In vitro Investigation on the Susceptibility of *Staphylococcus aureus* and β-hemolytic Streptococci toward Mupirocin and Fusidic Acid for Skin Infections in the Outpatient Sector – Update 2018

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Introduction

Mupirocin is characterized by a mode of action that is unique among antibiotics (inhibition of isoleucyl-tRNA synthetase) and has been used in Germany for more than 15 years in the outpatient sector as a topical antibiotic for the calculated therapy of small-scale bacterial skin infections (e.g. contagious impetigo), prescribed primarily in the context of pediatrics. In the inpatient sector, it is being used for the intranasal eradication of *Staphylococcus aureus* (including methicillin-resistant strains, MRSA). Initially, the use of mupirocin in the outpatient sector was frowned upon because of concerns that this would lead to the development of resistances. However, these fears were refuted by repeated *in vitro* susceptibility studies in 2004, 2007, 2010, 2013, and 2015[1–5]. In contrast, with fusidic acid, which has been used against gram-positive pathogens for five decades, higher and in some time periods even increasing resistance rates against staphylococci in the lower double-digit range were observed. This may suggest it could be worthwhile to scrutinize the future therapeutic use of fusidic acid. The aim of the present study was to determine the *in vitro* susceptibility of the two main pathogens causing bacterial skin infections, *S. aureus* and β-hemolytic streptococci, to mupirocin and fusidic acid and to establish a current resistance profile.

Materials and Methods

Isolates: 200 isolates of *Staphylococcus aureus* and 100 isolates of *Streptococcus* from groups A, B, C, F and G from patients with skin infections (including contagious impetigo, pyoderma, neurodermatitis, dermatitis) were examined. The isolates originated almost exclusively from the outpatient sector (or, in a few cases, from emergency outpatient wards) and were collected from March to July 2018. All tested isolates of staphylococci were susceptible to oxacillin (MSSA). 40.7 % of the isolates were taken from children and adolescents up to 18 years of age. Susceptibility to oxacillin was routinely checked for each *S. aureus* isolate to rule out MRSA strains.

Susceptibility test: MIC values for mupirocin and fusidic acid were determined by means of an Etest according to the manufacturer's instructions in keeping with the current version of the EUCAST regulations for routine resistance determination. For the sake of comparability with previous surveys, they were rated in accordance with the literature[6,7]. Resistant and intermediate germs were collectively reported as (R) (see Table 1).

Agent	(**S**)usceptible	(**R**)esistant
Mupirocin	≤ 4 mg/L	≥ 8 mg/L
Fusidic acid	≤ 0.5 mg/L	≥ 2 mg/L

Table 1: Reference thresholds for the assessment of MIC values.

Results

All isolates of *S. aureus* and *Streptococcus* were fully susceptible to mupirocin. In contrast, 13.0 % of the staphylococci as well as all streptococci isolates were resistant to fusidic acid (Fig. 1 and Table 2).

Agent	Resistance of *S. aureus*		Resistance of *Streptococcus* spp.	
	2004–2015	2018	2004–2015	2018
Mupirocin	0.7–1.4 %	0 %	0 %	0 %
Fusidic acid	7.0–14.0 %	13.0 %	100 %	100 %

Table 2: Resistance rates of staphylococci and streptococci against mupirocin and fusidic acid in the periods 2004–2015[1–5] and 2018.

Discussion

Despite the extended topical use of mupirocin transcending MRSA eradication, particularly in younger patients with bacterial skin infections in the resident sector, no decrease in the suscebtibility rate of staphylococci or streptococci has yet been observed (Fig. 2).

