

## EMERGING HIGH-LEVEL MUPIROCIN RESISTANCE AMONG MRSA ISOLATES IN IRELAND

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The antimicrobial drug mupirocin (an isoleucine analogue) is a protein synthesis inhibitor that acts by binding irreversibly to isoleucyl t-RNA synthetase (IleS) [1]. It is mainly used as an ointment (2% in paraffin base) and is very effective in eliminating methicillin-resistant *Staphylococcus aureus* (MRSA) from colonised nasal passages when used in conjunction with other MRSA decolonisation regimens [2]. Guidelines from the Strategy for the control of Antimicrobial Resistance in Ireland (SARI) Infection Control Subcommittee warn that the dosage (three times a day for five days) should not be repeated more than once to avoid emergence of resistance [2]. Two forms of resistance are reported:

- Low-level resistance with minimum inhibitory concentrations (MIC) of 8 to 256 mg/L due to a mutation in IleS
- High-level resistance (MIC  $\geq$  512 mg/L) due to acquisition of the plasmid-mediated *mupA* gene which encodes a second isoleucyl t-RNA synthetase [1].

Ireland's National Methicillin-Resistant *Staphylococcus aureus* (MRSA) Reference Laboratory (NMRSARL) monitors rates of resistance to clinically useful antibiotics among MRSA isolates recovered from blood of patients in Irish hospitals [3].

High-level mupirocin resistance (MpR) was detected among 37 of 2,586 (1.4%) MRSA blood-stream isolates sent to NMRSARL between 1 January 1999 and 31 December 2005 (Period 1) compared with 29 of 997 isolates (2.9%) sent between 1 January 2006 and 31 December 2007 (Period 2) ( $p=0.005$ ). In addition to this significant increase in the proportion of high-level mupirocin-resistant isolates, NMRSARL also noted a change in the epidemiological types associated with mupirocin-resistant MRSA [the antibiogram-resistogram-pulsed field group (AR-PFG) typing method used in NMRSARL is outlined below].

Prior to 2005, the majority of MpR blood-stream isolates (97%; 29/30) exhibited AR-PFG types 13-00 or 14-00. In contrast, during Period 2, only seven MpR isolates (24%, 7/29) exhibited these AR-PFG types but 55% (16/29) exhibited an unfamiliar AR pattern which included resistance to the aminoglycosides gentamicin, kanamycin and tobramycin but with PFG 01 patterns which are associated with the AR06 AR type. Fourteen percent of MpR isolates (4/29) exhibited AR-PFG 06-01. For the purposes of the present communication, MpR isolates exhibiting the unfamiliar AR pattern with aminoglycoside resistance and PFG 01 are designated MpR Strain 1 and MpR isolates with AR-PFG type 06-01 are designated MpR Strain 2.

During Period 2, 86 MpR MRSA from sources other than blood were submitted to NMRSARL from 12 institutions; 16% (14/86)

exhibited AR-PFG 13-00 or 14-00, 7% (6/86) exhibited a variety of patterns but 66 isolates (77%, 66/86) from 11 institutions exhibited MpR Strains 1 or 2. The earliest recognised isolates of both strains were recovered from patients in Institution 1 (MpR Strain 1, June 2004; MpR Strain 2 October 2005). The table details the source of all MpR Strains 1 or 2 isolates investigated (22 from blood and 68 from other sites). The majority of isolates (93%; 84/90) were recovered from patients in institutions in or around Dublin. The centres from which Institutions 6 and 7 received MpR Strains 1 and 2 were long-term care facilities and anecdotal evidence from Institution 1 suggests that the earliest isolates in that institution were also recovered from patients in long-term care.

All isolates were investigated by PFGE and all showed closely related PFG 01 patterns including PFGE pattern 01018 which is exhibited by >50% of AR06 isolates investigated in NMRSARL in any one year [3]. Additional molecular work is required to further characterise these isolates because the combination of aminoglycoside resistance with PFG 01 seen in MpR Strain 1 is unusual among MRSA recovered from patients in Ireland and suggests that AR-06 isolates may be acquiring *mupA*, perhaps in conjunction with other resistance determinants.

