**Staphylococcus aureus** resistance to topical antimicrobials in atopic dermatitis*

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**Abstract:** Background: Topical antimicrobial drugs are indicated for limited superficial pyodermitis treatment, although they are largely used as self-prescribed medication for a variety of inflammatory dermatoses, including atopic dermatitis. Monitoring bacterial susceptibility to these drugs is difficult, given the paucity of laboratory standardization. Objective: To evaluate the prevalence of *Staphylococcus aureus* topical antimicrobial drug resistance in atopic dermatitis patients. Methods: We conducted a cross-sectional study of children and adults diagnosed with atopic dermatitis and *S. aureus* colonization. We used miscellaneous literature reported breakpoints to define *S. aureus* resistance to mupirocin, fusidic acid, gentamicin, neomycin, and bacitracin. Results: A total of 91 patients were included and 100 *S. aureus* isolates were analyzed. All strains were methicillin-susceptible *S. aureus*. We found a low prevalence of mupirocin and fusidic acid resistance (1.1% and 5.9%, respectively), but high levels of neomycin and bacitracin resistance (42.6% and 100%, respectively). Fusidic acid resistance was associated with more severe atopic dermatitis, demonstrated by higher EASI scores (median 17.8 vs 5.7, p=.009). Our results also corroborate the literature on the absence of cross-resistance between the aminoglycosides neomycin and gentamicin. Conclusions: Our data, in a southern Brazilian sample of AD patients, revealed a low prevalence of mupirocin and fusidic acid resistance of *S. aureus* atopic eczema colonizer strains. However, for neomycin and bacitracin, which are commonly used topical antimicrobial drugs in Brazil, high levels of resistance were identified. Further restrictions on the use of these antimicrobials seem necessary to keep resistance as low as possible. Keywords: Anti-infective agents, local; Dermatitis, atopic; Drug resistance, bacterial; *Staphylococcus aureus*

**INTRODUCTION**

Antimicrobial drugs applied topically offer several advantages over systemic administration, including avoidance of systemic toxicity and side effects, the decreased induction of bacterial resistance, high local concentration of antibacterial agents and low costs.\(^1\) Moreover, the broad use of this class of drugs is largely the result of self-preservation of over-the-counter preparations containing antibiotics, including ointments, eye-drops and otological solutions, uses that are supported by little or no scientific evidence.\(^2\)

*Staphylococcus aureus* is the major causative agent of skin and soft tissue infections and treatment of *S. aureus* infections has become more difficult with time due to the emergence of multidrug-resistant strains.\(^3\) Atopic dermatitis (AD) is a chronic skin condition that has been strongly linked to the presence of *S. aureus*, while cutaneous infection constitutes an important mechanism of worsening disease.\(^4\) Thus, patients are frequently prescribed or self-prescribe antimicrobial medication, often topical preparations of antimicrobials associated with corticosteroids.

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However, there is growing concern over resistance to topical antimicrobials. Some of these drugs, such as fusidic acid, can also be used systemically in the treatment of methicillin-resistant *S. aureus* (MRSA) infections. Employing topical preparations in superficial infections and a variety of inflammatory dermatosis, including AD, has been deemed responsible for the emergence of fusidic acid-resistant *S. aureus* (FRSA) strains. Some authors have called for its topical use to be restricted or even abolished. Nevertheless, mupirocin can only be administered topically and its efficacy on *S. aureus* carriage eradication has disseminated its use for nasal decolonization. High-level mupirocin resistance, defined by minimum inhibitory concentration (MIC) 225µg/mL, has been increasingly reported and has emerged as a significant problem. It has been associated with multidrug-resistant MRSA isolates, and in a clinical setting, with decolonization failure. Finally, despite the wide use in several countries, information in the literature about topical neomycin and bacitracin antimicrobial activity remains limited.

Topical antimicrobial susceptibility testing is not routinely performed at laboratory centers. With the exception of mupirocin and fusidic acid, which have been discussed in many publications concerning bacterial resistance in recent years, data on other topical antimicrobial drugs are scarce. This raises concerns regarding the monitoring of these agents’ continued efficacy.

The aims of this study were to: determine the prevalence of *S. aureus* topical antimicrobial resistance in AD patients according to standard procedures (for mupirocin and fusidic acid); verify neomycin and bacitracin activities against *S. aureus* isolates according to historical MIC breakpoints; analyze neomycin cross-resistance with gentamicin; and suggest ways to monitor the activity of commonly used topical antimicrobial drugs in a clinical setting.

