***In vitro* antimicrobial activity of miconazole and polymyxin B against canine meticillin-resistant *Staphylococcus aureus* and meticillin-resistant *Staphylococcus pseudintermedius* isolates**

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Background – Meticillin-resistant *Staphylococcus aureus* (MRSA) and meticillin-resistant *Staphylococcus pseudintermedius* (MRSP) infections are increasingly reported in dogs, and these bacteria may be isolated from ear infections.

Hypothesis/Objectives – The main aim of the present study was to investigate the *in vitro* antimicrobial activity of miconazole, polymyxin B and a combination of both against 24 canine MRSA and 50 canine MRSP isolates. The minimal inhibitory concentration (MIC) values of 12 other antimicrobial agents were also determined.

Methods – All MIC values were determined according to a broth microdilution assay.

Results – Acquired resistance was found to all tested agents, except for linezolid, miconazole and polymyxin B. The MIC values for miconazole and polymyxin B against MRSA were in the range of 4–8 and 8–64 µg/mL, respectively, while the MIC values for miconazole and polymyxin B against MRSP were in the range of 1–2 and 0.25–4 µg/mL, respectively. Using a combination of miconazole and polymyxin B, there was no evidence for enhanced *in vitro* activity of the combination (i.e. synergy) of both products. Nevertheless, MIC₉₀ values of the combination of these antimicrobial agents and of a commercial product containing both agents were at least 1000 times lower than the concentration present in the commercial product.

Conclusions and clinical importance – These results indicate that the topical use of a combination of miconazole and polymyxin B in a 43.5:1 ratio may have potential for the treatment of MRSA-mediated and MRSP-associated otitis externa in dogs.

Introduction

Staphylococcus pseudintermedius is an opportunistic pathogen that is part of the *Staphylococcus intermedius* group (SIG) and is mainly found in dogs and cats.^{1,2} In most animals, it belongs to the resident flora.^{3,4} Meticillin-resistant *S. pseudintermedius* (MRSP) is being increasingly isolated from pets and sporadically from humans.^{5,6} For many years, meticillin-resistant *Staphylococcus aureus* (MRSA) was considered a human pathogen. Recent reports indicate that MRSA has emerged as a pathogen of animals as well.⁵ The presence of the *mecA* gene in both MRSP and MRSA, which results in

the production of an alternative penicillin-binding protein (PBP), namely PBP2a, renders these organisms resistant to all β-lactam antimicrobials used in veterinary medicine. Moreover, many of these isolates show additional resistance to other classes of antimicrobials commonly used in veterinary medicine.^{7,8} Most reported MRSP and MRSA infections in dogs involve skin, ear, wound and postoperative infections.⁵

Otitis externa is a common problem in dogs. Various treatment approaches can be used, including systemic antimicrobials, topical treatments or a combination of both systemic and topical treatment. Topical treatment has several advantages over systemic treatment; it is cheaper, easier to perform, results in higher local antimicrobial concentrations, and there is no or very limited antimicrobial selection pressure on sites outside the treated area.⁹ Even though there are several all-in-one commercial products that are used to treat canine otitis, there is limited information on the susceptibility of pathogens causing otitis against both the products as sold, and

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the single active compounds. Surolan® (Elanco Animal Health; Greenfield, IL, USA) is a combination of miconazole nitrate, polymyxin B sulfate and prednisolone acetate that is licensed to treat canine otitis.

The effect of polymyxin B on bacteria is attributed to its ability to destabilize the lipopolysaccharide structure.^{10,11} Polymyxin B also has an effect on the cell membrane of fungi, making them more sensitive to other antimicrobials.¹² The activity of miconazole against fungi derives primarily from inhibition of the biosynthesis of ergosterol, an essential component of the fungal plasma membrane.¹³ Miconazole, however, is also effective against bacteria through binding to flavohaemoglobin, which eventually results in oxidative stress followed by cell death.¹⁴ The combination of polymyxin B and miconazole has been shown to be successful for the treatment of infections caused by various pathogens, including multidrug-resistant pathogens, such as *Pseudomonas* spp. and enterococci.^{15,16}

It was the aim of the present study to determine the susceptibility of canine MRSP and MRSA isolates against several antimicrobial agents, including miconazole, polymyxin B, the combination of both miconazole and polymyxin B, and the combination of these two agents in a 43.5:1 ratio (Surolan®).

