Susceptibility of *Staphylococcus aureus* to Topical Agents in the United States: A Sentinel Study

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ABSTRACT

Background: Mupirocin has been used topically for treating skin and skin structure infections and for nasal decolonization before surgical interventions. Pleuromutilin compounds, including retapamulin, provide similar treatment/interventional options. Rates of resistance of *Staphylococcus aureus* to mupirocin and other agents used to treat skin and skin structure infections vary between countries and medical centers, including those in the United States. These resistance rates may be associated with higher usage and/or improper epidemiologic practices.

Objective: This study aimed to determine rates of resistance to topical and other class agents against *S aureus* isolates collected from SSSIs.

Methods: Isolates were obtained from outpatients at 6 US dermatology centers in 5 states. Demographic data were collected from medical records, and each patient completed a study questionnaire on recent history of skin infections, antibiotic use, and hospitalization. Each isolate was tested against cephalothin, clindamycin, erythromycin, gentamicin, mupirocin, tetracycline, retapamulin, and trimethoprim/sulfamethoxazole.

Results: Although methicillin-resistance rates varied between centers (range, 15.8%–35.5%), macrolide resistance was ~50% at all of the sites in this study. Mupirocin-resistant isolates were observed much more frequently from 1 center (33.9%), and nearly all demonstrated high-level resistance. Only 1 retapamulin-resistant isolate (0.5%) was observed, with a minimum inhibitory concentration of 16 μg/mL. The other agents had relatively low resistance rates, which varied between centers and were dependent on susceptibility to methicillin.

Conclusions: Although the rate of mupirocin-resistant *S aureus* isolates collected in this investigation was >10%, retapamulin resistance was infrequent. Surveillance of topical agents to determine resistance rates against targeted bacteria is necessary. (*Clin Ther.* 2014;▮:▮▮▮–▮▮▮)

Key words: bacterial resistance, mupirocin, retapamulin, skin and skin structure infections, *Staphylococcus aureus*.

INTRODUCTION

Newer-generation agents from natural products and their semisynthetic derivatives have provided alternatives to other antibacterial agents that have been extensively used for the treatment of skin and skin structure infections (SSSIs).[1] In 1950, pleuromutilin-derived agents were discovered to have antimicrobial activity. The structural nature of these compounds over a decade later provided the development of this molecular class as an important antimicrobial option.[2] Pleuromutilin derivatives were initially limited to veterinary use, and more recently this class has been developed for infections in humans.[3,4] Retapamulin is a semisynthetic pleuromutilin derivative with antimicrobial activity against common gram-positive pathogens associated with SSSIs.[4–8] Retapamulin is best suited as a topical agent for the treatment of uncomplicated SSSIs.[9,10] The US Food and Drug Administration approved the use of retapamulin in 2007 for the topical treatment of impetigo. The European Medicines Agency has approved retapamulin for expanded indications, including impetigo as well as infected small lacerations, abrasions, or sutured wounds. Although most pleuromutilin-derived compounds are used topically, systemic applications are currently being developed for use in humans.[2,3]

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Staphylococcus aureus and *Streptococcus pyogenes* are among the most common gram-positive pathogens associated with complicated and uncomplicated SSSIs.[11] *S aureus*, in particular, can be difficult to treat empirically. Resistance to β-lactams, macrolide-lincosamide-streptogramin agents, fluoroquinolones, and mupirocin among *S aureus* isolates has been reported extensively in the literature.[12] Cross resistance among these commonly used agents is more prevalent among methicillin-resistant *S aureus* (MRSA) strains. Retapamulin provides reliable activity against methicillin-susceptible *S aureus*, MRSA, and *S pyogenes*, including multidrug-resistant (MDR) isolates, and may obviate exposure to systemic agents.[5,12] Infection models have confirmed the efficacious utility of retapamulin as a topical antimicrobial agent for some infections.[13] Another key feature of retapamulin is that it has a low propensity to select resistant mutations of both *S aureus* and *S pyogenes* spontaneously or by repeated exposure.[14]

As with all other antimicrobial agents currently used in clinical practice, pleuromutilin derivatives are not immune to bacterial-resistance mechanisms. It is now understood that the chloramphenicol-florfenicol resistance gene (*cfr*) contributes to resistance to pleuromutilin derivatives and macrolide-lincosamide-streptogramin agents, as well as linezolid.[15] Mutations of the ribosomal protein L3 gene (*rplC*) can confer resistance to several agents that target the ribosome, although retapamulin resistance has not been associated with this particular genetic mutation.[16] The *Isa(E)* gene, isolated from MRSA in swine, can be located on a multiresistance plasmid and confers resistance to ribosomal targeting agents, including pleuromutilins.[17] This particular resistance gene is associated with MDR and may be alarming if persistence, transfer, and dissemination are associated with infections in humans.

This study evaluated the in vitro activity of retapamulin, mupirocin, and comparator agents against *S aureus* isolates collected during 2010–2012 from patients' SSSIs in dermatology clinics located in the United States.

MATERIALS AND METHODS

All samples were derived from outpatients; eligible patients included all age groups with SSSIs from 6 dermatology clinics in 5 states (Alabama, Arkansas, California [2 sites], Florida, and Texas). Centers were instructed to provide consecutively collected samples, limited to 1 sample from each patient. The vast majority of samples were collected from deep swabs, with fewer numbers collected by needle aspiration, biopsy, or other methods. The sources of infection from the submitted specimens were categorized as wound (n = 256), abscess/pus (109), exudates (80), tissue (25), and other bodily fluids or otherwise unknown sources (28). Demographic data, including patients' age, specimen source, hospital location, and clinical diagnosis, were collected. Patients completed a study questionnaire on recent history of skin infections, antibiotic use, and hospitalization. Institutional review board approval of the study protocol was obtained from sites requiring it, and patient confidentiality was confirmed.

Samples were cultured onto blood agar plates immediately on receipt, and plates were examined the following day. Based on colony morphology, *S aureus* isolates were identified by Gram-staining results and growth on mannitol salt agar and were further confirmed by latex agglutination testing. The identification of each isolate and subsequent susceptibility testing of isolates, including D-testing and cefoxitin, retapamulin, and mupirocin disk determinations, were performed according to the Clinical and Laboratory Standards Institute (CLSI) guidelines and in accordance with good laboratory practice.[18] Antimicrobial testing was performed using common lot broth microdilution panels. Ancillary products and retapamulin and mupirocin disk reagents were obtained from commercial manufacturers.

Broth microdilution susceptibility testing methods and susceptibility interpretations were those recommended by the CLSI.[19] Each isolate was tested against cephalothin, clindamycin, erythromycin, gentamicin, mupirocin, tetracycline, retapamulin and trimethoprim/sulfamethoxazole (TMP/SMX). Additionally, the D-test was used to determine inducible clindamycin resistance, which was included on the broth-microdilution panels. Disk-diffusion testing was performed against all isolates using cefoxitin (30 μg) disk to determine methicillin resistance to *S aureus* (MRSA) using CLSI methods and interpretations.[18,20] Mupirocin (5 and 200 μg) and retapamulin (2 μg) disk-diffusion testing was also performed.

Tentative microbiological cutoff breakpoints using minimum inhibitory concentration (MIC) and disk-diffusion testing for retapamulin and mupirocin have been previously published.[21,22] The proposed