**METHODS**

**Patients and isolates**

We conducted a cross-sectional study of children and adults diagnosed with AD who consecutively attended two outpatient dermatologic clinics in Porto Alegre, southern Brazil, over a one-year period (December 2009 to December 2010). The diagnosis of AD was made by the treating dermatologist, based on standard criteria. Patients who had at least one dermatitis lesion at the time of their dermatologic visit were invited to participate. Following agreement from patients or children's parents, we collected patient demographics and information on their medical histories. The following data were recorded: self-reported use of topical and systemic antimicrobials over the previous year, skin infection episodes and hospitalization periods. Recurrent cutaneous infections were defined as involving three or more episodes by year. We also performed physical examinations to evaluate eczema severity according to the Eczema Area and Severity Index (EASI) score guidelines.

For microbiological analyses, two sites from every patient were sampled with a sterile swab with transport medium in each case, namely: the anterior nose cavity and an eczema plaque without clinical signs of infection (pustules, serous crusts, purulent exudate). Swabs were sent to the microbiology laboratory and samples were inoculated onto Brain Heart Infusion agar with 5% sheep blood and mannitol agar, and subsequently incubated at 35°C overnight. Each plate was examined for colonial morphology consistent with *S. aureus*. Isolates were identified according to standard procedures. Colonization was defined as positive culture for *S. aureus* on nasal cavities or cutaneous lesions and an absence of clinical signs of infection.

This study was approved by the Institutional Research Ethics Committee of the Universidade Federal de Ciências da Saúde de Porto Alegre. Prior to participation, informed consent was obtained from all patients and children’s parents or legal guardians.

**Susceptibility Tests**

All strains were tested by disk diffusion assay on Mueller-Hinton agar with standardized procedures, according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI). All isolates were tested beforehand for methicillin susceptibility, and all were categorized as methicillin-susceptible *S. aureus* (MSSA). The antibiotics disks used in this study were: gentamicin (10µg); neomycin (30µg); bacitracin (10µg); mupirocin (5µg); and fusidic acid (10µg). MIC was determined for bacitracin, mupirocin and fusidic acid using Etest® (BIOMERIEUX, Marcy-l’Etoile, France); and for neomycin using the broth microdilution method, according to the CLSI protocol.

We used CLSI breakpoints to define gentamicin-resistant strains according to the disk diffusion assay. Recent CLSI publications provide no interpretative criteria for antibiotics of exclusive topical use, except for mupirocin. The technique for the mupirocin disk diffusion test from the CLSI constitutes merely a screening test that utilizes 256µg disks to detect high-level mupirocin resistance in *S. aureus* strains. The other test interpretations were as follows. For mupirocin and fusidic acid MICs, breakpoints available from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) publication were used. Bacitracin MIC criteria were available in the document from the *Comité de l’Antibiogramme de la Société Française de Microbiologie* (SFM). Neomycin MIC interpretative criteria were based on historical reports. For the mupirocin 5µg disk diffusion test, breakpoints outlined in publications from the British Society for Antimicrobial Chemotherapy (BSAC) Methods for Antimicrobial Susceptibility Testing were employed. There are two different inhibition zone sizes in EUCAST and BSAC publications for the Fusidic acid 10µg disk diffusion test. In accordance with both criteria, we sought to display fusidic acid resistance prevalence. No interpretative criteria were found for the neomycin 30µg and bacitracin 10µg disk diffusion test in the literature.

**Statistical Analysis**

Statistical analyses were conducted on SPSS software, version 17.0 (Chicago, IL, USA). Sampling was performed for a prospective study of MRSA colonization prevalence in AD patients, based on an expected frequency of 18.3%. Ninety-three patients were required to estimate population prevalence with significance set at 0.05% and power at 90%. Continuous variables were summarized by mean or median values (and their respective variability measures) according to distribution symmetry, verified by Kolmogorov-Smirnov test. MIC$_{50}$ and MIC$_{90}$ were defined as the minimum inhibitory concentrations, encompassing 50 and 90% of isolates tested, respectively.

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For the statistical analysis, we included one isolate from each patient with positive cultures. For patients with two positive samples, we selected the isolate with the smallest inhibition zone diameter and the highest MIC for each antibiotic. For the comparative analysis, we applied the t-Student test for continuous variables with nearly normal distribution, and the Mann-Whitney test for continuous variables with asymmetric distribution, with significance set at \( p < 0.05 \). A two-sided Pearson’s chi-squared analysis or Fisher’s exact test, with \( p < 0.05 \), was used to compare the categorical variables. The linearity relation between continuous variables was investigated via the Spearman’s Correlation coefficient.

