

Mupirocin resistance in methicillin-resistant *Staphylococcus aureus* and mupirocin consumption over 10 years in a tertiary hospital

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Introduction and Aims

- Topical mupirocin is widely used to eradicate carriage and prevent infection with methicillin-resistant *Staphylococcus aureus* (MRSA).
- Mupirocin inhibits bacterial protein synthesis by reversibly binding to the enzyme isoleucyl-tRNA-synthetase.¹
- Two levels of mupirocin resistance have been described: low-level resistance (L-MuR) and high-level resistance (H-MuR) (Table 1).²
- Resistance is reported in up to 65% of MRSA isolates in some institutions.³
- There have been conflicting reports regarding the association between mupirocin use and the emergence of resistance.^{3,4}
- At the University of Geneva Hospitals, mupirocin resistance in MRSA was noted to increase from 9% in 1999 to 80% in 2007 (Figure 1). In 2008, more than 99% of resistant isolates had L-MuR and a sample of 12 non-clonal L-MuR isolates all possessed the V588F point mutation in the isoleucyl-tRNA-synthetase gene⁵ which was responsible for this resistance phenotype.

This study aimed to:

- Determine the prevalence and molecular mechanisms of mupirocin resistance in MRSA blood culture isolates in our institution.
- Correlate mupirocin use and prevalence of resistance over time.

Table 1. Phenotypic and genotypic resistance to mupirocin²

Phenotype	MIC (µg/mL)	Molecular Mechanism
Sensitive (Mu-S)	≤ 4	Wild type
Low-level Resistance (L-MuR)	8 - 64	Mutations in native tRNA synthetase
High-level Resistance (H-MuR)	≥ 512	Plasmid-mediated <i>mupA</i> (novel tRNA synthetase)

Methods

- The study was conducted at the University of Geneva Hospitals (HUG), Switzerland, a tertiary care centre with 2032 beds and 48 314 admissions in 2008. Topical intranasal mupirocin has been used at HUG to decolonise known MRSA carriers since 1994.
- The first 20 non-duplicate MRSA blood culture isolates per year (1999-2008) were selected (1 isolate per patient). Non-viable/contaminated isolates were excluded.
- Isolates were screened for mupirocin resistance using a 0.5 McFarland suspension on Mueller-Hinton agar with a 5µg disk (Becton Dickinson) at 35°C for 18-24 hours.⁶ Resistance was defined as a zone of inhibition of <14mm.
- Resistant isolates had MICs with Etests (AB Biodisk, Solna, Sweden)⁷: MIC 8-256 µg/mL = L-MuR; MIC ≥ 512 µg/mL = H-MuR.
- All MRSA isolates had an allelic discrimination assay for the V588F point mutation⁵ and resistant isolates had a *mupA* PCR.⁸
- Mupirocin consumption data (2000-2008) were obtained from pharmacy records.
- Results were analysed using Stata software, version 11.0.

Results

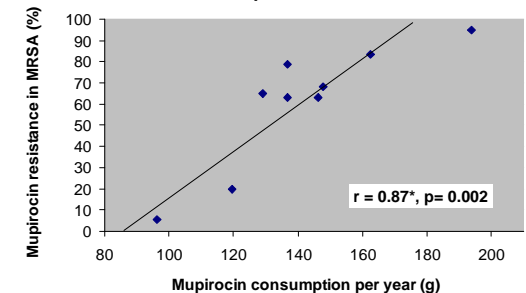
- 200 MRSA blood culture isolates from 1999 to 2008 were retrieved. 12 were excluded (9 contaminated, 3 non-viable). 188 isolates were further evaluated.
- Resistance to mupirocin was found in 0 of 17 isolates in 1999; 18 of 19 isolates (95%) in 2005; 15 of 19 isolates (79%) in 2008 (Figure 2).
- The majority of resistant isolates had L-MuR (89 of 103 isolates, 86%).
- The V588F point mutation was found in all L-MuR MRSA but was also present in 12 of 14 (86%) H-MuR MRSA and 2 of 85 (2%) sensitive MRSA (Table 2).
- mupA* gene was found in all H-MuR MRSA but also in 3 of 89 (3%) L-MuR MRSA.

Table 2. Mupirocin resistance in MRSA blood cultures

Phenotypic Resistance	Genotypic Resistance		Total no. (%)
	V588F	<i>mupA</i>	
Sensitive	2	Not tested	85 (45)
L-MuR	89	3	89 (47)
H-MuR	12	14	14 (7)
Total	103	17	188 (100)
Sensitivity	100%	100%	
Specificity	86%	97%	

- The trend in the consumption of mupirocin between 2000 and 2008 paralleled the prevalence of resistance in MRSA blood cultures. There was an increase in mupirocin use from 96g to 194g between 2000 and 2005, then decrease to 137g in 2008 (Figure 2).
- Mupirocin consumption and prevalence of resistance for a given year showed a statistically significant linear correlation ($r=0.87$, $p=0.002$; Figure 3).

Figure 3. Relationship between mupirocin consumption per year and mupirocin resistance



*Pearson's correlation coefficient

Conclusions

- The prevalence of mupirocin resistance in our institution is increasing and predominantly consists of L-MuR characterised by the V588F point mutation.
- This correlates with an increase in mupirocin use over this period.
- Emergence of mupirocin resistance and its impact should be monitored in institutions considering widespread use of this antibiotic for decolonisation.

References

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Figure 1. Mupirocin resistance in MRSA 1999 to 2008

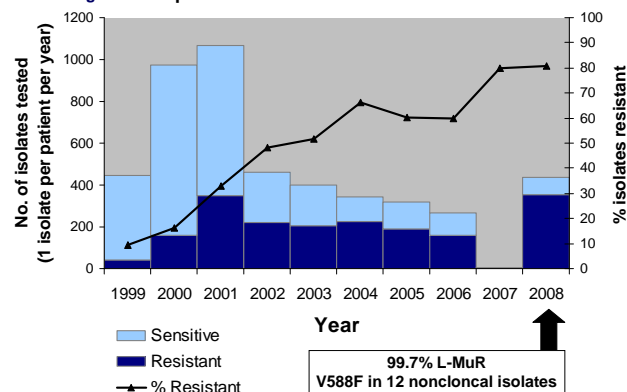


Figure 2. Mupirocin resistance in MRSA blood cultures and mupirocin consumption 1999 to 2008

