High prevalence of mupirocin resistance associated with resistance to other antimicrobial agents in Staphylococcus aureus isolated from patients in private health care, Western Cape

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Staphylococcus aureus is an opportunistic pathogen which results in high morbidity and mortality. Decolonisation of the carriers by the intranasal administration of mupirocin is frequently prescribed in infection control practice. The aim of this study was to establish the prevalence of mupirocin resistance in our setting and to investigate the association between mupirocin resistance and resistance to other antimicrobial agents. We simultaneously evaluated laboratory procedures for the sensitivity testing of mupirocin. Standardised disc sensitivity testing for high-level resistance to mupirocin was performed on a prospective sample of 997 unique clinical isolates of S. aureus. The results were confirmed with molecular testing. We also evaluated the reliability of automated sensitivity testing by Vitek® 2. Statistical methods were used to estimate associations between high-level resistance to mupirocin and resistance to other antimicrobial agents. High-level mupirocin resistance prevalence was 23.37% [95% confidence interval (CI): 20.77-26.12]. The phenotypic results agreed with the molecular tests for the mupA gene. Raw agreement between standardised disc sensitivity and the automated method was 94.38%, with a weighted kappa of 0.8767 (95% CI: 0.83-0.90). We found statistically significant associations between high-level mupirocin resistance and resistance to clavulanic acid, fusidic acid, fluoroquinolones, co-trimoxazole and macrolide-lincosamide-streptogramin B phenotypes. The high prevalence of mupirocin resistance in this setting necessitates sensitivity testing before decolonisation with mupirocin. The correlation between high-level mupirocin resistance and resistance to other antimicrobial agents implies selective pressure for more resistant strains, which should be considered in the practice of antimicrobial stewardship.

Introduction

Staphylococcus aureus carriage and infection

Staphylococcus aureus is an organism that is exceptionally well adapted to its human host, and may cause both common and serious infections. As a coloniser, it occurs in as many as 70% of people, in either a transient or a permanent carrier state. The most common site of colonisation is the anterior nares, although the nasopharynx, axillae, gut and inguinal areas may also yield positive culture. Most staphylococcal infections are caused by endogenous strains, and it is recognised that the nasal carriage presents a risk for infection, particularly in patients undergoing surgery or other medical interventions.

Methicillin-resistant S. aureus (MRSA), in particular, is recognised as one of the healthcare-associated infections which may have a negative impact on outcome, in terms of morbidity and mortality. Although guidelines and practice differ significantly between countries, healthcare sectors and institutions, screening for carrier status and the decolonisation of carriers as a means of preventing infection is often advocated and widely practised. Intrasenal mupirocin is commonly prescribed in decontamination regimens. However, loss of sensitivity to mupirocin, resulting in clinical decolonisation failure, has been described with increasing frequency.

In practice, the cost of screening has to be weighed against proven benefit to patient outcome. A broader form of universal decolonisation, e.g. decontaminating patients, irrespective of their carrier status, in order to save the cost of laboratory investigations, is an alternative approach to screening patients for MRSA, as well as isolating them, until the decontamination has been effected. The success of such a strategy was established by a cluster randomised trial that was recently published. However, caution was expressed that the selective pressure of these strategies could lead to increasing resistance to decontaminating agents, such as mupirocin.

Therefore, implementation of any strategy in the local setting has to be considered against knowledge of the prevalence of resistance to agents that are used, and also monitoring of the effect of usage on antimicrobial resistance in order to avoid so-called “collateral damage” through the selection of strains resistant to other classes of antimicrobial agents than the one administered.
**Resistance to mupirocin**

Mupirocin is a topical antibiotic in an ointment formulation. It is widely prescribed to treat superficial staphylococcal and streptococcal infections. Over the past few decades, a nasal formulation has been used to eradicate the nasal carriage of *S. aureus*. Mupirocin consists of a combination of different pseudomonic acids which reversibly bind to the isoleucyl-tRNA synthetase in Gram-positive organisms, resulting in the inhibition of protein synthesis. It is bacteriostatic at low concentrations and bactericidal at high concentrations.

