000-2002(I) and 2003-2006(II)

Bacteria: **Antibiotic:**		***S. pseudintermedius***	***Proteus spp.***	***Pseudomonas aeruginosa***
Cephalosporin	I	0	17	NP
	II	13	44	NP
	P value	0.018	0.264	
amoxicillin-clavulanate	I	3	0	NP
	II	20	44	NP
	P value	0.019	0.078	
potentiated sulfonamide	I	12.5	67	NP
	II	17	67	NP
	P value	0.528	1.0	
fluoroquinolone	I	2.5	0	0
	II	11	0	50
	P value	0.129		0.047

NP – not performed

Table 3: Susceptibility degree of the common bacteria: comparison between two periods 2000-2002(I) and 2003-2006(II)

Bacteria: **Antibiotic:**		***S. pseudintermedius***	***Proteus spp.***	***Pseudomonas aeruginosa***
Cephalosporin	I	2.18	0.81	NP
	II	1.74	0.54	NP
	P value	0.009	0.31	
Amoxicillin-clavulanate	I	1.87	1.20	NP
	II	1.47	0.65	NP
	P value	0.009	0.037	
Potentiated sulfonamide	I	1.0	0.54	NP
	II	0.9	0.53	NP
	P value	0.534	0.97	
Fluoroquinolone	I	1.33	1.57	1.36
	II	1.24	1.20	0.72
	P value	0.365	0.055	0.38

NP – not performed

isolates was resistant to cephalothin and 3% were resistant to amoxicillin-clavulanate, while between 2003-2006 13% were resistant to cephalothin and 20% to amoxicillin-clavulanate. No differences were found among resistances to potentiated sulfonamides and enrofloxacin between the two periods. Resistance of *Proteus spp*. to cephalosporins increased from 17% in the first period to 44% in the second period but this was not statistically significant (*P* =0.264). No resistance of the *Proteus* isolates to amoxicillin-clavulanate was noticed in the first period, and in the second period it increased to 44%, almost achieving statistical significance (*P* =0.078). The resistance of *Pseudomonas aeruginosa* to fluoroquinolones was found only in the second period (*P*=0.047).

Antibiotic resistance and the site of infection

Twenty percent of *S. pseudintermedius* isolates from skin infections were resistant to cephalothin while only 3% of ear samples were resistant (*P*=0.011). Similar results were found for *S. pseudintermedius* resistance to amoxicillin-clavulanate (25% of skin samples whereas 8% of ear samples were resistant. *P*=0.051). The same tendency but without statistical significance was found for *Proteus spp*. resistance to cephalosporins (50% of skin samples and 27% of ear samples, *P*=0.409) and to amoxicillin-clavulanate (50% of skin samples and 20% of ear samples, *P*=0.262). Contrary results were found for *Proteus spp*. resistance to potentiated sulfonamides: 82% of ear isolates *vs*. 25% of skin isolates were resistant (*P*=0.039).

Association between resistances of *S. pseudintermedius* to different antibiotics, and between different bacteria to the same antibiotic

No association was found between resistances of *S. pseudintermedius* to one antibiotic and its resistance to other antibiotics. A negative correlation was found between susceptibility of *S. pseudintermedius* and *Proteus spp*. to potentiated sulfonamides when isolated from the same sample: when *S. pseudintermedius* was susceptible to this antibiotic *Proteus spp*. was resistant (*P*= 0.04). No other differences were found between other bacteria in their susceptibility or resistance to a particular antibiotic.

Antibiotics resistances and signalment

A greater number of cases of *S. pseudintermedius* resistance to potentiated sulfonamides were seen in females compared to males: 29% *vs*. 7% (*P*=0.011). No differences were found between males and females in the resistance of *S. pseudintermedius* to other antibiotics or resistance of other bacteria to the examined antibiotics. There was no difference regard-

ing antibiotic resistance of the various isolated bacteria in relation to the age of onset of the infection in the dogs in this study. Resistance of *S. pseudintermedius* to potentiated sulfonamides and enrofloxacin was found in 27% of the isolates obtained from Labrador retrievers, however none of the isolates was resistant to cephalexin. On the other hand, 14% of the *S. pseudintermedius* isolates from Shar peis were resistant to cephalexin whereas none were resistant to amoxicillin-clavulanate or enrofloxacin. Resistance to amoxicillin-clavulanate was found in 21% of *S. pseudintermedius* bacteria isolated from mix breed dogs. All the above differences between breeds were not statistically significant. All the isolates of *Proteus spp*. from mix breeds were resistant to cephalothin. None of the German shepherd dog isolates was resistant to cephalexin (P=0.032). No differences were found between the different breeds in respect to resistance of *Pseudomonas aeruginosa* to enrofloxacin.