To evaluate the discrimination power of 30\( \mu \)g neomycin disk inhibition zone diameter according to neomycin MIC, all \( S. \) aureus isolates available were investigated and the area under the ROC (Receiver Operating Characteristic) curve was determined. We established the breakpoint of inhibition zone diameter to designate neomycin resistance according to neomycin MIC by calculating the sensitivity and specificity arithmetic mean and taking the point with the highest mean.

To evaluate aminoglycoside cross-resistance likelihood between gentamicin and neomycin, a logistic regression model was run, including gentamicin resistance defined by inhibition zone size, neomycin MIC and demographic variables, like sex, age and medical history. In all analyses, the significance level was set as \( p < 0.05 \).

RESULTS

A total of 91 patients were included in the study. Sixty-eight patients had at least one positive culture for \( S. \) aureus (48.4% of the swabs from cutaneous lesions and 61.5% from nasal cavities were positive). Topical antimicrobial resistance frequency is summarized in graph 1. All isolates were resistant to bacitracin. Concerning aminoglycosides, 42.6% and 14.7% were resistant to neomycin and gentamicin, respectively. Five isolates exhibited resistance to mupirocin upon the 5\( \mu \)g disk diffusion assay, but only one (1.1%) was confirmed by MIC test. The existence of two different criteria led to significant discrepancies in interpretation of 10\( \mu \)g disk diffusion assay of fusidic acid. According to the BSAC\(^{21} \) breakpoint, 22.1% of isolates were resistant and this proportion dropped to 7.4% when the EUCAST\(^{22} \) breakpoint was used. MIC criteria (the same in both references) confirmed only four (5.9%) isolates to be resistant to fusidic acid. The MIC\(_{50}\) and MIC\(_{90}\) values for the 68 isolates available for analysis are displayed in table 1.

Demographic characteristics are shown in table 2, associated with colonization by resistant \( S. \) aureus. This analysis could not be performed for mupirocin due to the small number of resistant isolates. The only statistically significant association detected was between the EASI score and fusidic acid resistance (the greater the severity of AD, the higher the probability of colonization by FRSA, \( p = 0.009 \)).

Since testing neomycin susceptibility using a 30\( \mu \)g disk diffusion assay was not standardized, we performed an ROC curve analysis and set a value of \( \geq 16\)mm for the inhibition zone diameter to define susceptibility (according to the MIC reference) (Graph 2). Regarding aminoglycoside cross-resistance, our logistic regression model did not demonstrate an association between gentamicin and neomycin resistance (\( p = 0.896 \)), adjusted by demographic and medical variables (Table 3).

**GRAPH 1:** Relative frequencies of \( S. \) aureus isolates resistant to topical antimicrobials, cultured from the nose and cutaneous lesions of AD patients (n=68)

**TABLE 1:** MIC\(_{50}\) and MIC\(_{90}\) of \( S. \) aureus isolates (n=68)

| Antibiotic    | MIC\(_{50}\) (\( \mu \)g/ml) | MIC\(_{90}\) (\( \mu \)g/ml) |
|---------------|-----------------------------|-----------------------------|
| Neomycin      | 1.5                         | 17.6                        |
| Bacitracin    | 96                          | >256                        |
| Mupirocin     | 0.19                        | 0.38                        |
| Fusidic acid  | 0.38                        | 0.75                        |

MIC\(_{50}\) and MIC\(_{90}\) were defined as the minimum inhibitory concentrations encompassing 50 and 90% of isolates tested, respectively.
Table 3: Cross-resistance between the aminoglycosides gentamicin and neomycin, adjusted by demographic variables (logistic regression model)

| Independent variables                    | Coefficient B | SE  | OR        | IC95%         | p   |
|------------------------------------------|---------------|-----|-----------|---------------|-----|
| Neomycin MIC                             | 1,18          | 0,89| 1,19      | 0,87-2,93     | 0,258|
| Male Sex                                 | 0,77          | 0,82| 2,15      | 0,43-10,81    | 0,352|
| Female Sex                               | 0,31          | 0,12| 0,87      | 0,11-2,11     | 0,352|
| Age (years)                              | 0,16          | 0,17| 1,02      | 0,84-1,66     | 0,334|
| Topical antibiotics use                  | 19,5          | 14,62| 0,99      | 0,21-3,03     | 0,999|
| Previous skin infection                  | -0,40         | 1,29| 0,67      | 0,053-8,427   | 0,757|
| Recurrent cutaneous infections           | 2,15          | 1,54| 3,29      | 0,88-18,54    | 0,214|
| Systemic antibiotics use                 | 0,88          | 1,37| 2,41      | 0,16-55,31    | 0,520|
| Hospitalization                          | -0,121        | 0,17| 0,88      | 0,63-1,24     | 0,483|
| Disease duration (years) £               | -0,01         | 0,09| 0,99      | 0,91-1,01     | 0,828|