The mechanisms of mupirocin resistance have been elucidated: Low-level resistance can be caused by an alteration in the isoleucyl-tRNA synthetase gene, *ileS*. This mutation is stable and non-transferrable. High-level resistance is mostly associated with the presence of the *mupA* gene, which encodes an alternate isoleucyl-tRNA synthetase. High-level resistance in the absence of this gene has been encountered, suggesting resistance by other mechanisms. Furthermore, the *mupA* gene is associated with mobile genetic elements and is mostly plasmid borne, which may facilitate the spread of this resistance mechanism. These plasmids also carry resistance genes to other antimicrobial agents, such as macrolides, gentamicin, tetracycline and trimethoprim.

Although sensitivity to mupirocin is not affected by the same genetic elements as resistance to beta-lactam agents, such as cloxacillin, an association between MRSA and mupirocin resistance has been noted in the literature.

Sensitivity to mupirocin is described according to three categories:

- **Low-level mupirocin resistance** with a MIC of 8-64 µg/ml.
- **High-level resistance** with a MIC above 512 µg/ml.

Isolates with values of > 64 µg/ml and < 512 µg/ml are extremely rare. The clinical failure of decolonisation therapy has been associated with high-level resistance, and low-level resistance is considered to be of less importance. However, the prevalence of low-level resistance is generally low. Therefore, it is more difficult to assess its impact.

Laboratory guidelines recommend the use of a 5 µg/ml antimicrobial sensitivity disc to screen for possible resistance, followed by confirmation of high-level resistance by testing the organism against a 200 µg/ml disc. As strains with a MIC of 128 or 256 µg/ml are uncommon, it is considered adequate to classify isolates as either sensitive, low-level resistant or high-level resistant. An alternative approach is to confirm the presence of the *mupA* gene by polymerase chain reaction (PCR), but this may be prohibitively expensive when large numbers of isolates are to be screened, and other mechanisms of resistance cannot be excluded.

The objectives of this research were to establish the prevalence of high-level resistance to mupirocin in clinical isolates of *S. aureus* in our patient population, and to estimate the association of such resistance and resistance to other classes of antimicrobial agents in order to consider the effect of the use of mupirocin on the selection of antimicrobial-resistant strains. We also confirmed the results using a molecular test for the presence of the *mupA* gene, and evaluated automated testing at a lower breakpoint as a screening test for resistance.

**Method**

A prospective cross-sectional design was chosen to establish the prevalence of mupirocin resistance in clinical isolates collected from patients served by our diagnostic laboratory.

**Study setting and patient population**

The study was conducted in the reference laboratory of PathCare Laboratories located at N1 City, Goodwood. The laboratory is accredited by the South African National Accreditation System, and provides diagnostic services to patients treated by general practitioners and specialists in the community or in healthcare facilities ranging from private practises, hospices and frail care centres, to private hospitals in the Western Cape.

**Inclusion criteria**

Isolates of *S. aureus* cultured from clinical specimens submitted during the study period of three months (June 2013 to August 2013) to the PathCare reference laboratory were considered for inclusion. These included diagnostic specimens, as well as preoperative specimens submitted for culture to determine colonisation.

**Exclusion criteria**

The similarity of strains can only be confirmed by molecular strain typing methods, which were prohibitively expensive for our sample size. In order to minimise the possibility of duplicate strains, additional isolates originating from the same patient within a period of three days were excluded. Because the laboratory protocol for antimicrobial sensitivity testing of urine isolates differs significantly from that used for isolates from other sources, urine samples were also excluded.

**Ethical issues**

The protocol of this project was approved by the research committee of the Faculty of Medicine and Health Sciences, Stellenbosch University (N13/04/050). As analysis of the data excluded identifiers and the study did not influence the management of patients in any way, a waiver of individual consent was granted.

