Mupirocin – Are we in danger of losing it?

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Mupirocin (pseudomonic acid A) is one of four structurally related antibiotics, pseudomonic acids A, B, C and D, that were isolated originally from *Pseudomonas fluorescens* (1). It has a unique chemical structure that consists of a short fatty acid side chain linked via an ester bond to monic acid (2). Mupirocin inhibits RNA and protein synthesis by selectively binding to the bacterial isoleucyl-tRNA synthetase (*IleS*), preventing the formation of isoleucyl-tRNA, which, in turn, halts the incorporation of isoleucine into the nascent polypeptide chain (3). This mechanism of action is unique to mupirocin, and cross resistance between mupirocin and other antibiotics has not been reported (4).

Mupirocin is formulated as a 2% ointment preparation in a water-miscible polyethylene glycol base or as a cream preparation in a soft paraffin base. With direct application of mupirocin to the skin, mucous membranes or other tissues, very high local concentrations are achieved. There is negligible systemic absorption when mupirocin is applied topically (5). Application of the ointment, followed by the use of an occlusive dressing, enhances the penetration of mupirocin five- to 10-fold, but the amount that is absorbed is calculated to be less than 0.24% of the applied amount.

Once present in the stratum corneum, mupirocin is primarily eliminated via the upward movement and eventual desquamation of skin cells, rather than via metabolism (5).

Mupirocin is significantly more active in vitro in a weakly acid environment (pH of 5.5 to 6) than at a pH of 8, which may be important in the treatment of skin infections because the pH of skin is approximately 5.5 (6-8). The use of mupirocin includes the prophylaxis and treatment of primary and secondary infections of the skin, skin appendages and mucous membranes. In addition, mupirocin is used increasingly for the eradication of methicillin-resistant *Staphylococcus aureus* (MRSA), an indication that was not intended originally.

Mupirocin is active primarily against Gram-positive organisms. It is bactericidal against *S aureus* and *Staphylococcus epidermidis*, including methicillin-resistant and other antibiotic-resistant strains at concentrations that are achieved with topical application (6,8). It is also readily bactericidal against several *Streptococcus* species, including *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus viridans*, but is inactive against anaerobic streptococci and enterococci. Mupirocin has no activity against Gram-negative organisms, anaerobes and fungi, and exhibits minimal activity against normal skin flora such as *Micrococcus*, *Corynebacterium and Propionibacterium* species (6).

Definitions of mupirocin resistance vary and no National Committee for Clinical Laboratory Standards guidelines exist for topical agents, but most studies have recognized low-level (minimal inhibitory concentration [MIC] of 8 mg/L to 256 mg/L) and high-level (MIC of 512 mg/L or greater) resistance (4). Low-level resistance is thought to arise from point mutations in the chromosomally encoded *IleS* gene. This resistance is considered stable and nontransferable (4). The development of high-level mupirocin resistance results from the acquisition of a plasmid that contains the *mupA* resistance element, which contains a modified *IleS-2* gene (9,10). Such isolates typically carry two

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distinct *IleS-2* genes: the constitutive chromosomally based gene that may, itself, encode for variable levels of mupirocin resistance, and the acquired high-level resistance plasmid-based gene (10,11). Farmer et al (12) showed that the antibiotic concentration that halved isoleucyl-tRNA synthetase activity correlated well with the MIC of 3.3×10^{-2} mg/L for mupirocin-susceptible strains, 1.3×10^{-1} mg/L for low-level resistant strains, and 7.5 mg/L in high-level resistant strains (12). The origin of *mupA* is not known, but it has been found in strains of staphylococci that existed before the release of mupirocin (4), and may have a natural reservoir. Low-level mupirocin-resistant organisms may be induced in vitro and were observed in an early in vivo study (4). Low-level mupirocin resistance is not considered to be significant clinically, given that the concentration of mupirocin in the 2% ointment exceeds 20,000 mg/L (4,13). However, clinical failure due to high-level mupirocin resistance (MIC of 512 mg/L or greater) is well recognized.

Cookson (4) suggested that increasing reports of high-level mupirocin resistance in staphylococci may limit the effectiveness of this agent in the future, particularly for the control of MRSA. Prolonged use and multiple courses of mupirocin seem to be the factors that are associated most frequently with the development of mupirocin resistance. Long term use of mupirocin was first reported to lead to the development of irreversible resistance in staphylococci over a decade ago (14,15), and has been reported in several parts of the world, including Europe (4,16,17), Australia (18) and the Americas (19,20). Unfortunately, not all of these reports have distinguished high-level from low-level resistance, but interpretive criteria for correlating inhibitory zone diameters with MICs based on agar dilution or E test strips (21,22) may provide some guidance in interpreting these reports.

