

Mupirocin and *Staphylococcus aureus*: a recent paradigm of emerging antibiotic resistance

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Objectives: To describe trends in mupirocin resistance among *Staphylococcus aureus* in New Zealand (NZ), following the availability of mupirocin in 1986.

Patients and methods: Data from a variety of sources were used for this study: susceptibility data collected annually from diagnostic laboratories throughout NZ; a local survey of mupirocin-resistant *S. aureus* in the Auckland area in 1997; a national survey of *S. aureus* antimicrobial susceptibility in 1999; and the national methicillin-resistant *S. aureus* (MRSA) surveillance programme.

Results: All data sources show that there was a steady increase in mupirocin resistance among *S. aureus* throughout the 1990s, and rates in NZ are now markedly higher than those reported in most other comparable countries. By 1999, resistance averaged 28%, with higher rates among community-acquired compared with hospital-acquired isolates, and with a wide geographical variation in resistance. Resistance was more common among *S. aureus* generally than MRSA.

Conclusion: We postulate that the steady rise in mupirocin resistance among *S. aureus* in NZ throughout the 1990s may be due, at least in part, to the over the counter availability of mupirocin from 1991 to 2000. The current patterns of mupirocin consumption need to be reviewed and its use rationalized to maximize the chances of this antibiotic retaining beneficial antistaphylococcal activity.

Keywords: mupirocin, *Staphylococcus aureus*, resistance

Introduction

Mupirocin (pseudomonic acid A) is a topical antibiotic with a unique action, binding competitively to bacterial isoleucyl-tRNA synthetase (IRS) and inhibiting bacterial protein synthesis. It has a high level of activity against staphylococci and streptococci,¹ and is used in the treatment of superficial skin infections and in controlling the spread of methicillin-resistant *Staphylococcus aureus* (MRSA). Intranasal application for 5 days has been shown to be effective in eliminating MRSA and methicillin-susceptible *S. aureus* (MSSA) in healthy people, although re-colonization is seen in up to 67% of subjects 6 months later.^{2,3} Short-term intranasal mupirocin application may reduce post-operative infection rates and

vascular and continuous ambulatory peritoneal dialysis (CAPD) catheter-related infections in dialysis patients.⁴⁻⁶

Two mupirocin-resistant phenotypes, low-level (LMR) and high-level resistance (HMR), have been identified. LMR is thought to be the result of mutational change in the chromosomally encoded *ileS-2* (*mupA*) gene,⁷ and has been shown to develop in *S. aureus* isolates exposed *in vitro* to progressively higher concentrations of mupirocin.⁸ The proposed genetic basis for HMR is the acquisition of a transferable plasmid containing the *ileS-2* gene encoding an additional IRS enzyme.⁹

While the NCCLS does not provide interpretive criteria for susceptibility testing of topical agents, suggested breakpoints (MIC < 8 mg/L = susceptible, MIC 8–256 mg/L = LMR, MIC ≥ 512 mg/L = HMR) have been published and are widely

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used.¹⁰ However, there is uncertainty over their clinical relevance. Most reports of resistance have not been accompanied by details of clinical follow-up, and there are few data correlating resistance with clinical outcomes. It has been suggested that LMR can be overcome by a high concentration of mupirocin, which is provided by the 2% (20 000 mg/L) topical preparation, especially when applied to the nasal mucosa where skin penetration is irrelevant. In one study, five of seven patients, from whom MRSA with LMR was isolated, were successfully cleared by topical mupirocin alone.³ However, Harbath *et al.*¹¹ observed an increased risk of persistent MRSA carriage after mupirocin treatment in those patients colonized with LMR strains of MRSA.

Mupirocin was introduced into clinical practice in the UK in 1985, and the first report of staphylococcal resistance came 2 years later.¹² Since then, varying rates of resistance have been reported. In 1993, an Irish survey of 1152 hospital and community isolates of *S. aureus* found 2% mupirocin resistance.¹³ In 1997, 3.9% of *S. aureus* isolates collected from 19 European hospitals were mupirocin resistant. Resistance was more common among MRSA than MSSA.¹⁴ In North America in 1990–1995, mupirocin resistance in MRSA was noted to be high (24%) in a veterans' hospital where MRSA colonization was endemic and mupirocin commonly used.¹⁵ Similarly, in a Brazilian hospital, where mupirocin use was common, the prevalence of mupirocin resistance among MRSA was over 50% in 1994–1995, compared with 6% in a nearby hospital where mupirocin use was infrequent.¹⁶

Mupirocin has been marketed in New Zealand (NZ) since 1986, and from October 1991 to March 2000 could be bought over the counter (OTC) without a prescription. In this paper, we track the emergence of resistance, compare it with the situation elsewhere in the world and discuss strategies for future management of this antibiotic.

Materials and methods

Data sources

Data on mupirocin resistance among *S. aureus* were extracted from four sources that are described in Table 1.