Materials and methods

A total of 50 canine MRSP strains isolated from ear or skin infections from Spain ($n = 7$), Germany ($n = 13$), The Netherlands ($n = 15$) and Canada ($n = 15$) and 24 canine MRSA isolates selected from different locations in North America ($n = 14$) and Europe ($n = 10$) were identified with phenotypic tests and PCR as described before.^{17–20}

For further characterization of the isolates, the minimal inhibitory concentrations (MICs) of amikacin, ciprofloxacin, clindamycin, erythromycin, fusidic acid, gentamicin, linezolid, mupirocin, neomycin, rifampicin, potentiated sulfonamides and tetracycline was determined using the broth microdilution Sensititre NLV 65 system according to the manufacturer's instructions (Trek Diagnostic Systems Ltd, East Grinstead, West Sussex, UK). As no clinical breakpoints for local treatment of otitis in dogs are available, the epidemiological cut-off values applicable to *S. aureus*²¹ were applied to determine the percentage of isolates classified as nonwild-type.

The MICs of polymyxin B, miconazole, the combination of polymyxin B and miconazole, and the product Surolan® (containing 23 mg/mL miconazole and 0.53 mg/mL polymyxin B) were evaluated using an in-house broth microdilution assay according to Clinical and Laboratory Standards Institute (CLSI) guidelines.²² The combination of polymyxin B and miconazole was tested in a 1:43.5 ratio, which is the same as present in the commercially available product. As no clinical breakpoints for local treatment of otitis in dogs are available, nor are epidemiological cut-off values available for polymyxin B and miconazole in *S. aureus*,²¹ the presence of nonwild-type isolates was assumed when MIC values showed a bimodal or multimodal distribution or tailing as described previously.^{23,24} *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Escherichia coli* ATCC 25922 were used as quality control strains.

Two strains of MRSP were exposed to several dilutions of the combination of polymyxin B and miconazole for several days to see whether rapid development of resistance occurs. In short, a fresh series of 3 mL Mueller Hinton broth (Becton Dickinson, Breda, The Netherlands) was prepared daily containing concentrations of 0.25, 0.5, 1, 2 and 4 times the MIC of the combination of polymyxin B and miconazole for these strains (in the 1:43.5 ratio).

Fresh cultures of two strains with MICs of the combination of miconazole and polymyxin B of 11.2 and 0.26 µg/mL, respec-

tively (which corresponds to a 5×10^4 -fold dilution of the commercial product), were used to inoculate 5 mL brain-heart infusion broth tubes (BioTrading, Mijdrecht, The Netherlands). Tubes were incubated overnight at 37°C and purity was checked. The next day, 10 µL of the broth was used to inoculate broth tubes containing the series of concentrations of miconazole and polymyxin B as described above, and one tube containing no antimicrobials was used as a growth control. After incubation at 37°C for 18–24 h, the broth tubes were visually evaluated for bacterial growth. The tube containing the highest concentration of antimicrobials and showing growth was used to inoculate the next series of broth tubes as described above. This was repeated for seven consecutive incubations, and MIC values were determined on the isolates obtained from the last incubation as described above.

Results

The results of the antimicrobial susceptibility testing are presented in Tables 1–4. For the broth microdilution assay, all MIC values of the quality control strains were within the acceptable ranges, as described by CLSI.²² In general, resistance to multiple antimicrobial classes was commonly identified among the MRSA and MRSP isolates (Tables 1 and 2).

The MIC values for miconazole and polymyxin B were in the range of 4–8 and 8–64 µg/mL, respectively, for the MRSA strains (Table 3), and in the range of 1–2 and 0.25–4 µg/mL, respectively, for the MRSP strains (Table 4). The monomodal distribution of the MIC values suggests no acquired resistance in any of the tested MRSA or MRSP strains towards both miconazole and polymyxin B.

All MIC values for the pure miconazole–polymyxin B combination were in the range of 2.8/0.064 and 22.5/0.52 µg/mL for both MRSA and MRSP. The MIC values for the miconazole–polymyxin B combination in the commercial product were in a similar range, even though these MIC values tended to be slightly higher than for the pure miconazole–polymyxin B combination for the MRSA strains. Nevertheless, MIC₉₀ values of the pure combination of agents and of the combination of agents in a 1:43.5 ratio were at least 1024 times lower than the concentrations present in the previously mentioned commercial product for MRSA and MRSP strains.

