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Short Research Paper

Staphylococcus epidermidis isolates from nares and prosthetic joint infections are mupirocin susceptible

Lavin Salih[1], Staffan Tevell[1,2], Emeli Månsson[1,3], Åsa Nilsdotter-Augustinsson[4], Bengt Hellmark[1], Bo Söderquist[1]✉

1. School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
2. Department of Infectious Diseases, Karlstad Hospital, Sweden
3. RegionVästmanland - Uppsala University, Centre for Clinical Research, Hospital of Västmanland, Västerås, Sweden
4. Division of Infectious Diseases, Department of Clinical and Experimental Medicine, Faculty of Health Sciences, Linköping University, and Department of Infectious Diseases, County Council of Östergötland, Linköping, Sweden

✉ Corresponding author: Bo Söderquist, MD, PhD, Professor, Department of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital, SE-701 85, Örebro, Sweden. Telephone: +46-19-6023571; e-mail: bo.soderquist@oru.se

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Abstract

The objective of the present study was to investigate the antibiotic susceptibility including mupirocin among *Staphylococcus. epidermidis* isolated from prosthetic joint infections (PJIs) (n=183) and nasal isolates (n=75) from patients intended to undergo prosthetic joint replacements. Susceptibility to mupirocin (used for eradication of nasal carriership of *Staphylococcus aureus*) was investigated by gradient test, and susceptibility to various other antimicrobial agents was investigated by disc diffusion test. All isolates, except three from PJIs and one from the nares, were fully susceptible to mupirocin. Multi-drug resistance (≥3 antibiotic classes) was found in 154/183 (84.2%) of the PJI isolates but only in 2/75 (2.7%) of the nares isolates, indicating that *S. epidermidis* causing PJIs do not originate from the nares.

Key words: Staphylococcus epidermidis, Prosthetic joint infections, Mupirocin, Antibiotic susceptibility testing

Introduction

Prosthetic joint surgery is a medical-technical success which offers an improved quality of life to many patients. However, in rare cases, the primary joint implants may become infected, with long-lasting prosthetic joint infections (PJIs) as a result. PJI is a complication affecting 1–2% of hip and knee arthroplasties [1,2]. These infections account for significant health care expenses due to prolonged hospitalization, long-term antimicrobial treatment, and revision surgeries, as well as increased mortality and morbidity, with patients suffering disability and pain [1,2]. *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS), predominantly *S. epidermidis*, are the most common aetiological agents of PJIs [1,2]. These staphylococci are part of the human normal flora, colonizing both the skin and mucous membranes, including the nares. The presence of microorganisms in a surgical wound is a prerequisite for the establishment of an infection, and the pathogens are commonly regarded as originating from the patient's endogenous flora. Pre-operative strategies in order to reduce the number of bacteria on the skin, and accordingly wound contamination, include preoperative showers with antiseptic agents such as chlorhexidine soap. However, bacteria can almost always be isolated from a surgical wound. Nasal colonization with *S. aureus* is a risk factor for surgical site infections such as PJIs [3]. Furthermore, previous studies have shown that nasal decolonization of *S. aureus* with mupirocin has been effective in reducing surgical site infections and thus decreasing the occurrence of deep PJIs [4].

Mupirocin, also known as pseudomonic acid A, is an antibiotic agent originally extracted from

Pseudomonas fluorescens. It acts on bacterial isoleucyl-t-RNA synthetase and therefore inhibits the protein synthesis [5]. Due to the degradation of acids in the human body, the agent can only be administrated topically on the skin and mucous membranes, and so it is manufactured as ointment. Emerging resistance due to point mutations in *MupA* and *MupB* genes involved in encoding isoleucyl-tRNAs have been reported [5,6].

Decolonization with intranasal mupirocin, in combination with topical chlorhexidine baths, has also been used in neonates at intensive care units with the aim of decreasing infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) [7]. However, the presence of high levels of resistance to mupirocin among CoNS isolated from preterm neonates has been reported [8].

The aim of the present study was to investigate susceptibility to mupirocin among *S. epidermidis* isolated from PJIs and nasal isolates from patients intended to undergo prosthetic joint replacements. If *S. epidermidis* present in the nares, and thereby also on the human skin, can be eradicated by the use of topical mupirocin before arthroplastic surgery, this may offer a way to prevent PJIs.

Methods and materials

A total of 183 isolates of *S. epidermidis* obtained during revision surgery from patients with PJIs of the hip (n=126), knee (n=41), shoulder (n=12), or elbow (n=4) at the University Hospitals of Örebro and Linköping from 1999 to 2015 and from 1993 to 2015, respectively were included. In addition, nasal isolates (n=75) from patients intended to undergo prosthetic joint replacements from 2013 to 2015 were used for comparison. All isolates were identified as *S. epidermidis* by MALDI-TOF MS (Microflex LT and Biotyper 3.1, Bruker Daltonics, Bremen, Germany). The isolates were stored in preservation medium (Trypticase soy broth with 0.3% yeast extract and 29% horse serum) at -70°C pending further analysis. In addition, 75 nasal isolates of *S. epidermidis* were obtained from patients prior to elective arthroplastic surgery.