**Specimen characteristics**

We collected the demographical data on patients from which the specimens originated, including age and sex, the type of specimen taken (respiratory specimen, swab, pus, tissue, and blood and cerebrospinal fluid) and the type of doctor who submitted the specimen (generalist, surgeon, physician, paediatrician, otolaryngologist and gynaecologist).

**Isolation and identification of isolates**

*S. aureus* isolated from clinical specimens was identified according to standard laboratory operating procedures. This included either identification by Vitek® MS or by Vitek® 2 (bioMerieux Worldwide).
Routine antimicrobial sensitivity testing and interpretation

Antimicrobial sensitivity was determined by the Vitek® 2 automated system for most isolates, or by disc sensitivity testing in the case of blood culture. All tests and quality assurance procedures were performed and interpreted according to the standards set by the Clinical Laboratory Standards Institute (CLSI). The CLSI guidelines do not provide interpretation criteria for the sensitivity testing of fusidic acid. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria interprets fusidic acid activity as either sensitive (≤ 1 mg/l) or resistant (>1 mg/l) without an intermediate category. We used this criterion to interpret the breakpoint testing performed by the Vitek® 2 automated system. Where the macrolide-lincosamide-streptogramin B (MLSB) phenotype (inducible clindamycin resistance encoded by the plasmid-borne gene, 

We used this method to screen isolates for decreased susceptibility to mupirocin (low-level resistance), a standardised inoculum (1.5 x 10⁸ colony-forming units/ml) of each isolate was plated on Mueller-Hinton agar produced in house. A sensitivity disc containing 5 µg/ml mupirocin (Quantum Biotechnologies, Johannesburg) was placed on the inoculum and incubated for a minimum of 24 hours at 35°C ambient air. Isolates without a visible zone of inhibition around the 5 µg/ml disc were subsequently tested with a disc containing 200 µg/ml of mupirocin to establish high-level resistance. An interpretation of the zone sizes was carried out (Table I).

<table>
<thead>
<tr>
<th>Inhibition zone diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 µg/ml disc</td>
<td>200 µg/ml disc</td>
</tr>
<tr>
<td>Any zone</td>
<td>Any zone</td>
</tr>
<tr>
<td>No zone</td>
<td>Any zone</td>
</tr>
<tr>
<td>No zone</td>
<td>No zone</td>
</tr>
</tbody>
</table>

This method was evaluated and approved by our laboratory quality assurance procedures using S. aureus ATCC® BAA-1708 (known to carry the mupA gene) as a control for resistance, and S. aureus ATCC® 25923 as a control for sensitivity.

To further validate our disc sensitivity testing, a real-time PCR assay was set up, according to a method previously described, to detect the presence of the mupA gene in a restricted random sample (n = 5 in each group), representative of isolates that tested sensitive, low-level resistant and high-level resistant to mupirocin. The same strains used for the quality assurance of disc testing were used as positive and negative controls for the molecular tests.

Although it is not routinely reported, the panel of antimicrobial agents routinely tested with the Vitek® technology includes mupirocin. The main reason for not reporting these results is that the method of testing and reporting is not standardised according to the CLSI or EUCAST criteria. As these data were available, we captured the Vitek® results for mupirocin in order to evaluate the reliability of this method by comparing it to our standardised disc sensitivity method.

Analysis of data

Data were analysed using SAS® version 9.3. The prevalence of antimicrobial resistance, including mupirocin resistance, was calculated as percentages with 95% confidence intervals (CIs). Exact methods were used to calculate CIs in cases where the prevalence of resistance was very low. Raw agreement between automated sensitivity testing by Vitek® 2 and standardised disc testing was calculated as the number of concurrences for resistance and sensitivity, divided by the total number of isolates tested. A weighted kappa was produced as a statistical measure of agreement. Data concerning mupirocin and antimicrobial resistance were compared using contingency tables and associations estimated using the chi-square test. Fischer’s exact test was used in cases where the conditions for the chi-square test were not met. The Mann-Whitney U test was used to estimate the association between mupirocin resistance and continuous data not normally distributed. A p-value of less than 0.05 was used throughout to assess statistical significance.