DNA macrorestriction analysis

DNA macrorestriction analysis of the mupirocin-resistant isolates, identified during the 1999 national survey (Table 1, data source 3), was performed using a modified published method.¹⁷

Mupirocin sales

Data on mupirocin sales were obtained from GlaxoSmith-Kline NZ. The sales are quantified in units, where 1 unit is 15 g of a 2% preparation.

Results

There are no data on mupirocin susceptibility before its introduction into NZ in 1986. Figure 1 shows the increase in mupirocin resistance among community and hospital isolates of *S. aureus* in the Auckland area, and among hospital isolates in the Christchurch area between 1992 and 2000 (Table 1, data source 1), and the amount of mupirocin sold in NZ between 1990 and 2000. Resistance was more prevalent in the Auckland area, and more prevalent in community-acquired, than hospital-acquired, *S. aureus*.

In a 1999 national survey (Table 1, data source 3), which included both hospital- and community-acquired *S. aureus* isolated throughout NZ, the prevalence of mupirocin resistance averaged 28.0%, and again mupirocin resistance was more common among community-acquired isolates (Table 2). In this survey, regional differences were also noted. Forty per cent of *S. aureus* isolates from the northernmost part of the country (Northland Health District) were resistant, compared with 10.3% in the southernmost part (Southland and Otago Health Districts). In general, resistance increased from south to north along the length of NZ.

Most data on mupirocin resistance in *S. aureus* do not distinguish between LMR and HMR. However, this distinction is available for isolates included in the 1999 national survey and a 1997 local survey (Table 1, data sources 3 and 2, respectively). In the 1997 survey of community-acquired mupirocin-resistant *S. aureus* in the Auckland area, 85% had HMR and 15% LMR.¹⁸ In contrast, in the 1999 national survey, the prevalence of HMR and LMR was similar among community-acquired *S. aureus*, whereas HMR was more prevalent than LMR among hospital-acquired isolates (Table 2). DNA macrorestriction typing of 134 mupirocin-resistant *S. aureus* included in the 1999 survey was performed to determine clonality. The majority (96%) belonged to one of three distinct macrorestriction profiles or types. Almost all HMR isolates belonged to two of these three types, whereas the LMR isolates were predominately the third type.

Mupirocin resistance among MRSA (Table 1, data source 4) was first detected in 1988, and was unexpectedly high (8.9%) due to an outbreak of infections with a resistant strain in one hospital. Subsequently, in the early 1990s, <2% of MRSA were resistant. Resistance started to increase in 1993 and during the 6 years between 1993 and 1998, 3–6% of MRSA were mupirocin resistant. No data are available for 1999. In 2000, resistance increased to 12.4%, and most (90%) of this resistance was HMR.

Discussion

We believe that mupirocin resistance in NZ has arisen largely in the community, where mupirocin has been readily available without prescription. In contrast to most reports from other

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Table 1. Sources of data on mupirocin resistance among *S. aureus* in New Zealand

	Data source number			
	1	2	3	4
Time period covered (inclusive)	1992–2000	1997	1999	1987–2000
Survey type	continuous surveillance	short-term survey	short-term survey	continuous surveillance to 1998 and then short-term surveys ^a
Type ^b and geographical location of laboratories contributing data or isolates	three Auckland hospitals one Christchurch hospital one Auckland community ^c	Auckland community	hospital and community, nationwide	hospital and community, nationwide
Sample inclusion criteria	all <i>S. aureus</i> isolated	consecutive isolates of mupirocin-resistant <i>S. aureus</i>	all <i>S. aureus</i> isolated during survey period	all MRSA identified and referred to the national reference laboratory
Sample number	86 420	103	583	6329
Mupirocin susceptibility testing method	NCCLS disc or dilution breakpoint	Etest MIC	NCCLS agar dilution	NCCLS agar dilution
Data type	prevalence of mupirocin resistance among <i>S. aureus</i>	distribution of LMR and HMR ^d among resistant isolates	prevalence of LMR and HMR among <i>S. aureus</i>	prevalence of LMR and HMR among MRSA

^aBetween 1987 and 1998 all MRSA isolates were referred to the national reference laboratory (ESR) for strain identification and susceptibility testing as part of the national MRSA surveillance programme. No data were available for 1999. Since 2000, MRSA surveillance has been based on short-term annual surveys, with all MRSA isolates during the defined survey period referred to ESR.

^bHospital-based laboratories process specimens mainly from hospital inpatients; community laboratories process specimens mainly from non-hospitalized patients.

^cNot all laboratories provided data each year.

^dLMR, low-level mupirocin resistance MIC 8–256 mg/L; HMR, high-level mupirocin resistance MIC \geq 512 mg/L.

countries, mupirocin resistance in NZ is more common in community-acquired, than hospital-acquired, *S. aureus*, and is more prevalent among *S. aureus* generally than MRSA. The observation that mupirocin resistance is more common among all *S. aureus* than MRSA is because the two MRSA strains that together account for 80% of MRSA isolations in NZ, WSPP MRSA and EMRSA-15, are both susceptible to mupirocin. The relatively restricted use of mupirocin in the NZ hospital setting may have limited MRSA exposure to mupirocin and any subsequent development of resistance. However, the WSPP MRSA strain is a community-acquired MRSA and is most common in the northern parts of NZ, which have the highest prevalence of mupirocin resistance among *S. aureus*.

