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Review

Clinical relevance of mupirocin resistance in *Staphylococcus aureus*

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SUMMARY

Mupirocin is a topical antibiotic used for decolonization of meticillin-susceptible *S. aureus* (MSSA) and meticillin-resistant *S. aureus* (MRSA), both in patients and in healthcare personnel, and for treatment of local skin and soft tissue infections caused by *S. aureus* and streptococcal species. Mupirocin prevents bacterial protein synthesis by inhibiting the bacterial isoleucyl-tRNA synthetase (IleRS). Low-level resistance against mupirocin, defined as minimum inhibitory concentration (MIC) of 8–256 mg/L, results from a point mutation in the native *IleRS*, and high-level resistance (MIC ≥512 mg/L) is mediated by the *mupA* (*ileS-2*) gene, located on mobile genetic elements decoding for an alternate *IleRS*. EUCAST and BSAC clinical thresholds for *S. aureus* are ≤1 mg/L for susceptible and >256 mg/L for resistant, placing the susceptible threshold at the epidemiological cut-off value (ECOFF). Isolates with MICs above the wild type (ECOFF 1 mg/L) but without a recognized resistance mechanism (MIC ≤4 mg/L) will thus be reported intermediate. Resistance to mupirocin, both high- and low-level, reduces the effectiveness of decolonizing strategies for *S. aureus* or MRSA. Low-level resistant isolates may initially be eradicated as effectively as susceptible isolates, but recolonization appears to be more usual. Increased use of mupirocin has been associated with emergence of resistance through enhanced selective pressure and cross-transmission. Unrestricted over-the-counter use and treatment of wounds and pressure sores with mupirocin are especially strongly associated with resistance. Yet emergence of mupirocin resistance following increased use has not been reported consistently, and an integrated understanding of all factors underlying the dynamics of mupirocin resistance in hospitals and communities is lacking.

Introduction

Staphylococcus aureus is an important cause of severe healthcare-associated infections worldwide, and in many parts of the world a considerable proportion of *S. aureus* isolates is resistant to many classes of antibiotics. *S. aureus* infections are associated with increased morbidity, mortality, and higher healthcare costs, especially when infections are caused by meticillin-resistant *S. aureus* (MRSA).[1,2] Moreover, increasing incidences of hospital-acquired infections caused by MRSA add to the total burden of hospital-acquired infections, rather than replacing other infections.[3] Nasal colonization with *S. aureus* is a risk factor for subsequent nosocomial *S. aureus* infection, and pre-surgical decolonization of *S. aureus* colonization has been associated with a 58% reduction in post-surgical *S. aureus* infections.[4] Topical application of mupirocin reduced rates of *S. aureus* infections by 80% and 63% for haemodialysis patients

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and peritoneal dialysis patients, respectively.[5] In intensive care unit (ICU) patients, with an average stay of three days, universal nasal decolonization with mupirocin and chlorhexidine body washing was associated with a 37% reduction of MRSA clinical isolates and 44% reduction of first bloodstream infection from any pathogen.[6]

Finally, mupirocin effectively reduces MRSA carriage, in patients and in colonized healthcare workers, with an estimated success rate of 90% 1 week after treatment and ~60% after a longer follow-up period.[7] This will reduce colonization pressure and cross-transmission of MRSA in healthcare settings.[8]

Mupirocin (pseudomonic acid A) is a topical antibiotic and the cornerstone of decolonization regimens for meticillin-susceptible *S. aureus* (MSSA) and MRSA, both in patients and in healthcare personnel. Furthermore, mupirocin is used for the treatment of local skin and soft tissue infections caused by *S. aureus* and streptococcal species. Resistance of *S. aureus* to mupirocin would jeopardize the efficacy of these regimens.

This review focuses on the clinical consequences of mupirocin resistance on decolonization of *S. aureus* and MRSA, and on the associations between mupirocin use and mupirocin resistance.

