The utility of empirical mupirocin for eradication of methicillin-resistant *Staphylococcus aureus* colonisation in Far North Queensland, Australia

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Abstract

Methicillin-resistant Staphylococcus aureus (MRSA) infections are common in Far North Queensland (FNQ) and their incidence is increasing. Decolonisation regimens that include topical mupirocin are recommended in Australian guidelines to reduce recurrent infection. Mupirocin resistance was identified in 3,932/15,851 (24.8%) methicillin-sensitive Staphylococcus aureus (MSSA) isolates and in 533/5,134 (10.4%) MRSA isolates from FNQ between 1997 and 2016. Factors associated with mupirocin resistance in multivariate analysis were an MSSA isolate, age < 40 years, rural residence and female gender. These data support the use of mupirocin in MRSA decolonisation in FNQ, although addressing the underlying social determinants of health that drive the incidence of S. aureus infections remain a priority for local healthcare provision.

Keywords: Mupirocin; Staphylococcus aureus; MRSA; decolonisation; Tropical Australia

Background and methods

Recurrent staphylococcal skin infections (SSI) are common in Far North Queensland (FNQ), and the proportion caused by methicillin-resistant Staphylococcus aureus (MRSA) is increasing.1,2 This is a challenging therapeutic problem, particularly in rural and remote areas where the social determinants of health contribute to higher rates of staphylococcal colonisation and infection.3–5 Decolonisation regimens that include nasal mupirocin are recommended to eradicate S. aureus carriage6,7 and may reduce recurrent infections.8

This study examined mupirocin resistance in S. aureus isolates in FNQ to determine the utility of mupirocin in local empirical staphylococcal decolonisation regimens. There was a focus on rural and remote areas where there are high rates of MRSA infection and limited access to timely microbiology testing. Far North Queensland, an area of around 380,000 km² in tropical northeastern Australia, extends from Tully in the south to the Torres Strait Islands in the north; 65% of the population of 280,000 people live in the urban Cairns region.9 Approximately 17% of the FNQ population identify as Aboriginal and/or Torres Strait Islander Australians.9

We interrogated the Queensland Health electronic laboratory database (AUSLAB) for S. aureus isolates from both inpatient and outpatient clinical specimens in FNQ between 1 January 1997 and 31 December 2016. Patient demographics and the isolates’ antibiograms were recorded. Isolates were deemed urban if they were collected in Cairns, and rural if not. Repeat isolates collected within < 12 months from the same patient were excluded, as were isolates from non-FNQ residents. Isolates were defined as MRSA if there was in vitro resistance to oxacillin or cefoxitin. Mupirocin resistance testing was performed using the Vitek2 system (bioMérieux, France) with 2 mg/L used as the resistance breakpoint. Further testing to distinguish between low-level and high-level mupirocin resistance was not performed. Statistical
Table 1: Characteristics of mupirocin sensitive and resistant \textit{S. aureus} isolates in Far North Queensland, Australia, 1 January 1997 – 31 December 2016

<table>
<thead>
<tr>
<th>Category</th>
<th>Mupirocin sensitive</th>
<th>Mupirocin resistant</th>
<th>(p) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All isolates</td>
<td>16,520 (78.7%)</td>
<td>4,465 (21.3%)</td>
<td></td>
</tr>
<tr>
<td>MSSA(^b)</td>
<td>11,919 (75.2%)</td>
<td>3,932 (24.8%)</td>
<td></td>
</tr>
<tr>
<td>MRSA(^c)</td>
<td>4,601 (89.6%)</td>
<td>533 (10.4%)</td>
<td></td>
</tr>
<tr>
<td>Median age (interquartile range)</td>
<td>36 (17–56)</td>
<td>25 (9–44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt; 40 years old</td>
<td>9,008 (54.5%)</td>
<td>3,091 (69.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>7,016 (42.7%)</td>
<td>2,029 (45.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First Nations Australian</td>
<td>6,654 (42.7%)</td>
<td>1,795 (43.2%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Remote isolate</td>
<td>10,410 (63.0%)</td>
<td>3,082 (69.0%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^a\) Groups were compared using the chi-squared test.
\(^b\) MSSA: methicillin-sensitive \textit{Staphylococcus aureus}.
\(^c\) MRSA: methicillin-resistant \textit{Staphylococcus aureus}.

Analysis was performed with statistical software (Stata version 14.2, USA). Groups were compared using the chi-squared test and multivariate logistic regression analysis, as appropriate, whilst trends over time were determined using an extension of the Wilcoxon rank-sum test. The study was approved by the FNQ Human Research Ethics Committee (HREC/16/QCH/112–1085).

Results and discussion

There were 46,304 \textit{S. aureus} isolates found in AUSLAB from clinical specimens in FNQ for the study period. Of these isolates, 20,985 had mupirocin susceptibility testing performed during the study period; mupirocin resistance was present in 4,465 (21.3%). Mupirocin resistance was identified in 3,932/15,851 methicillin-sensitive \textit{Staphylococcus aureus} (MSSA) isolates (24.8%) and in 533/5,134 MRSA isolates (10.4%) (Table 1). There was no change in the proportion of isolates with mupirocin resistance during the study period (\(p\) for trend = 0.50). In multivariate analysis, mupirocin resistance was more likely in MSSA isolates, in people < 40 years of age, in people from rural locations, and in females (Table 2). Aboriginal and/or Torres Strait Islander ethnicity was not associated with mupirocin resistance.