While testing the emergence of resistance, the strains showed growth in the tubes with 0.25 times the MIC of miconazole and polymyxin B after days 1 and 4 and in tubes with a concentration of 0.25 and 0.5 times the MIC of miconazole and polymyxin B after days 2, 3, 5, 6 and 7. All MICs of the strains that were exposed to the combination of miconazole and polymyxin B for 7 days were in the same range as those of the strains prior to exposure.

Discussion

Treatment of infections caused by multiresistant MRSP and MRSA strains is a challenge for veterinary medicine. Our results confirm previous reports showing that canine MRSA and MRSP strains are often resistant towards macrolides, tetracyclines and certain fluoroquinolones and aminoglycosides. Resistance is also observed against certain antimicrobials that are more commonly used in human medicine, such as fusidic acid and mupirocin.^{7,25,26}

Table 1. Distribution of minimal inhibitory concentrations (MICs) of various antimicrobial agents against canine methicillin-resistant *Staphylococcus aureus* (MRSA) isolates using the Sensititre panel NLV65

Antimicrobial agent	Number of MRSA strains with MIC (µg/mL)*													
	≤0.12	≤0.25	0.25	≤0.5	0.5	1	2	4	8	16	32	>32	64	>64
Erythromycin		1			6	1	1	1				16		
Clindamycin		9		3	1	1						10		
Rifampicin†		23										1		
Fusidate		19					2	1	2					
Gentamicin				15		3	1	1	1		3			1
Amikacin						2	5	7	4	5	1			
Neomycin				3		2	3	1	2	3	3		3	4
Ciprofloxacin				8				1		4	3		4	4
Tetracycline				11			1	1	1	5	2		3	
Mupirocin				23				1						
Sulfa/trim (20/1)‡	17		3		2			1		1				
Linezolid				1		5	16	2						

*The vertical bars represent wild-type cut-off values for *S. aureus* as described by The European Committee on Antimicrobial Susceptibility Testing²¹.

†Wild type strains show rifampicin MIC values smaller than or equal to 0.03 µg/mL.

‡Trimethoprim MIC values are shown, Sulfa/trim: sulfamethoxazole/trimethoprim.

Table 2. Distribution of MICs of various antimicrobial agents against canine methicillin-resistant *S. pseudintermedius* (MRSP) isolates using the Sensititre panel NLV65

Antimicrobial agent	Number of MRSP strains with MIC (µg/mL)*													
	≤0.12	≤0.25	0.25	≤0.5	0.5	1	2	4	8	16	32	>32	64	>64
Erythromycin		4			4	1							42	
Clindamycin		7		1	1								41	
Rifampicin†		50												
Fusidate		45			2	2	1							
Gentamicin				5			1	5	5	29	4			1
Amikacin						6	26	16	1				1	
Neomycin				7				4	30	7	2			
Ciprofloxacin				3		2				1	4		40	
Tetracycline				14		1				1	1		25	8
Mupirocin				48		2								
Sulfa/trim (20/1)‡				4		1	1		32	12				
Linezolid						1	46	3						

*The vertical bars represent wild type cut-off values for *S. aureus* as described by The European Committee on Antimicrobial Susceptibility Testing²¹.

†Wild type strains show rifampicin MIC values smaller than or equal to 0.03 µg/mL.

‡Trimethoprim MIC values are shown, Sulfa/trim: sulfamethoxazole/trimethoprim.

Table 3. Distribution of MICs of miconazole, polymyxin B, the pure miconazole–polymyxin B combination and the commercial miconazole–polymyxin B combination in Surolan[®] (Elanco Animal Health, Greenfield, IN, USA) against canine MRSA isolates using a broth microdilution assay

Antimicrobial agent	Number of MRSA strains with MIC (µg/mL)*										
	0.25	0.5	1	2	4	8	16	32	64	128	>128
Miconazole					20	4					
Polymyxin B						1	2	15	6		
	0.7/0.016	1.4/0.032	2.8/0.064†	5.6/0.13	11.2/0.26	22.5/0.52‡	45/1	90/2	180/4	360/8	>360/8
Miconazole–polymyxin B			5	13	3	3					
Surolan§				1	9	14					

*Miconazole–polymyxin B concentrations are shown.