Some of the reports of the development of mupirocin resistance are striking in the magnitude of increase in percentage of resistant isolates that has been noted over time. Miller et al (19) reported an increase in mupirocin resistance among MRSA isolates from 2.7% in 1990 to 65% in 1993. Almost 75% of the isolates demonstrated no discernible zone of inhibition, which suggests that most of the isolates possessed high-level resistance. The increase in mupirocin resistance was associated with the widespread use of mupirocin for the decolonization of patients during an MRSA epidemic in this Canadian institution (19). In two hospitals in Brazil, a similar pattern was noted, with an overall prevalence of mupirocin resistance of 63% (with 61% exhibiting high-level resistance) in the facility that used mupirocin on a daily basis for colonized MRSA patients, compared with 6% in the facility where mupirocin was used rarely (23). At a Veteran Affairs medical centre in the United States, a significant temporal increase in mupirocin resistance was noted over three years (24) among strains of MRSA on a background of high mupirocin usage. The prevalence of high-level mupirocin resistance was 42% in this centre. This latter report also included a case control study that showed that the presence of a decubitus ulcer correlated with high-level mupirocin resistant isolates of *S aureus*. In Warsaw, Poland, an outbreak of mupirocin-resistant staphylococci occurred on two wards of a large teaching hospital after the introduction of the use of mupirocin for the treatment of skin infections (25). Over a 17-month period, 53 mupirocin-resistant isolates of *S aureus*, *S epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus xylosus* and *Staphylococcus capitis* were identified, representing 19.5% of all staphylococcal isolates that were identified in the two wards during that time. The majority (87%) of the isolates were found to harbour high-level resistance to mupirocin. Almost all of the isolates were also resistant to methicillin. Although the *S aureus* isolates were found to represent a single epidemic clone, the *S epidermidis* population was much more diverse. Of note, six isolates of *S epidermidis* were demonstrated to express both low- and high-level resistance mechanisms simultaneously – the first identification of such dual mupirocin-resistant phenotype-bearing strains. In Japan, no isolates of methicillin-susceptible *S aureus* or MRSA collected from 43 hospitals nationwide in 1993 were found to have mupirocin resistance. However, following the introduction of intranasally administered mupirocin, mupirocin resistance was detected in 5.3% of MRSA strains and 23.3% of coagulase-negative staphylococci (*Staphylococcus hominis*, *S epidermidis*, *S chromogenes*) that were collected from the nares of patients over four years (26).

Mupirocin has been used extensively to prevent *S aureus* infections in patients undergoing peritoneal dialysis. Recently, two reports described the emergence of high-level resistance to mupirocin in both methicillin-susceptible and methicillin-resistant strains of *S aureus* in patients undergoing chronic peritoneal dialysis. Perez-Fontan et al (27) reported the emergence of MRSA in peritoneal dialysis patients and their partners over 10 years of using topical mupirocin. From 1990 to 1996, no high-level mupirocin resistance was noted. Mupirocin resistance subsequently developed and increased to 8.3% between 1997 and 1998, and to 12.4% between 1999 and 2000. Resistance was associated frequently with repeated mupirocin treatments for recolonization. The cumulative incidence of *S aureus* exit site infection from 1997 to 2000 was 32.3% in patients who were colonized by MRSA compared with 14.5% in those patients who were colonized by mupirocin-sensitive strains, which suggested that resistance has significant clinical impact. In addition, Annigeri et al (28) reported the significant emergence of high-level resistance to *S aureus* after a four-year use of mupirocin as prophylaxis for exit site infections. Of all the *S aureus* isolates collected in a point prevalence survey four years after the initiation of the use of mupirocin, 15% were found to have high-level resistance to mupirocin, which was significantly increased compared with a similar survey after one year's use, when no resistance was

detected. None of the isolates were resistant to methicillin in this study (28).

The emergence of high-level resistance to mupirocin in both outbreak and nonoutbreak settings, and among different patient populations, is a cause for concern. Collectively, these studies suggest that prolonged and widespread use of mupirocin is associated with the development of resistance. The spread of this resistance may occur through horizontal transfer of microorganisms carrying *mupA*, or through transfer of the *mupA* containing plasmid in both coagulase-positive and coagulase-negative staphylococci. With rising rates of MRSA in Canada, the judicious use of topical mupirocin cannot be overemphasized. In addition, in settings where mupirocin is used to any significant degree, reliable methods to determine and monitor resistance to this agent should be implemented by microbiology laboratories to provide an early warning system to facilitate interventions to minimize its spread.

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