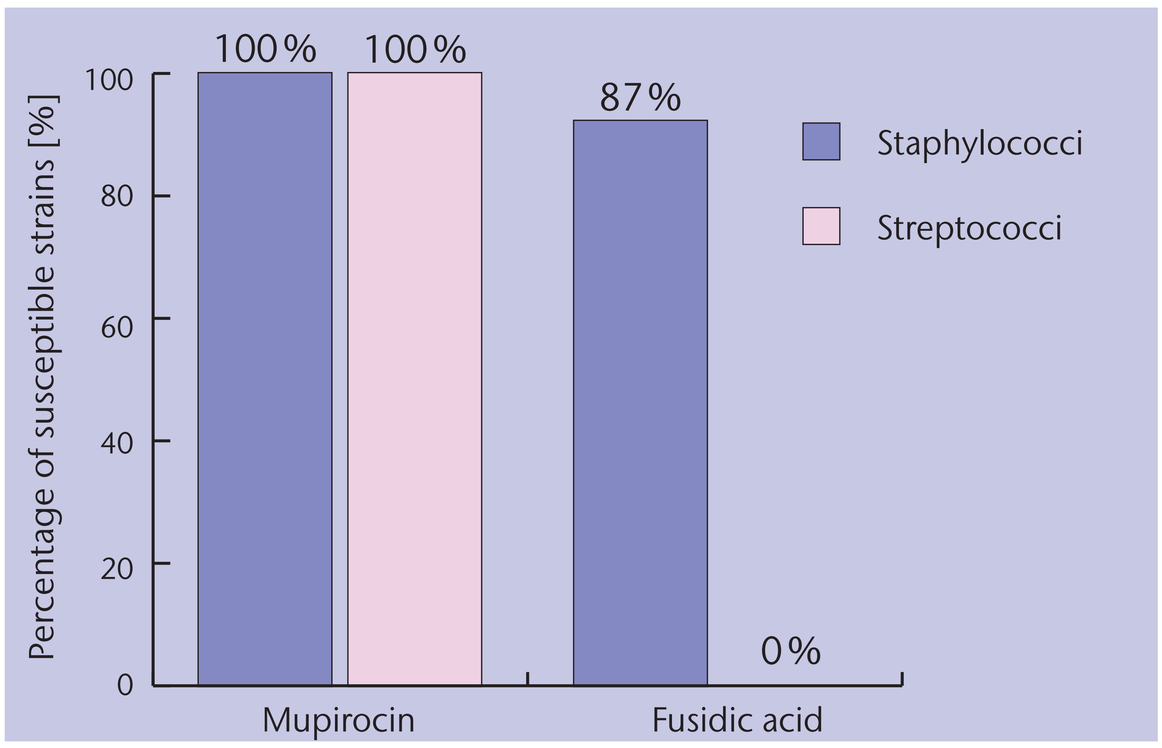

Fig. 1: Susceptibility of pathogens according to the Etest in 2018.

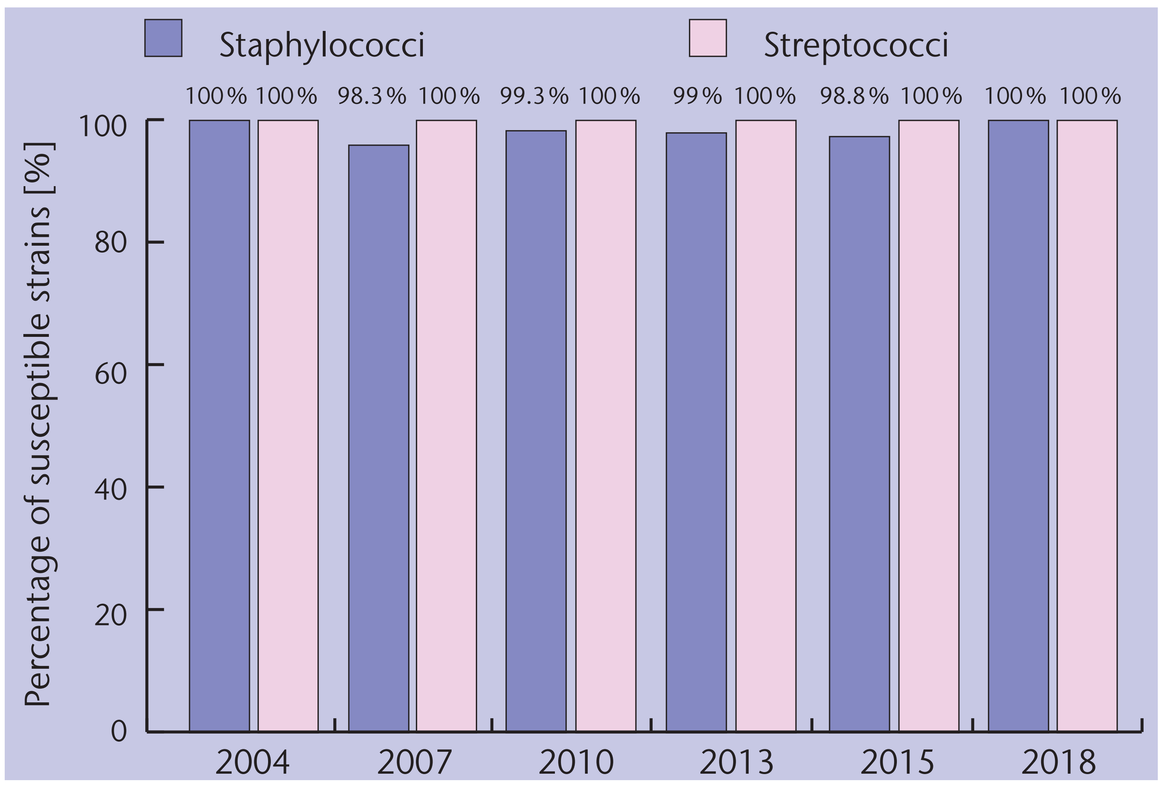

Fig. 2: Development of susceptibility to mupirocin in the period 2004–2018.

The susceptibility of *S. aureus* (MSSA) and β-hemolytic streptococci toward mupirocin remains at about 100 %, showing no change over previous studies from recent years. Hence, there is currently no evidence of an increasing resistance. Based on the responsible use of mupirocin within a calculated therapy, the resistance of *S. aureus* and β-hemolytic streptococci to mupirocin has remained stable for more than 10 years. Methicillin-resistant staphylococci (MRSA) from the outpatient sector (community-acquired, (ca)MRSA) are almost completely covered by mupirocin.[8] For several reasons, the possible development of resistance in MRSA strains from the inpatient sector (hospital-acquired, (ha)MRSA) has to be considered separately.[9] In addition to possible genetic differences between the strains, the patient groups from the inpatient sector can also not be compared with those from the outpatient sector. Risk factors for colonization with (ha)MRSA are long/frequent inpatient stays, a patient age over 60 years or open wounds.[10]

For fusidic acid, which exhibits no activity against β-hemolytic streptococci, the resistance rate in *S. aureus* (13.0 %) was observed to be stable as compared to 2015 (12.7 %).

Conclusion: Due to the excellent resistance situation, mupirocin may still be considered as a fully effective therapeutic option for calculated topical therapy of small-scale skin infections with *S. aureus* and/or streptococci in the outpatient sector. If possible, the use of fusidic acid should be considered only if the local resistance situation is known and the nature of the pathogen is proven.

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