SE: standard error. OR: odds ratio. £: model parameters: Pseudo-R2=0.237; -2 log Likelihood=46.750; Hosmer and Lemeshow (p=0.896).
infections, like community acquired MRSA infections (CA-MRSA), any agent with an antistaphylococcal activity plays an important role in the limited armamentarium against these microorganisms, especially if the drug can also combat severe systemic infections, as fusidic acid does. In the literature, there is growing evidence of numerous clinical benefits of topical applied antibiotics (apart from impetigo treatment), notably S. aureus decolonization. In AD patients, despite a recent randomized placebo controlled study that suggested the efficacy of antiseptics and mupirocin in decreasing the clinical severity of the disease, pooled evidence failed to demonstrate that antimicrobial administration (topical or systemic) aimed at reducing S. aureus colonization is clinically useful. However, the benefit of mupirocin use for S. aureus decolonization in other clinical circumstances has been demonstrated by many other studies. Intranasal mupirocin was associated with a significant reduction in surgical-site infections and proven to be a cost-effective approach in prosthetic orthopedic surgery. A systematic review showed a significant reduction in S. aureus nosocomial infections associated with intranasal mupirocin decolonization. Nonetheless, reports of S. aureus mupirocin resistance associated with eradication treatment have raised concerns over continued clinical efficacy.

Clinical evidence demonstrates that judicious use to decolonize identified nasal carriers without S. aureus active infection should reduce resistance levels. As S. aureus decolonization clinical benefits become relevant and mupirocin becomes less active, studies of alternatives are necessary. Resistance to neomycin, bacitracin and polymyxin B was found to be rare in the USA, despite its long period of over-the-counter sales. A small study described successful MRSA decolonization using a triple compound (bacitracin, polymyxin B and gramicidin) in 9 out of 11 patients.

The clinical significance of this in vitro study of topical antimicrobial resistance is uncertain and debate persists about appropriate breakpoints for susceptibility in laboratory testing. A topical product with a widely published breakpoint is mupirocin - susceptible at MIC≤1µg/mL and high-level resistance at MIC≥256µg/mL. Experts believe that only high-level mupirocin resistance may have clinical significance, and this breakpoint corresponds to an approximate 1:100 dilution of the marketed product. However, initial evidence shows that low-level mupirocin resistance combined with a genotypic chlorhexidine resistance significantly increases the failure of MRSA decolonization therapy. With the exception of mupirocin, breakpoints used for topical antibiotic susceptibility testing are not widely available. Neomycin and bacitracin historical breakpoints used in this study were selected to predict success in treating systemic infections at lower in vivo concentrations, not for treating superficial infections at higher concentrations. Bacitracin employment in systemic infections proved limited early due to its high nephrotoxicity, while neomycin was withdrawn following the development of less toxic aminoglycosides. This lack of standardization compromises topical antimicrobial resistance research and monitoring. In the absence of standardization, we considered neomycin historical MIC breakpoints and proposed an inhibition zone diameter of 16mm to define resistance by using a 30µg neomycin disk to routinely monitor neomycin resistance in laboratory centers. Due to the 100% bacitracin resistance we found, it was not possible to establish a breakpoint for the bacitracin disk diffusion routine test.

**CONCLUSIONS**

Our data, from a southern Brazilian sample of AD patients, showed a low prevalence of mupirocin and fusidic acid resistance of S. aureus atopic eczema colonizer strains. However, for neomycin and bacitracin, commonly used topical antimicrobial drugs in Brazil, high levels of resistance were found. Although based on the an-
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In this article, the authors discuss the role of topical antibiotics in the treatment of dermatological conditions, particularly in the context of antimicrobial resistance. They present evidence that the use of topical antimicrobials can lead to the development of resistance, and they emphasize the importance of considering the potential impact of these drugs in the broader context of antimicrobial resistance.

The authors also highlight the need for further research to determine the efficacy and safety of alternative treatments for dermatological conditions, beyond the use of topical antimicrobials. They argue that the widespread use of these drugs may contribute to the overall problem of antimicrobial resistance, which affects not only dermatological conditions but also many other areas of medicine.

Overall, the article provides a comprehensive overview of the current state of knowledge regarding the use of topical antimicrobials in dermatology, and it underscores the importance of continued research and development of alternative treatments to prevent further dissemination of resistance.

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