Study limitations and issues of validity

The study was laboratory based and limited clinical information was available. Technologists and scientists performing sensitivity testing with the various methods were blinded to the previous results to enhance the internal validity of the study.

Results

After applying the exclusion criteria described previously, data on 997 isolates were included for further analysis. The majority of these specimens were submitted for diagnostic purposes. Only a small percentage of swabs (4.7%) were submitted to determine colonisation.

Demographical data

The included specimens represented 481 female and 515 male patients. The sex of one patient was unknown (n = 997). There was no significant difference in the proportion of males and females (p-value 0.27).
The age of one of the subjects could not be determined. The median age was 51 years for the remaining 996 cases, ranging from newborn babies to those aged 99 years.

The majority of isolates were originated from swabs (77.43%). Other specimen types were represented as follows: respiratory specimens (9.82%), aspirates (6.02%), tissue samples (5.52%), vascular catheters (0.70%), cerebrospinal fluid (0.3%) and blood culture (0.2%).

The distribution of the different categories of clinicians who submitted the samples from which isolates were taken is displayed in Figure 1.

Prevalence of clinically resistant antimicrobial phenotypes

The main antimicrobial resistance characteristics of *S. aureus* in this population are displayed in Table II. All isolates were susceptible to linezolid and the glycopeptides.

The prevalence of mupirocin resistance according to disc sensitivity testing

Forty-three of the 997 isolates exhibited low-level resistance (4.31% with 95% CI: 3.22-5.76), while 234/997 exhibited high-level resistance. Therefore, the prevalence of high-level resistance in this setting was calculated to be 23.37%, with 95% CI: 20.77-26.12.

The presence of molecular markers of resistance

Molecular tests corresponded with the categorisation of sensitivity of the isolates according to disc sensitivity testing for every isolate tested. They confirmed the presence of the *mupA* gene in each isolate from the sample selected from the group that displayed high-level resistance to mupirocin. The *mupA* gene amplification was negative in all mupirocin sensitive isolates, including those displaying only low-level resistance to mupirocin.

### Table II: The prevalence of different antimicrobial resistance phenotypes

<table>
<thead>
<tr>
<th>Antimicrobial resistance phenotype</th>
<th>Percentage of isolates displaying that phenotype, n = 997</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBP alteration (MRSA)</td>
<td>19.56</td>
<td>17.14-22.16</td>
</tr>
<tr>
<td>Quinolone resistance</td>
<td>19.46</td>
<td>17.04-22.05</td>
</tr>
<tr>
<td>Fusidic acid resistance</td>
<td>15.06*</td>
<td>12.84-17.28</td>
</tr>
<tr>
<td>Rifampicin resistance</td>
<td>1.71</td>
<td>0.91-2.72</td>
</tr>
<tr>
<td>Co-trimoxazole resistance</td>
<td>9.33</td>
<td>7.51-11.31</td>
</tr>
<tr>
<td>Tetracycline resistance</td>
<td>5.13*</td>
<td>3.84-6.68</td>
</tr>
<tr>
<td>Gentamicin resistance</td>
<td>6.92</td>
<td>5.42-8.68</td>
</tr>
</tbody>
</table>

CI: confidence interval, PBP: penicillin binding protein, MLS$_S$: macrolide-inducible streptogramin B, MRSA: methicillin-resistant *Staphylococcus aureus*

*n = 996, because of missing data for fusidic acid sensitivity on one isolate

*n = 995, as two isolates from the blood cultures were not tested for tetracycline resistance*

### Table III: Comparison of mupirocin sensitivity testing using the Vitek® 2 system and standardised disc sensitivity testing performed and interpreted according to the Clinical and Laboratory Standards Institute criteria

<table>
<thead>
<tr>
<th>Disc testing</th>
<th>Vitek® 2 testing</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resistant</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Loss of sensitivity (LLR plus HLR)</td>
<td>256</td>
<td>20</td>
</tr>
<tr>
<td>Sensitive</td>
<td>34</td>
<td>685</td>
</tr>
<tr>
<td>Total</td>
<td>290</td>
<td>705</td>
</tr>
</tbody>
</table>

