



# Brazilian Journal of OTORHINOLARYNGOLOGY

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## ORIGINAL ARTICLE

### Evaluating the ototoxicity of a antiMRSA peptide KR-12-a2<sup>☆</sup>

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Received 24 September 2016; accepted 4 May 2017

#### KEYWORDS

KR-12-a2;  
AntiMRSA peptide;  
Topical application;  
Ototoxicity

#### Abstract

**Introduction:** Methicillin-Resistant *Staphylococcus Aureus* (MRSA) is an emerging problem for the treatment of chronic suppurative otitis media, and also for pediatric tympanostomy tube otorrhea. To date, there are no effective topical antibiotic drugs to treat MRSA otorrhea.

**Objective:** In this study, we evaluated the ototoxicity of topical KR-12-a2 solution on the cochlea when it applied topically in the middle ear of guinea pigs.

**Methods:** The antimicrobial activity of KR-12-a2 against MRSA strains was examined by using the inhibition zone test. Topical application of KR-12-a2 solution, Gentamicin (GM) and Phosphate Buffered Saline (PBS) were applied in the middle ear of the guinea pigs after inserting ventilation tubes. Ototoxicity was assessed by Auditory Brainstem Evoked Response (ABR) and Scanning Electron Microscope (SEM) examination.

**Results:** KR-12-a2 produced an inhibition zone against MRSA from 6.25 µg. Hearing threshold in the KR-12-a2 and PBS groups were similar to that before ventilation tube insertion. However, the GM group showed elevation of the hearing threshold and there were statistically significant differences compared to the PBS or the KR-12-a2 group. In the SEM findings, the KR-12-a2 group showed intact outer hair cells. However, the GM group showed total loss of outer hair cells. In our experiment, topically applied KR-12-a2 solution did not cause hearing loss or cochlear damage in guinea pigs.

**Conclusion:** In our experiment, topically applied KR-12-a2 solution did not cause hearing loss or cochlear damage in guinea pigs. The KR-12-a2 solution can be used as ototopical drops for treating MRSA otorrhea; however, further evaluations, such as the definition of optimal concentration and combination, are necessary.

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<sup>☆</sup> Please cite this article as: Sung CM, Yang HC, Cho YB, Shin SY, Jang CH. Evaluating the ototoxicity of a antiMRSA peptide KR-12-a2. Braz J Otorhinolaryngol. 2017. <http://dx.doi.org/10.1016/j.bjorl.2017.05.002>

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Peer Review under the responsibility of Associação Brasileira de Otorrinolaringologia e Cirurgia Cérvico-Facial.

<http://dx.doi.org/10.1016/j.bjorl.2017.05.002>

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## PALAVRAS-CHAVE

KR-12-a2;  
Peptídeo Anti-MRSA;  
Aplicação tópica;  
Ototoxicidade

## Avaliando a ototoxicidade de um peptídeo anti-MRSA KR-12-a2

## Resumo

**Introdução:** O *Staphylococcus aureus* Resistente à Meticilina (MRSA) é um problema emergente não só para a otite média supurativa crônica, mas também para casos de otorreia crônica em crianças com tubo de ventilação. Até o momento, não há antibióticos tópicos efetivos para a otorreia causada por MRSA.

**Objetivo:** Nesse estudo, avaliamos a ototoxicidade da solução tópica de KR-12-a2 na cóclea quando aplicada topicamente na orelha média de cobaias.

**Método:** A atividade antimicrobiana de KR-12-a2 contra cepas de MRSA foi avaliada utilizando-se o teste de zona de inibição de crescimento. Foram aplicados na orelhas médias de 3 grupos de cobaias, ou Solução tópica de KR-12-a2, ou Gentamicina (GM) ou solução salina tamponada com fosfato (PBS) após timpanostomia. A ototoxicidade foi avaliada através do exame auditivo de Potencial Evocado Auditivo do Tronco Encefálico (PEATE) e por microscopia eletrônica de varredura (SEM).