Antibiotic susceptibility testing by disc diffusion test was performed according to EUCAST guidelines (http://www.eucast.org). Multi-drug resistance (MDR) was defined as resistance against ≥ 3 antibiotic classes. The antibiotics tested were fusidic acid 10µg, gentamicin 10µg, erythromycin 15µg, clindamycin 2µg, sulphamethoxazole-trimethoprim 25µg, rifampicin 5µg, norfloxacin 10µg, and cefoxitin 30µg (all discs from Oxoid, Basingstoke, UK). The clinical breakpoints were according to the recommendations of EUCAST. The minimum inhibitory concentration (MIC) for mupirocin was determined by Etest (bioMérieux, Marcy l'Etoile, France). The breakpoints for nasal decolonization of *S. aureus* according to NordicAST (http://www.nordicast.org) is S ≤1 mg/L and R >256 mg/L, respectively.

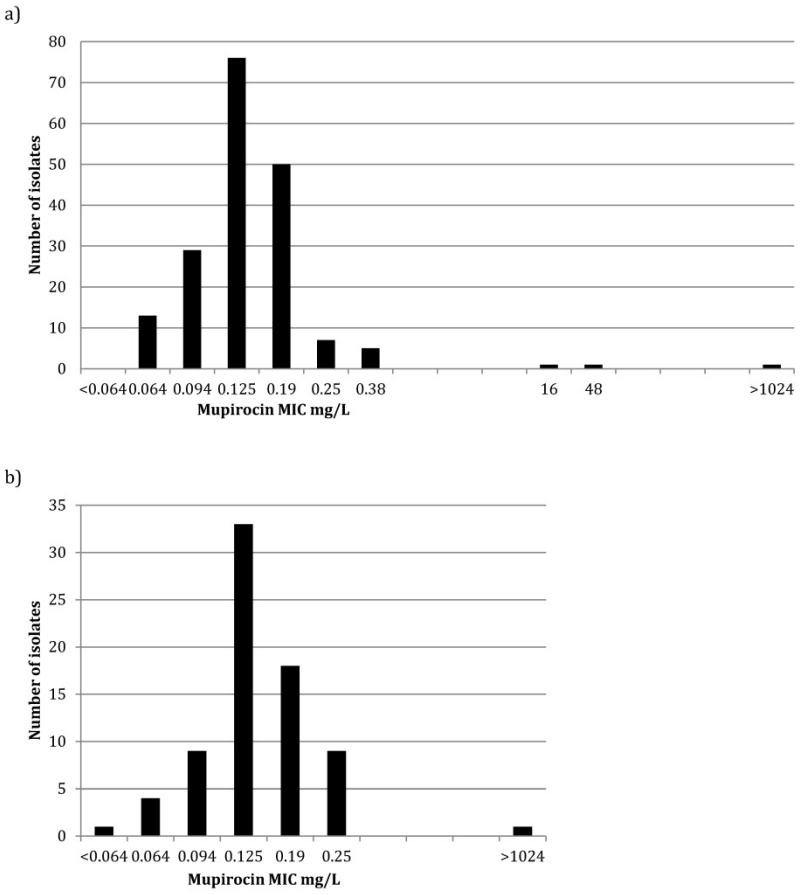

Figure 1. Distribution of minimum inhibitory concentrations (MICs) of mupirocin among S. epidermidis isolates obtained from prosthetic joint infections (a) and from nares (b). The breakpoints for nasal decolonization of S. aureus according to NordicAST (http://www.nordicast.org) is S ≤1 mg/L and R >256 mg/L, respectively.

Results

All but three isolates of *S. epidermidis* from PJIs were fully susceptible to mupirocin, with MIC values ranging from 0.064 to >1024 mg/L (Figure 1a). MIC_{50} and MIC_{90} were 0.125 and 0.19, respectively. All but one of the nasal *S. epidermidis* isolates were susceptible to mupirocin, with MIC values ranging from <0.064 to >1024 mg/L (Figure 1b). MIC_{50} and MIC_{90} were again 0.125 and 0.19, respectively.

Table 1. Antibiotic susceptibility testing of S. epidermidis isolates obtained from prosthetic joint infections (PJIs) and from nares of patients intended for elective arthroplastic surgery. Multi-drug resistance (MDR) was defined as resistance against ≥3 antibiotic classes.