TABLE 1

Numbers of patients from whom high-level mupirocin-resistant MRSA Strains 1 or 2 were submitted for investigation

Institution	MpR Strain 1		MpR Strain 2 <sup>a</sup>	
	Blood	Various sites	Blood	Various sites
1	6	18	2	NR
2	4	7	NR	NR
3	3	6	NR	2
4	1	NR	1	NR
5	NR	NR	1	NR
6 <sup>b</sup>	NR	8	NR	9
7 <sup>b</sup>	NR	7	NR	3
8	NR	2	NR	NR
9	3	NR	NR	NR
Other (n = 4)	NR	5 <sup>c</sup>	1	1
Total	17	53	5	15

<sup>a</sup> The antibiogram-resistogram pattern of this strain may vary with regard to fusidic acid and/or trimethoprim.

<sup>b</sup> The laboratories in these institutions serve long-term care facilities.

<sup>c</sup> Two isolates were recovered from veterinary sources; 4 isolates were susceptible to gentamicin. NR, no isolate received.

## Discussion

The *mupA* gene is usually plasmid-mediated, is frequently carried on a large conjugative plasmid capable of mediating the co-transfer of other resistance determinants but isolates carrying a chromosomally-located *mupA* gene with resistance to gentamicin and kanamycin have also been reported [4,5]. If this has occurred with AR-PFG 06-01, it may give rise to a significant infection control problem. AR-PFG 06-01 accounts for more than 85% of MRSA blood-stream isolates in Ireland, indicating its propensity for spread and difficulty in control [3]. If high-level mupirocin resistance were to become widespread in this strain, a highly effective means of decolonisation of MRSA may be lost.

Prolonged, widespread or uncontrolled use, and multiple courses of mupirocin are all associated with the development of mupirocin resistance [2,6,7,8,9]. In New Zealand where mupirocin was available without prescription in the 1990s, the rate of high-level resistance in *S. aureus* was 14.2% in 1999 occurring mainly among community-acquired isolates [8]. Exposure of coagulase-negative staphylococci (CoNS) on skin surfaces during prolonged or repeated topical application of mupirocin may lead to the development of a reservoir of high-level resistance determinants in CoNS which may then be transferred to *S. aureus* in patients on mupirocin therapy [7]. A recent study from Canada showed that high-level mupirocin resistance in MRSA increased from 1.6% between 1995 and 1999 to 7% in the period 2000 – 2004 [10]. In that study, Mpr MRSA isolates were also associated with community acquisition and were fusidic acid resistant. A rate of 8.6% was reported in 2007 from a study in surgical intensive care unit in the United States, where the isolates were predominantly healthcare-associated [11]. In Europe, studies have reported rates of 2.6% in 1997 in MRSA recovered from hospitals in 19 countries; 6% in Ireland in 1999; 3% in Austria, Germany and Switzerland in 2001 and 18% in Spain in 2002 [12,13,14,15].

Walker and colleagues have shown that rates of high-level mupirocin resistance followed mupirocin usage but that a significant decline in the rate of resistance occurred with restriction of mupirocin prescribing [16]. Similarly, experience from western Australia showed that stringent control of mupirocin use could reduce the rate of high-level resistance among MRSA from 15% in 1993 to 0.3% in 1997 [8].

## Conclusions

If stable chromosomal high-level mupirocin resistance were to become prevalent, reducing the antibiotic selection pressure may not lead to a reduction in rates of resistance and control measures will have to rely on prevention of transmission. It would be prudent, therefore, that institutions monitor the use of mupirocin to ensure that misuse, including inappropriate, prolonged or repeated use be avoided, especially among long-term patients so that this most valuable antimicrobial drug is not lost to therapeutic practice.

Note on MRSA epidemiological typing: NMRSARL types MRSA isolates by antibiogram-resistogram (AR) typing and by pulsed field gel electrophoresis (PFGE). AR types are assigned two-digit numbers (for example: AR06, AR07, AR13 etc.) and PFGE patterns are assigned five-digit PFGE type (PFT) numbers abbreviated to two-digit PFGE type groups (PFG) [3]. Since 2001, the predominant AR-PFG type has been 06-01 (similar to UK EMRSA-15; genotype ST22-MRSA-IV) [3]. AR-PFG 06-01 isolates exhibit non-multi-antibiotic resistant phenotypes, are susceptible to aminoglycosides

and, in any one year, approximately 50% of isolates exhibit one PFGE pattern (PFT 01018) [3].

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