Comparison of the degree of susceptibility between the periods: 2000-2002 and 2003-2006

Comparison of the degree of susceptibility between the periods – 2000-2002 and 2003-2006 is presented in Table 3. The average degree of susceptibility of *S. pseudintermedius* to cephalosporins during the period 2000-2002 was 2.18, and in the period 2003-2006, 1.74 (P= 0.009). The average degree of susceptibility of *S. pseudintermedius* to amoxicillin-clavulanate during the period 2000-2002 was 1.87, and in the period 2003-2006 it reached 1.47 (P= 0.009). No differences were found in the degrees of susceptibility of *S. pseudintermedius* to potentiated sulfonamides or to enrofloxacin between the two periods.

The average degree of susceptibility of *Proteus spp*. to amoxicillin-clavulanate during the period 2000-2002 was 1.20 compared to 0.65 during the period 2003-2006 (P= 0.037).

The average degree of susceptibility of *Proteus spp*. to enrofloxacin was 1.57 during the period 2000-2002 and was 1.2 during the period 2003-2006 (P= 0.055).

Association between susceptibility tests results and the site of infection

The average degree of susceptibility of *S. pseudintermedius* isolated from ear samples to amoxicillin-clavulanate was 1.76, and from skin samples was 1.29 (P=0.014). The average degree of susceptibility of *Proteus spp*. isolated from ears to potentiated sulfonamides was 0.29 and from skin was 1.19 (P=0.063). No differences were found between susceptibility tests results of these bacteria to the other antibiotics.

Association between susceptibility tests results and signalment

No differences were found between susceptibility tests results and the sex of the dogs or the age of onset of the infections. Susceptibility of *S. pseudintermedius* to enrofloxacin was lower in the Labrador retriever than in other breeds (0.81 vs. 1.3, P=0.067). No other differences were found among the various breeds and the degree of susceptibility of the other bacteria to the various antibiotics.

DISCUSSION

This study demonstrates increased resistance and decreased susceptibility of *S. pseudintermedius* and *Proteus spp*. to various kinds of antibiotics during a period of 7 years. *S. intermedius* isolated from dogs has been recently recognized and re-named as *S. pseudintermedius*. However, this study was preformed when the bacteria was isolated as *S. intermedius*. Reports of increased resistance to antibiotics of *Staphylococci* in Europe between the1980's and the 1990's are summarized by Lloyd (8). However, in the majority of reports different antibiotics were evaluated. An increased resistance of *Staphylococci* from dogs with pyoderma in Sweden to penicillinase-stable β-lactam antimicrobials was reported by Holms (13) over a period of 5 years in the late 1990's. Furthermore, *S. pseudintermedius* lacking susceptibility to β-lactamase–resistant antimicrobials is now being recognized in both infected dogs and cats in Europe (14) and the United States (15).

In the first period of our study (2000-2002) no resistance of *S. pseudintermedius* to cephalosporins was observed, which is in agreement with results of other studies (3, 16-18). However during the second period of our study (2003-2006), 20% of the isolates were resistant. The results presented in our study are lower than those reported in a recent study (14), but much higher than other studies which were conducted during the same period, in which results showed that almost no resistant strains were detectable (4, 17, 19).

The overall resistance to amoxicillin-clavulanate in our study was observed in 12% of *S. pseudintermedius* isolates. This contradicts other studies in which no resistance to this antibiotic was found (3, 4, 17-19). In our study an increased

resistance of *Proteus spp*. to amoxicillin-clavulanate was also noted. This also contradicts other results in which most of the bacteria examined, excluding *Pseudomonas* showed low resistance to this antibiotic (17).

The highest frequency of *S. pseudintermedius* and *Proteus spp*. resistance in our study was to potentiated sulfonamides (15% and 67%, respectively) and this pattern was not different between the two periods that were examined. The resistance of *S. pseudintermedius* is similar to that of another study (4) however in regard to *Proteus* our results were higher than reported elsewhere (4, 17). Although the resistance of *S. pseudintermedius* and *Proteus spp*. to potentiated sulfonamides was found to be twice the frequency than that to cephalosporins, a progressive time related increase in resistance was noticed only to cephalosporin. Furthermore, although these two microorganisms showed similar patterns of resistance to these antibiotics, they had conflicting behavior towards potentiated sulfonamides where one was susceptible while the other was resistant. This finding does not support theories of transfer of resistance between different kinds of microorganisms colonizing the same site. This could be due to the lack of plasmids found within this bacterial population (21). Although plasmids are commonly found within strains of *S. aureus*, this has not been demonstrated within strains of *S. pseudintermedius* (5).