**Resultados:** O KR-12-a2 produziu uma zona de inibição contra MRSA a partir de 6,25 µg. Alterações do limiar de audição no grupo KR-12-a2 e no grupo PBS foram semelhantes aos observados antes da inserção do tubo de ventilação. No entanto, o grupo GM apresentou um limiar auditivo mais elevado, estatisticamente significativo em comparação ao grupo PBS ou ao grupo KR-12-a2. Nos achados da SEM, o grupo KR-12-a2 apresentou células ciliadas externas intactas. No entanto, o grupo GM apresentou perda total das células ciliadas externas. Em nosso experimento, a solução de KR-12-a2 aplicada topicamente não causou perda auditiva ou dano coclear em cobaias.

**Conclusão:** Em nosso experimento, a solução de KR-12-a2 aplicada topicamente não causou perda auditiva ou dano coclear em cobaias. A solução de KR-12-a2 pode ser utilizada como gotas otológicas para o tratamento da otorreia causada por MRSA; no entanto, são necessárias outras avaliações, para a definição da concentração e das combinações ideais.

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## Introduction

Antibiotic resistance is rapidly becoming a clinically significant problem to the healthcare system. Treatment of chronic Otitis Media caused by bacteria, resistant to multiple antimicrobial agents, has emerged as one of the greatest challenges faced by clinicians. Consequently, Methicillin-Resistant *Staphylococcus Aureus* (MRSA) infections cannot be treated with commercially available ciprofloxacin ototopical drops.<sup>1,2</sup> The prevalence of MRSA in Chronic Suppurative Otitis Media (CSOM) is known to be more than ~60–70% among *S. Aureus* isolates from hospitals in Korea.<sup>3</sup> Besides CSOM, MRSA is an emerging problem related to chronic pediatric tympanostomy tube otorrhea. To date, standard treatment protocols have not been developed, and there is a diverse spectrum of reported medical treatments. The additional use of oral antibiotics such as linezolid,<sup>4</sup> trimethoprim-sulfamethoxazole,<sup>5</sup> fusidic acid,<sup>6</sup> or rifampin to treat MRSA otorrhea may be helpful, but after systemic administration, the effective bioavailable concentration in the middle ear to eradicate infection cannot be accurately measured or described. Otological drug delivery presents a highly promising alternative to oral antibiotics for the administration of therapeutics to the middle ear.

The use of vancomycin for the treatment of MRSA infections has increased.<sup>7</sup> One of the authors of this paper used

topical vancomycin to treat patients with MRSA CSOM and obtained good results.<sup>8</sup> However, the concern regarding the use of vancomycin is the possible emergence of vancomycin-resistant strains such as Vancomycin-Intermediate *S. Aureus* (VISA) and Vancomycin-Resistant *Enterococcus* (VRE). In clinical settings, its less frequent use may facilitate decreases in the appearance of vancomycin-resistant strains. Therefore, it is necessary to develop new antimicrobial compounds against the MRSA. Recently, Antimicrobial Peptides (AMPs) have been considered as novel antibiotics against drug-resistant microorganisms, such as MRSA, and some of them are being evaluated in clinical trials.<sup>9</sup> AMPs are fundamental components of the mammalian innate immunity that control microbial infections and represent the first line of defense against different pathogens on epidermal and mucosal epithelial surfaces. AMPs play a significant role in host innate immunity defense to prevent first infections<sup>10</sup> and are produced by macrophages, blood cells, and epithelial cells in mammals. The AMPs identified in humans include members of the cathelicidin, defensin, thrombocidin, and histatin families.<sup>11</sup>

Expression of an AMP in the skin of the external auditory canal skin and in the middle ear has been reported.<sup>12–14</sup> Human cathelicidin LL-37 is a 37 residue-long cationic, amphipathic  $\alpha$ -helical antimicrobial peptide.<sup>15</sup> Besides its direct bactericidal action, LL-37 is known to have a potent

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