	PJIs (n=183) Resistant (%)	Nares (n=75) Resistant (%)
Cefoxitin	137 (74.9%)	5 (6.7%)
Fusidic acid	81 (44.3%)	8 (10.7%)
Clindamycin	105 (57.4%)	2 (2.7%)
Erythromycin	115 (62.8%)	14 (18.7%)
Gentamicin	130 (71.0%)	2 (2.7%)
Rifampicin	52 (28.4%)	0 (0%)
Sulfamethoxazole/ trimethoprim	134 (73.2%)	7 (9.3%)
Norfloxacin	148 (80.9%)	3 (4.0%)
Mupirocin	3 (1.6%)	1 (1.3%)
MDR	154 (84.2%)	2 (2.7%)

The results of the antibiotic susceptibility testing of *S. epidermidis* isolated from PJIs and nares, respectively, are shown in Table 1. The majority of the PJI isolates displayed resistance against various antibiotic agents, and 154/183 (84.2%) were found to be MDR. Resistance to methicillin, investigated by using cefoxitin (< 24 mm zone diameter), was present in 137/183 (74.9%) of PJI isolates and 5/75 of nasal isolates (6.7%) ($p<0.0001$; Fisher's exact test). The majority of the 75 isolates obtained from the nares were susceptible to most of the tested antibiotic agents (Table 1). Two of the nasal isolates displayed the MDR phenotype ($p<0.0001$; Fisher's exact test).

Discussion

This study investigated the antimicrobial susceptibility of *S. epidermidis* isolated from PJIs and nares, with a special focus on the antimicrobial agent mupirocin. The purpose of the investigation was to find out if *S. epidermidis* isolates present in the nares of patients intended to undergo elective implant surgery were susceptible to mupirocin, and thus if nasal eradication of *S. epidermidis* with mupirocin could be a strategy for preventing PJI.

Since antimicrobial susceptibility testing for mupirocin of the nasal *S. epidermidis* isolates showed that almost all isolates were susceptible, it could be possible, in parallel with eradication strategies for *S. aureus* [3,4,7,8], to eradicate a nasal carriership of *S. epidermidis.* Thus, the use of mupirocin ointment as a topical treatment in the nares before surgery could be hypothesized to prevent surgical site infections and PJIs caused by the commensal, yet possibly invasive, *S. epidermidis.*

This finding of high susceptibility to mupirocin among *S. epidermidis* isolated both from the nares and from PJIs is not fully consistent with previous studies from France [9], where 6.6% of CoNS isolated from nostrils of patients admitted for orthopaedic surgery were resistant to mupirocin, and from the US [10], where 24% of CoNS isolated from PJIs were resistant. In the present study, 1.3% of CoNS isolated from nares of orthopaedic surgery patients and 1.6% from PJIs, respectively, were not fully susceptible to mupirocin. This indicates that it is important to investigate local conditions regarding mupirocin sensitivity before commencing mupirocin prevention strategies for post-operative infections. In Sweden, mupirocin is not routinely used for decolonization pre-operatively. The consumption of mupirocin is very limited and mainly restricted to eradication of MRSA carriership.

There was a significant difference in prevalence of MDR between *S. epidermidis* isolated from the nares and from PJIs; the MDR phenotype was almost absent among isolates from nares, but present in the majority of the PJI isolates. This indicates that strains causing PJIs do not obviously originate from the nares, and thus may not be part of the normal flora of the patients prior to arthroplastic surgery. Furthermore, we have previously shown that the dominating sequence types (ST) among PJI isolates were ST2 and ST215 compared to a wide diversity among commensals by applying MLST [11]. The origin of the MDR *S. epidermidis* isolates of patients affected by PJIs thus becomes an intriguing question. Is there an alteration of the skin flora following the pre-operative chlorhexidine showers, and subsequent re-colonization by MDR *S. epidermidis* from the hospital environment and/or hospital staff? Further studies regarding the origin of MDR *S. epidermidis* causing PJIs are highly warranted and of great importance in order to better understand the pathogenesis of PJI and to prevent PJIs.

In conclusion, the majority of *S. epidermidis* isolates obtained both from nares and PJIs were susceptible to mupirocin. However, MDR was found in most of the PJI isolates but only in a few isolates from the nares, indicating that *S. epidermidis* causing PJIs do not represent colonizers of the nares and hence the normal skin flora. The origin of these MDR *S. epidermidis* thus has to be sought elsewhere.

Acknowledgement

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Ethical statement

This work deals with clinical bacterial isolates from human infections. No tissue material or other

biological material was stored from the patients, only subcultured bacterial isolates. Swedish law does not require ethical approval for work with bacterial isolates from humans. All information regarding these isolates was anonymized. The collection of nasal isolates was performed following informed consent and was approved by the Regional Ethical Review Board of Uppsala, Sweden (ref: 2012/092).

Competing Interests

The authors have declared that no competing interest exists.

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