Frequency missing = 2 (Vitek® sensitivity testing was not performed on the blood culture isolates)

HLR: high-level resistance, LLR: low-level resistance

### Table IV: The association between antimicrobial resistance and clinical resistance to mupirocin

<table>
<thead>
<tr>
<th>Antimicrobial resistance phenotype</th>
<th>Test statistic</th>
<th>Probability*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusidic acid resistance</td>
<td>440.25</td>
<td>0.0000</td>
</tr>
<tr>
<td>Quinolone resistance</td>
<td>277.43</td>
<td>0.0000</td>
</tr>
<tr>
<td>MLS$_S$ (macrolide-inducible resistance)</td>
<td>124.17</td>
<td>0.0000</td>
</tr>
<tr>
<td>PBP alteration (MRSA)</td>
<td>97.85</td>
<td>0.0000</td>
</tr>
<tr>
<td>Co-trimoxazole resistance</td>
<td>10.74</td>
<td>0.0010</td>
</tr>
<tr>
<td>Gentamicin resistance</td>
<td>3.48</td>
<td>0.0623</td>
</tr>
<tr>
<td>Tetracycline resistance</td>
<td>2.71</td>
<td>0.0993</td>
</tr>
<tr>
<td>Rifampicin resistance</td>
<td>1.30</td>
<td>0.3870**</td>
</tr>
</tbody>
</table>

MLS$_S$: macrolide-inducible streptogramin B, MRSA: methicillin-resistant *Staphylococcus aureus*, PBP: penicillin binding protein

Probabilities were calculated using the chi-square test, unless otherwise indicated

*A p-value of < 0.05 was considered to be of statistical significance. Values that met this criterion are displayed in bold

**The p-value was calculated using Fisher’s exact test as criteria for the chi-square test were not met*

### Correlation between Vitek® 2 and disc sensitivity testing for mupirocin

Two hundred and ninety (n = 995) isolates tested resistant to mupirocin on the Vitek® 2 (Vitek® data for two of the isolates were unavailable). We compared the reliability of these results with standardised disc sensitivity testing, where 276 isolates exhibited loss of sensitivity to mupirocin when the low-level resistance and high-level resistance groups were combined. This is cross-tabulated in Table III.

The two methods agreed with regard to sensitivity for 685 isolates, and with respect to resistance for 256 isolates. The Vitek® method missed 20 isolates that were identified as having some level of resistance by the disc method and overcalled resistance in 34 instances that had tested sensitive using the disc method.

Raw agreement between the two methods was 94.57%. Agreement beyond chance was calculated as a weighted kappa of 0.88 (95% CI: 0.83-0.90).
Table V: Association between patient attributes and clinical resistance to mupirocin

<table>
<thead>
<tr>
<th>Patient attribute</th>
<th>Test value</th>
<th>Probability*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.76</td>
<td>0.68</td>
</tr>
<tr>
<td>District</td>
<td>7.06</td>
<td>0.22</td>
</tr>
<tr>
<td>Category of practitioner</td>
<td>33.28</td>
<td><strong>0.00</strong></td>
</tr>
<tr>
<td>Age</td>
<td>3.01</td>
<td>0.08**</td>
</tr>
</tbody>
</table>

Probabilities were calculated using the chi-square test, unless otherwise indicated

* A p value of < 0.05 was considered to be of statistical significance. Values that met this criterion are displayed in bold
** A non-parametric Mann-Whitney U test was used to estimate an association for the variable “age”, which was not normally distributed

Table VI: The ranking of the variable practitioner categories according to the rate of encountered mupirocin resistance