Mechanism of resistance

Mupirocin was first derived from *Pseudomonas fluorescens* and prevents bacterial protein synthesis by inhibiting the bacterial isoleucyl-tRNA synthetase (IleRS). It is highly active against staphylococci, streptococci and certain Gram-negative bacteria including *Haemophilus influenzae* and *Neisseria gonorrhoeae*.[9] Low-level resistance against mupirocin, defined as a minimum inhibitory concentration (MIC) of 8–256 mg/L, results from a point mutation in the native isoleucyl RNA synthetase gene, *IleRS*, and such mutations have appeared not to be associated with substantial fitness costs.[10–12] High-level resistance (MIC ≥512 mg/L) in staphylococci is mediated by the *mupA* (*ileS-2*) gene, typically located on mobile genetic elements which decode for an alternate *IleRS*.[13] High-level mupirocin resistance in *S. aureus* is almost always mediated through acquisition of the plasmid-based *mupA*, and has been associated with multidrug resistance (resistant to ≥3 non-beta-lactam antibiotics) in MRSA.[14–17] However, the presence of *mupA* may be associated with different phenotypes. *MupA* has been detected in *S. aureus* isolates expressing low-level mupirocin resistance, possibly because of chromosomal location of *mupA*.[18,19] *S. aureus* harbouring plasmid-encoded *mupA* susceptible to mupirocin have also been reported, even without mutations in the *mupA* gene.[20,21] Plasmids carrying *mupA* have been detected in all major circulating MRSA clones, suggesting inter-clonal transfer of these plasmids.[22–24] Intra-species transfer of *mupA* between *S. epidermidis* and *S. aureus* has also been demonstrated, both *in vitro* as *in vivo* during mupirocin prophylaxis, which implies that mupirocin resistance in coagulase-negative staphylococci (CoNS) may serve as a source for resistance in *S. aureus*.[25,26] As co-resistance to gentamicin, tetracycline and macrolides may be located alongside *mupA* on the same plasmid, mupirocin treatment may offer selective pressure for antibiotics frequently used for the treatment of *S. aureus* infections.[23]

Recently, a new plasmid-mediated mechanism for high-level mupirocin resistance, *mupB*, was detected in *S. aureus*, but the prevalence of this mechanism remains to be determined.[27]

Epidemiology

Reported prevalence rates of high-level mupirocin resistance were 3% and 5% among MRSA isolates from nasal carriage and blood cultures, respectively, from 23 hospitals in the USA in 2009–2010 and 4% among 4980 MRSA isolates collected between 1995 and 2004 from 32 Canadian hospitals.[15,28] In Europe reported prevalence levels of mupirocin resistance varied widely between and within countries; from 3% for high-level resistance among MRSA isolates in Ireland in 2006–2007, 1% for high-level resistance among MRSA isolates from France in 2011–2012, to 13% (of 375 MRSA isolates) in a single hospital in Spain and 47% (of 75 *S. aureus* isolates) in Turkey.[22,29–31] In 1997 resistance rates of 2.6% were reported among MRSA isolates recovered from hospitals in 19 European countries, but more recent data are not available.[32] In nursing homes resistance rates among MRSA isolates were 5% in 2006–2009 in England and 12% in 2008–2011 in the USA.[33,34]

Reported prevalence rates of low-level resistance from single hospital studies range from zero to 80%.[35–39] Low-level resistance was rarely detected in France and Ireland, and was not detected in 319 clinical *S. aureus* isolates collected between 2000 and 2002 in Korea and in 200 clinical MRSA isolates collected between 2008 and 2009 in Pakistan.[31,38–40] In a Swiss hospital low-level resistance steadily increased from zero to 80% of clinical MRSA isolates between 1999 and 2008.[36]

Resistance in CoNS appears more widespread with 6.5% of clinical isolates being *mupA* positive in France in 2011–2012 and 22% of bloodstream CoNS isolates being *mupA* positive in a hospital from The Netherlands in 2011.[31,41]

Detection of mupirocin resistance

Multiple laboratory testing methods have been described for determining the MIC of mupirocin, including agar dilution, broth microdilution and E-test.[42–45] The Clinical and Laboratory Standards Institute (CLSI) recommends using broth microdilution or disc diffusion for screening for high-level mupirocin-resistant *S. aureus*, only differentiating between high-level resistance and the absence of high-level resistance (Table I). CLSI and the European Committee for Antimicrobial Susceptibility Testing (EUCAST) both recommend using 200 μg discs for detection of mupirocin resistance by disc diffusion, whereas the British Society for Antimicrobial Chemotherapy (BSAC) now recommends the use of 20 μg discs. EUCAST clinical thresholds for *S. aureus* are ≤1 mg/L for susceptible and >256 mg/L for resistant, placing the susceptible threshold at the epidemiological cut-off value (ECOFF); the Committee argues that it has not been shown that isolates with MICs of 2 mg/L do not have a significant resistance mechanism. Isolates with MICs above the wild type (ECOFF 1 mg/L) but without a recognized resistance mechanism (MIC ≤4 mg/L) will thus be reported intermediate. To date, no clinical data on the clinical relevance of *S. aureus* strains with these MIC levels (>1 and ≤4 mg/L) has been published. MIC susceptibility thresholds of BSAC coincide with EUCAST thresholds, but disc-diffusion cut-