The predominance of two DNA macrorestriction types among *S. aureus* with HMR, and one type among the LMR isolates included in the national survey in 1999, suggests that there has been horizontal spread of a limited number of mupirocin-resistant strains. This is not so surprising for chromosomally mediated LMR, but is less expected for plasmid-mediated HMR, where horizontal spread of the plas-

mid among genetically diverse strains of *S. aureus* is likely. This lack of diversity among the isolates with HMR may, in part, be due to the fact that although the isolates for the survey were collected within a period of a few weeks, they were collected from widely separated geographical areas.

Drug company sales figures show increasing consumption of mupirocin in NZ from 1992, which coincides with the change of licensing from prescription only to OTC in October 1991. Unfortunately, there are no data on the relative proportions of OTC versus prescription sales of mupirocin, but we speculate that the OTC availability resulted in increased consumption of mupirocin, particularly in the community setting. It remains to be seen whether reintroduction of prescription-only availability in 2000 will reverse this trend.

Such a reversal was observed in Western Australia after the introduction of restrictions on mupirocin use. In 1993, 15% of 178 clinical MRSA isolates in Western Australia had HMR. In response to this, the Health Department issued guidelines that recommended that mupirocin should not be used without laboratory control, that its use should not exceed 10 days and that a patient should not have a repeat prescription within

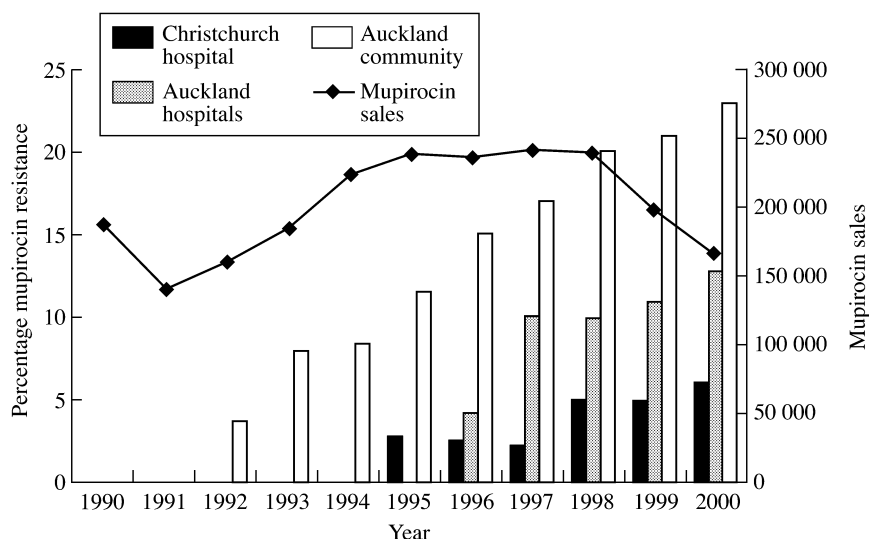


Figure 1. Mupirocin resistance among *S. aureus* isolates in hospital and community laboratories (Table 1, data source 1), and units of mupirocin sold per year, 1990–2000. No data were available for Christchurch and Auckland hospital laboratories, 1990–1994, or the Auckland community laboratory, 1990–1991.

Table 2. High- and low-level mupirocin resistance among hospital- and community-acquired *S. aureus* collected from laboratories throughout New Zealand in 1999^a

	Percentage resistant (number tested)		
	low-level resistance	high-level resistance	total
All isolates	13.8	14.2	28.0 (583)
Hospital acquired	6.0	13.8	19.8 (116)
Community acquired	16.0	14.2	30.2 (451)

^aTable 1, data source 3.

Data on source of isolates was known for 567 isolates.

1 month of completing the first course.¹⁹ Four years later only 0.3% of MRSA isolates referred to the reference laboratory were mupirocin resistant.²⁰

In addition to the measures recommended in the Western Australian guidelines, we make further recommendations. Application of mupirocin to superficially infected skin lesions is effective, but the treatment course should be directed by a doctor and be neither interrupted nor prolonged. As the likelihood of successful eradication of MRSA is low when colonization is endemic, or two or more body sites are colonized,²¹ careful consideration of mupirocin's use in this setting is advised. There is no role for its application to uninfected skin lacerations or surgical wounds in previously well individuals. There may be a role for intranasal application of mupirocin prophylactically in selected pre-operative patients.²²

In cautioning against the use of mupirocin, we do not advocate using fusidic acid topically as an alternative. Resistance to this topical agent is reported, and unlike mupirocin, it is

available in oral and intravenous formulations that are used for treatment of multiresistant *S. aureus* infections. As an alternative to topical antibiotic preparations, a hydrogen peroxide cream has been developed that has been found in one study to be as efficacious as topical fusidic acid in the treatment of impetigo.²³

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