<table>
<thead>
<tr>
<th>Categories of practitioner</th>
<th>Mupirocin resistance in specimens submitted by this category (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plastic surgeons</td>
<td>37.50</td>
</tr>
<tr>
<td>Dermatologists</td>
<td>32.36</td>
</tr>
<tr>
<td>Generalists</td>
<td>30.89</td>
</tr>
<tr>
<td>Orthopaedic surgeons</td>
<td>26.00</td>
</tr>
<tr>
<td>Physicians</td>
<td>25.36</td>
</tr>
<tr>
<td>Surgeons</td>
<td>22.04</td>
</tr>
<tr>
<td>Otolaryngologists</td>
<td>11.36</td>
</tr>
<tr>
<td>Paediatricians</td>
<td>8.11</td>
</tr>
<tr>
<td>Gynaecologists</td>
<td>8.00</td>
</tr>
</tbody>
</table>

Discussion

Demographic data

The age distribution of the patients from whom the isolates were cultured indicated a high prevalence in children < 5 years of age, and a bell-shaped distribution in adults, peaking at 63 years of age (data not shown). As may be expected, the majority of specimens were submitted by generalists representing primary health care and from the surgical disciplines; and from orthopaedic surgeons in particular as they deal with the majority of complicated soft tissue and skeletal infections from which S. aureus is the most frequently isolated pathogen.

Antimicrobial resistant phenotypes

The prevalence of MRSA and other dominant resistant phenotypes in the South African setting has been described in several papers. Data submitted to the South African Society for Clinical Microbiology surveillance programme indicated that 27% of S. aureus isolated from blood culture in 2012 were MRSA, 29% MLSB phenotypes, and 17% were resistant to fusidic acid, 3% to rifampicin, 2% to cotrimoxazole and 4% to gentamicin (unpublished data).

The link between antimicrobial consumption and antimicrobial resistance profiles is well established. Therefore, collections of isolates representing invasive infection (blood culture isolates) and nosocomial infection have a denser antimicrobial history, resulting in resistance to many classes of antimicrobial agents. Our sample was cross-sectional and included all specimen types, with the exception of urinary samples, originating from a comprehensive range of clinical settings. Therefore, although direct comparisons could not be made owing to differences in the inclusion criteria, the phenotypic pattern of resistance to antimicrobial agents followed a general trend.

The prevalence of mupirocin resistance

“Clinical resistance” is defined as isolates that are not likely to respond to the topical application of mupirocin. According to the literature, these are isolates with a MIC above 512 µg/ml, as indicated by resistance to discs containing 200 µg/ml of mupirocin. A range of mupirocin resistance rates has been reported in studies. For example, the SENTRY Antimicrobial Surveillance Program, conducted in 2000, reported that rates varied across the Americas and Europe according to geographical area from 1.9-5.6% in bloodstream S. aureus isolates. More recently, Fritz et al reported a relatively low prevalence of 0.9% mupirocin resistance in isolates isolated from patients with community-onset skin and soft tissue infections in the USA, while McDanel et al reported a 9% prevalence of high-level resistance in colonised nursing home residents.

Clinical microbiologists use a rule of thumb of 10% resistance to an agent to preclude its empirical use. This study indicated that the prevalence of high-level resistance to mupirocin in our setting was 23.37% (95% CI: 20.77-26.12). Therefore, it follows that sensitivity to mupirocin should be confirmed before it can be used as a decontaminating agent in our setting. This goes against the approach advocated by Haung et al, and should be factored into local infection control policies.
The correlation between Vitek® 2 and disc sensitivity testing for mupirocin

The agreement between the two methods was good, with a weighted kappa of 0.87. The Vitek® overcalled resistance in more cases than it missed resistance, which is the rarer error. Therefore, it is of value as a screening method, particularly as it forms part of the automated panel of sensitivity tests routinely used, and it can be reported without any additional effort or cost. However, resistance should be confirmed with disc sensitivity testing for high-level resistance, or a molecular test for the mupA gene.

Molecular testing

Molecular screening for *S. aureus* (MRSA and methicillin-sensitive isolates) for the surveillance of colonisation is frequently practised, especially where time is an issue. As we indicated that our population of high-level resistance isolates contained the mupA gene as a genetic element of resistance, it is proposed that molecular screening should be expanded to include testing for resistance to mupirocin.