†This value corresponds to an 8192-fold dilution of the miconazole–polymyxin B concentration in Surolan[®].

‡This value corresponds to a 1024-fold dilution of the miconazole–polymyxin B concentration in Surolan[®].

§These MIC values correspond to the miconazole–polymyxin B concentrations in Surolan[®].

The MIC values for miconazole and polymyxin B were in the range of 4–8 and 8–64 µg/mL, respectively, for MRSA strains, and in the range of 1–2 and 0.25–4 µg/mL,

respectively, for MRSP strains. Similar ranges of MIC values for miconazole have been reported in *S. aureus* and a single SIG strain.^{27–29} For polymyxin B, an MIC

Table 4. Distribution of MICs of miconazole, polymyxin B, the pure miconazole–polymyxin B combination and the commercial miconazole–polymyxin B combination in Surolan® (Elanco Animal Health) against canine MRSP isolates using a broth microdilution assay

Antimicrobial agent	Number of MRSP strains with MIC (µg/mL)*										
	0.25	0.5	1	2	4	8	16	32	64	128	>128
Miconazole			19	31							
Polymyxin B	2	4	8	33	3						
	0.7/0.016	1.4/0.032	2.8/0.064§	5.6/0.13	11.2/0.26	22.5/0.52†	45/1	90/2	180/4	360/8	>360/8
Miconazole–polymyxin B			1	6	39	3					1
Surolan†			1	6	39	3					1

*Miconazole–polymyxin B concentrations are shown.

†This value corresponds to a 1024-fold dilution of the miconazole–polymyxin B concentration in Surolan®.

‡These MIC values correspond to the miconazole–polymyxin B concentrations in Surolan®.

§This value corresponds to a 8192-fold dilution of the miconazole/polymyxin concentration in Surolan®.

value of 23 µg/mL for a single MRSA strain has been described recently.³⁰ The slightly lower MIC values of polymyxin B for *S. pseudintermedius* might be a species-specific characteristic, because polymyxin susceptibility has been used to discriminate *S. aureus* from *S. intermedius* group in the past.³¹ Considering the monomodal distribution of the MIC values, there were no indications to suggest acquired resistance in any of the tested MRSA or MRSP strains towards miconazole or polymyxin B, despite resistance of the tested isolates to many other antimicrobials. Even though staphylococci could be considered intrinsically resistant to polymyxin B and miconazole in the case of systemic treatment of *Staphylococcus* infections, these products may be effective for topical treatment because the concentrations achieved by systemic therapy are markedly lower than those obtained by local treatment. This hypothesis is supported by the fact that MIC₉₀ values of the pure combination of agents and of the combination of agents in Surolan® were at least 1024 times lower than the concentration of both polymyxin B and miconazole in Surolan® for MRSA and MRSP strains.

After exposing two MRSP strains to concentrations below the MIC for 7 days, no change in the MICs could be observed. This suggests that there is not a rapid development of resistance against this combination of products. However, this experimental set-up cannot be used to predict the emergence of all resistance mechanisms.

Using the miconazole/polymyxin B ratio as used in the commercial product, there were no indications of enhanced *in vitro* activity of the combination of both products. Even though Pietschmann *et al.*²⁸ reported the absence of synergy between miconazole and polymyxin B for an *S. intermedius* group strain, synergism was observed between both agents for *Escherichia coli*, *Pseudomonas aeruginosa* and *Malassezia pachydermatis*. Considering the higher *in vitro* antimicrobial activity of miconazole compared with polymyxin B for the tested MRSA and MRSP strains and considering the fact that in the commercial product the miconazole concentration is about 43 times higher than the polymyxin concentration, the *in vitro* anti-MRSA and anti-MRSP activity of Surolan® can be attributed mainly to miconazole.

The present *in vitro* results suggest that even though the active substances in Surolan® primarily target fungi

and Gram-negative bacteria, this combination of antimicrobial agents also holds features for topical treatment of canine otitis caused by MRSA and MRSP. The *in vivo* effectiveness of Surolan® in treating canine MRSA-mediated otitis therefore needs further research.