The rate of mupirocin resistance in FNQ is higher than the global rates of 7.6% and 13.8% reported in MSSA and MRSA respectively.\(^{10}\) It is also much higher than the rate of 1.2% (MSSA) and 0.8% (MRSA) described in Australian national data for 2016, although the higher rates in FNQ are partly explained by the fact that the national series only reports high-level resistance.\(^{11}\) The distinction between high- and low-level resistance is important, because although high-level mupirocin resistance predicts failure of decolonisation regimens containing mupirocin, the impact of low-level mupirocin resistance is less clear.\(^{12}\) Unfortunately, the retrospective nature of this FNQ study and the limited capacity of local laboratories precluded the determination of high- and low-level resistance.

Despite this limitation, these data do have implications for local clinical management. As mupirocin resistance rates in FNQ MRSA isolates are relatively low, our study suggests that topical mupirocin remains suitable for empirical use
Table 2: Multivariate logistic regression analysis of predictors of mupirocin resistance in *S. aureus* isolates, Far North Queensland, Australia, 1 January 1997 – 31 December 2016

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 40 years</td>
<td>1.94</td>
<td>1.80–2.08</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Rural location</td>
<td>1.25</td>
<td>1.16–1.34</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.11</td>
<td>1.04–1.19</td>
<td>0.002</td>
</tr>
<tr>
<td>MSSA isolate</td>
<td>2.85</td>
<td>2.59–3.14</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

- Variables were assessed using multivariate logistic regression analysis.
- MSSA: methicillin-sensitive *Staphylococcus aureus*.

in MRSA decolonisation regimens, although it cannot be unequivocally recommended for MSSA decolonisation.

The increased rates of mupirocin resistance observed in young people in FNQ may reflect higher rates of recent mupirocin exposure, a primary driver of resistance. Topical mupirocin was previously used extensively in FNQ for impetigo, which occurs more commonly in children, but has been superseded by oral trimethoprim/sulphamethoxazole or intramuscular benzylpenicillin. It might be anticipated, therefore, that mupirocin resistance will fall in young people in the future.

Rural location was also an independent predictor of mupirocin resistance. Australian data have demonstrated state to state variation, with Queensland reporting high-level mupirocin resistance rates of 3.1% (MRSA) and 3.5% (MSSA) compared with the Australian average of 0.8% (MRSA) and 1.2% (MSSA). Although this FNQ study presents more granular data than prior reports, it is unable to characterise the spatial epidemiology of mupirocin resistance in more detail (e.g., specific communities). Mupirocin resistance was more common in women, possibly due to asymmetric gender roles in child rearing and higher rates of mupirocin resistance in younger people. Gender variation in overall rates of *S. aureus* infection has previously been described although this was not apparent in a prior FNQ study.

Our study has limitations. Mupirocin testing was not performed on 55% of isolates; the reasons for this varied over the study timeframe. Isolates were more commonly collected in rural areas despite most FNQ residents having an urban address. Similarly, 49.8% of isolates were collected from Aboriginal and/or Torres Strait Islander Australians, who represent only 17% of the FNQ population. This is likely due to the disproportionate burden of skin infections borne by Indigenous Australians living in rural areas; regional variation in specimen collection practices, or the use of alternative pathology providers, may also contribute to this finding. The study also lacks concomitant clinical data.

Interventions that reduce the burden of recurrent *S. aureus* infections are necessary, as these infections are common, debilitating, and potentially life-threatening. The efficacy of topical mupirocin has been compared to other regimens, primarily in elective surgery cohorts. In one study, topical mupirocin achieved clearance rates similar to neomycin and superior to octenidine, although no reduction in infection was seen.

\[\text{ii} \quad \text{Of the four public laboratories in FNQ, only a single site (Cairns Hospital) has access to automated testing (Vitek 2). Manual methods for determining mupirocin resistance are not routine at these peripheral sites. As not all clinical specimens are referred to Cairns, many isolates did not have any mupirocin testing performed. Please see Appendix A, Table A.1 for a comparison of characteristics of isolates that did—or did not—have mupirocin resistance testing.}\]
In another, nasal iodine was marginally superior to mupirocin in preventing *S. aureus* infection.\textsuperscript{20}

In conclusion, our data support the empirical use of mupirocin in MRSA—but not MSSA—decolonisation in FNQ. Its role in other infections requires further evaluation. However, ultimately, a concerted public health effort addressing the underlying socioeconomic disadvantage that drives the acquisition and spread of *S. aureus* infections is likely to have a greater health impact than the optimisation of different eradication regimens.

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References


Appendix A: Supplementary material

Table A.1: Comparison of mupirocin testing across major variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Not tested N = 25,319</th>
<th>Tested N = 20,985</th>
<th>p value a</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA b</td>
<td>20,951 (83%)</td>
<td>15,851 (76%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>MRSA c</td>
<td>4,368 (17%)</td>
<td>5,134 (24%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Median age (interquartile range)</td>
<td>35 (16–56)</td>
<td>33 (15–53)</td>
<td>0.0001</td>
</tr>
<tr>
<td>&lt; 40 years old</td>
<td>14,114 (56%)</td>
<td>12,099 (58%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Female gender</td>
<td>11,250 (45%)</td>
<td>9,045 (43%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Indigenous Australian</td>
<td>9,325 (58%)</td>
<td>8,449 (43%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Remote isolate</td>
<td>18,588 (73%)</td>
<td>13,492 (64%)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

a Groups compared using the Chi-squared test.
b Methicillin-sensitive *S. aureus*.
c Methicillin-resistant *S. aureus*. 