The association between mupirocin resistance and antimicrobial sensitivity

This study indicated a statistically significant association between mupirocin resistance and resistance to several classes of antimicrobial agents, i.e. MRSA, MLS\_B, phenotypes, quinolones, co-trimoxazole, and most markedly, fusidic acid. This is biologically plausible as genetic material encoding for resistance to different classes of antimicrobial agents may be carried on the same mobile genetic elements. It is a cause for concern as it implies that mupirocin use will lead to environmental pressure for the selection of resistance to other classes of antimicrobial agents, and vice versa. Antimicrobial stewardship programmes are the most important action currently undertaken both internationally\textsuperscript{28} and locally in an attempt to address excessive or inappropriate antimicrobial usage. It has now become clear that it is important to look beyond the usage of systemic antimicrobial agents, and to adopt a more comprehensive approach to decolonisation and environmental stewardship.

Alternative agents to mupirocin should be considered to counteract the clinical failure of decolonisation regimens and to prevent the selection of multiple resistant strains. Thyme and tea tree oil is being studied for decolonisation purposes,\textsuperscript{30} while analogues of reutericyclin are an example of alternative agents that are currently under development for topical use.\textsuperscript{30}

The association of mupirocin resistance and other patient attributes

Practitioner categories were the only data category that was significantly associated with mupirocin resistance. This is plausible as certain specialities, such as orthopaedic surgeons, are more likely to use mupirocin as a decolonising agent before high-risk surgery, e.g. for prosthetic joint replacements. Plastic surgeons and dermatologists are also more likely to prescribe mupirocin as a topical agent to treat superficial infections. Therefore, an associated higher usage statistics could reflect as a higher prevalence of mupirocin resistance (Table VI).

Conclusion and recommendations

We found a surprisingly high prevalence of high-level resistance to mupirocin in our study population. This was significantly associated with several resistant phenotypes, including methicillin resistance, resistance to the quinolones, the macrolides and clindamycin (MLS\_B, phenotypes), and resistance to fusidic acid, in particular.

The failure of decontamination in the presence of mupirocin resistance is well documented in the literature.\textsuperscript{9,13,32} In the setting of private health care in the Cape Peninsula, it is advised that mupirocin is not included as a decontaminating agent in infection control regimes without prior sensitivity testing of the colonising isolates. Alternative agents should be considered for decolonisation in the case of resistant isolates, bearing in mind that resistance to such agents should also be monitored.

Greater attention should be given to the stewardship of topical antimicrobial agents, as resistance to mupirocin is significantly associated with fusidic acid resistance. The association between mupirocin resistance and resistance to systemic antimicrobial agents also poses a danger of selecting for resistance by using mupirocin as a decontaminating agent or as the topical treatment of a superficial infection.

With regard to laboratory methods to detect resistance to mupirocin, the results of automated methods, including mupirocin, as currently in use, could be reported for screening purposes, as these carry no additional cost, but in cases requiring the use of topical agents as either decolonisation or treatment, the results should be confirmed by either disc sensitivity testing for high-level resistance to mupirocin or molecular testing for the presence of the mupA gene.

Prevalence studies on mupirocin resistance should be repeated in other settings, including the public health sector, in order to compare data at provincial and even national level. The clinical impact of resistance to mupirocin should also be further examined, opening opportunities for collaborative studies between the laboratory and clinical epidemiologists.

Acknowledgements

This research project was conducted as part of the MSc in the Clinical Epidemiology Programme at Stellenbosch University.

We acknowledge the support of PathCare Laboratories and the effort made by the following staff members at the reference laboratory: Miss Leigh-Ann Le Grange for performing the mupirocin disc test, storing isolates for molecular testing and capturing data on the worksheets; Mrs Juanita Elliot for the preparation and quality assurance of the media; and Dr Nico de Villiers and Miss Jaclyn Gerber for performing the molecular detection of mupA in a clustered sample of isolates.

Conflict of interest

None of the authors have a commercial or other association that might have posed a conflict of interest concerning the research presented.

Declaration

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References