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Résumé

Contexte – Les infections liées aux *Staphylococcus aureus* résistants à la méticilline (MRSA) et aux *Staphylococcus pseudintermedius* résistants à la méticilline (MRSP) sont rapportées de plus en plus fréquemment chez le chien et peuvent être isolées à partir d'infections auriculaires.

Hypothèses/Objectifs – le principal objectif de notre étude était de déterminer l'activité antimicrobienne *in vitro* du miconazole, de la polymyxine B et d'une association des deux contre 24 isolats de MRSA et 50 isolats de MRSP canins. Les valeurs de CMI de 12 autres agents antimicrobiens ont également été déterminées.

Méthodes – Toutes les valeurs de CMI ont été déterminées par test de microdilution.

Résultats – Une résistance acquise a été trouvée pour tous les agents testés sauf pour le linezolid, le miconazole et la polymyxine B. Les valeurs de MIC pour le miconazole et la polymyxine B contre les MRSA étaient respectivement dans les limites de 4–8 µg/mL et 8–64 µg/mL. Les valeurs de MIC pour le miconazole et la polymyxine B contre les MRSP étaient respectivement dans les limites de 1–2 µg/mL et 0.25–4 µg/mL. Avec une association de miconazole et de polymyxine B, il n'y avait aucune preuve d'augmentation de l'activité *in vitro* (i.e. de synergie) des deux produits. Quoi qu'il en soit, les valeurs de MIC₉₀ de la combinaison de ces agents antimicrobiens et d'un produit commercial contenant les deux agents étaient au moins 1000 fois plus faible que la concentration présente dans le produit commercial.

Conclusions et importance clinique – Ces résultats montrent que l'utilisation topique d'une combinaison de miconazole et de polymyxine B à un ratio 43.5 : 1 peut avoir une efficacité dans le traitement des otites externes médiées par les MRSA et associées aux MRSP chez le chien.

Resumen

Introducción – *Staphylococcus aureus* resistente a Meticilina (MRSA) e infecciones por *S. pseudintermedius* resistente a meticilina (MRSP) se observan cada vez con más frecuencia en perros y se pueden aislar de infecciones del oído.

Hipótesis/objetivos – el objetivo principal del estudio fue investigar la actividad antimicrobiana *in vitro* de miconazol, polimixina B y de una combinación de ambos contra 24 MRSA caninos y 50 aislados caninos de MRSP. También se determinaron los valores de MIC de 12 otros agentes antimicrobianos.

Métodos – los valores MIC fueron determinados según un análisis de microdilución de la suspensión.

Resultados – se encontró resistencia adquirida a todos los agentes probados, a excepción de linezolid, miconazol y de polimixina B. Los valores de MIC para el miconazol y la polimixina B contra MRSA estaban en el rango de 4–8 µg/mL y 8–64 µg/mL respectivamente; los valores de MIC para miconazol y polimixina B frente a MRSP fueron del rango de 1–2 µg/mL y de 0.25–4 µg/mL respectivamente. Usando una combinación miconazol y polimixina B, no hubo evidencia de actividad sinérgica *in vitro*. Sin embargo, los valores

MIC₉₀ de la combinación de estos agentes antimicrobianos y de un producto comercial que contenía ambos agentes fueron por lo menos 1000 veces más bajas que la concentración presente en el producto comercial.

Conclusiones e importancia clínica – estos resultados indican que el uso tópico de una combinación de miconazol/polimixina B en un cociente de 43.5 : 1 puede tener potencial para el tratamiento de la otitis externa mediada por MRSA y MRSP.

Zusammenfassung

Hintergrund – Infektionen durch Methicillin-resistente *Staphylococcus aureus* (MRSA) und Methicillin-resistente *Staphylococcus pseudintermedius* (MRSP) werden in zunehmendem Maße bei Hunden beschrieben und diese Keime können bei Ohrinfektionen isoliert werden.

Hypothese /Ziele – Das wesentliche Ziel dieser Studie war es, die antimikrobielle *in vitro* Aktivität von Mikonazol, Polymyxin B und einer Kombination aus beiden Wirkstoffen bei der Behandlung von 24 caninen MRSA und 50 caninen MRSP Isolaten zu untersuchen. Die MIC Werte von 12 anderen antimikrobiellen Wirkstoffen wurden ebenfalls bestimmt.

Methoden – Alle MIC Werte wurden mit Hilfe eines Bouillon-Mikroverdünnungs-Assays bestimmt.