S. pseudintermedius resistance to fluoroquinolones was stable throughout the two periods of our study and was detected in 7% of the isolates, results which were similar to that of cephalosporins. It is possible that some of these bacteria were multi-drug resistant, but no molecular analysis was performed to confirm this possibility. Multi-drug resistant *Staphylococci* have been recovered from dogs receiving many antibiotics previously, including fluoroquinolones (5). *S. pseudintermedius* resistance to fluoroquinolones is considered very rare (16) and its frequency in this study is higher than in most reports (3, 4, 16-20, 22), but similar or lower than a report from Sweden where resistance, ranging from 8% to 12%, were reported between 1992 and 2002 (23).

All the *Proteus spp*. and the other gram negative bacteria in this study were susceptible to enrofloxacin except for *Pseudomonas*, which was resistant in 11% of the isolates. It is important to note that the *Pseudomonas* in this study was isolated only from ears. It is possible that topical application of fluoroquinolones can over-come the *in vitro* susceptibility tests results and be effective against *Pseudomonas* otitis (24). In one study of *Pseudomonas* otitis, resistance to different fluoroquinolones was much higher and ranged between 25-57% (25). A very high resistance rate (16-52%) to various fluoroquinolones was found also in another study in which isolates from ears and skin were examined (26). In our study no attempt was made to differentiate between the different fluoroquinolones. Only enrofoxacin was examined, and the results were then extended to other fluoroquinolones. This was also suggested by Lloyd and Noble (27). In another two reports (25, 26) the authors showed that this application is not necessarily true and may lead to treatment failure or a missed opportunity for successful treatment.

It can also be concluded that skin infection with gram negative bacteria can be successfully managed with fluoroquinolones or at least can be treated until results of culture and susceptibility are obtained. A complete susceptibility of gram negative rods to fluoroquinolones was reported by others (4). However in another report 12/59 strains of *E.coli* were resistant (20).

The high resistance rates that were found in this study in comparison to other reports can be explained by the fact that we examined bacterial isolates from diseased skin and ears only, while in other reports bacterial isolates from healthy skin and ears were also examined (3, 16, 19, 22). However, in another two reports no differences in antimicrobial susceptibility were found between isolates from healthy dogs and dogs with otitis externa (3, 22). Furthermore some of the reported resistances are from isolates obtained from infections other than pyoderma or otitis externa (16, 19, 20, 26).

In our study there was a significant reduction over time in the degree of susceptibility of *S. pseudintermedius* to cephalosporins and to amoxicillin-clavulanate and of *Proteus spp*. to amoxicillin-clavulanate and to fluoroquinolones. The susceptibility in our study was examined by the disc-diffusion method which may be less sensitive than MIC tests (28). A decrease in the susceptibility of *S. pseudintermedius* to amoxicillin-clavulanate between the years 1982-1991 and 2004-2007 was also found in another report that used the MIC method. Similar to our results, no difference in the susceptibility to fluoroquinolones were detected (20).

The reasons for increased resistances and decreased antibiotics susceptibilities were beyond the aims of this study. However, one possible explanation for increasing antimi-

crobial resistance is the wide usage of antibiotics (29, 30). Exposure to antimicrobial agents promotes emergence of resistance by facilitating the survival of resistant strains or inducing the expression of existing antimicrobial resistance genes (6). The dogs in our study suffered from ear and skin infections which are usually chronic. It is possible that previous antibiotic treatments increased resistance of the infective agents. However this cannot explain the increased resistance and decreased susceptibility between the two periods that were examined. Furthermore, in a survey in Europe no change in the susceptibility of *S. pseudintermedius* or *Pseudomonas* from canine skin and ear infection was noticed following the introduction of marbofloxacin (31). Another explanation for the differences found in resistance pattern between this study and other reports is the possible variability among geographic origins (3). Furthermore, the authors plan a future study in which the association between previous use of antibiotics and the development of bacterial resistance will be investigated.

The importance of these results is to encourage clinicians to use the most appropriate antibiotics following culture and susceptibility test results and also to discourage clinicians from the wide use of these antibiotics due to increased resistance and potential zoonosis, which may cause severe infections in both species (32). It is also important to mention the limitation of susceptibility tests, because *in vitro* results not always correlate with the antibiotic activity *in vivo* (3) and also different results can be obtained from different laboratories (33).

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