Ergebnisse – Eine erworbene Resistenz wurde gegen alle untersuchten Wirkstoffe, außer gegen Linolozid, Mikonazol und Polymyxin B festgestellt. Die MIC Werte für Mikonazol und Polymyxin B gegen MRSA lagen im Bereich von 4–8 µg/mL beziehungsweise 8–64 µg/mL, MIC Werte für Mikonazol und Polymyxin gegen MRSP lagen im Bereich von 1–2 µg/mL beziehungsweise 0.25–4 µg/mL. Trotz der Verwendung einer Kombination von Mikonazol und Polymyxin B gab es keine Evidenz für eine gesteigerte *in vitro* Aktivität der Kombination beider Produkte (im Sinne einer Synergie). Trotz allem waren die MIC₉₀ Werte dieser Kombination der antimikrobiellen Wirkstoffe und eines kommerziellen Produkts, welches beide Wirkstoffe beinhaltet, mindestens 1000-fach niedriger als die Konzentrationen, die im kommerziellen Produkt vorkommen.

Zusammenfassung und klinische Bedeutung – Diese Ergebnisse weisen darauf hin, dass die topische Verwendung von Mikonazol / Polymyxin B im Verhältnis 43,5 : 1 eine mögliche Behandlungsform für Otitis externa aufgrund von MRSA und MRSP bei Hunden darstellt.

要約

背景 – メチシリン耐性 *Staphylococcus aureus* (MRSA) とメチシリン耐性 *Staphylococcus pseudintermedius* (MRSP) 感染の報告は犬で増加しており、耳の感染症からも分離されている。

仮説/目的 – この研究の主な目的は、犬から分離した MRSA24 株と MRSP50 株に対するミコナゾール、ポリミキシン B、あるいは両方の組み合わせを用いて *in vitro* での抗菌作用を調査することである。その他の 12 種類の抗菌物質についても MIC 値を測定した。

方法 – すべての MIC 値は微量液体気積法によって決定した。

結果 – 獲得された耐性はリネゾリド、ミコナゾール、ポリミキシン B を除くすべての検査した物質で認められた。ミコナゾールとポリミキシン B の MRSA に対する MIC 値はそれぞれ 1–2 µg/mL と 0.25–4 µg/mL の範囲であった。ミコナゾールとポリミキシン B の組み合わせの使用では、両方の合剤に *in vitro* での活性の増加（つまり、相乗効果）の証拠は認められなかった。それにも関わらず、これらの抗菌物質の合剤および両方の物質を含んでいる市販の製品の MIC₉₀ 値は市販の製品より少なくとも 1000 倍以上は低かった。

結論と臨床的な重要性 – これらの結果はミコナゾール/ポリミキシンを 43.5 : 1 の比率に組み合わせた合剤が、犬の MRSA 介在性、MRSP 関連性外耳炎の治療に対して可能性があることを示唆した。

摘要

背景 – 越来越多关于犬感染耐甲氧西林金黄色葡萄球菌 (MRSA) 和耐甲氧西林假中间型葡萄球菌 (MRSP) 的报道, 二者可能是感染耳道的菌株。

假说/目的 – 当前研究的主要目的是研究咪康唑、多粘菌素B和两者结合对24只犬的MRSP和50只犬的MRSA菌株的体外抗菌活性。同时确定其他12种抗菌药物的MIC值。

方法 – 培养液微量稀释法确定所有MIC值。

结果 – 除利奈唑酮、咪康唑和多粘菌素B之外, 其他测试药物均存在耐药性。咪康唑与多粘菌素B抗MRSA的MIC值分别在 4–8 µg/mL 和 8–64 µg/mL 范围内, 咪康唑与多粘菌素B抗 MRSP 的MIC值分别在 1–2 µg/mL 和 0.25–4 µg/mL 范围内。联合使用咪康唑与多粘菌素B, 没有证据显示这两种产品的结合(即协同)能使体外活性增强。不过, 这两种抗菌药物联合及包含两者的商业产品的MIC₉₀值, 比商业产品现有浓度至少低1000倍。

结论和临床意义 – 这些结果表明, 以43.5:1的比例联合的咪康唑/多粘菌素B外用, 有能力治疗MRSA-介导和MRSP-相关犬外耳炎。