# Focus

## Topical antibiotics - more harm than good?

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Indiscrimate use of antibiotics in the community and hospital setting contributes to bacterial resistance. A focus which has often been overlooked is the implication of antibiotic resistance to agents commonly used for skin infections and in dermatology.

In dermatology the most important resistance problems are found among staphylococci, *Propionibacterium acnes* and, to some extent, streptococci.[1]

The story of increasing resistance of *Staphylococcus aureus* (*S. aureus*) to mupirocin is a fascinating saga which illustrates the problem of antibiotic resistance.

In 1971, pseudomonic acid A was isolated as a metabolite of pseudomonas fluorescens and shown to have antibacterial activity.[2] The name was later changed to mupirocin to avoid any suggestion it had anti-pseudomonal effect.

**Key points**

- Bacterial resistance to topical antibiotics is illustrated by increasing rates of mupirocin resistant *S. aureus*
- In Australia, mupirocin resistance was lowered by changing it from OTC to prescription only status
- The public need to be educated re the use of topical antibiotics for wound management
- Before using a topical antibiotic consider whether a topical antiseptic such as povidine iodine may be adequate

Mupirocin is bacteriostatic but appears to be bactericidal at a lower pH, approximating that of many parts of the skin. The spectrum of antibacterial activity includes most Gram-positive and a few Gram-negative organisms but clinical application is directed principally to Gram-positive cocci.[2-4]

It has been used successfully to treat Gram-positive infections of ulcers, wounds, burns and eczema and was especially useful in eradicating nasal carriage of MRSA from patients and health care workers.[2-5]

That mupirocin has a unique mode of action as a bifunctional inhibitor of both isoleucine and ATP, and showed a low incidence of purely low level resistance, initially meant that higher degrees of resistance were considered a remote possibility.[2,7] New Zealand is now in the unenviable position of being one of the countries most vehement in proving this wrong.[8,9,14]

**Mupirocin made available OTC**

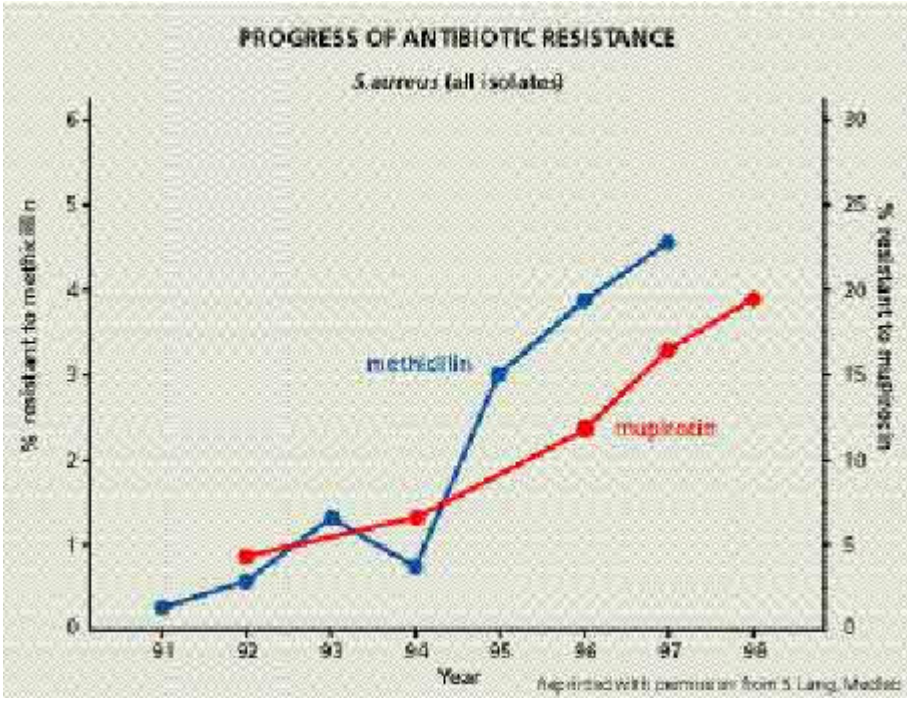
Mupirocin was introduced for clinical use in New Zealand in November 1986 and was made available "over the counter" (OTC) by the Department of Health in October 1991. Although *S. aureus* resistance to mupirocin was uncommon at this stage (0.3 per cent), no structured pre-marketing susceptibility surveillance was undertaken.[6]

In the first year of use Medlab reported a 3.7 per cent resistance rate in isolates of *S. aureus* (mainly high level) found among 4544 community acquired *S. aureus* skin and wound infections in Auckland.[8]

From November 1996 to October 1997, 1550 of 9700 (16 per cent) *S. aureus* tested were resistant to mupirocin (Figure).

Analysis of the study revealed patients with mupirocin-resistant *S. aureus* were significantly more likely to have used mupirocin than those with susceptible strains. Furthermore, there was a tendency for those with resistant isolates to have used mupirocin for more than one week at a time, and to have purchased it OTC.[8]

Cross infection was assumed to have occurred in 24 patients with mupirocin resistant *S. aureus* but no history of mupirocin use. More worringly, in 16 of these there was no history of mupirocin use by other members of the household.[8]




A national survey of *S. aureus* in March 1999 comprising 583 isolates from 38 hospital and community laboratories in New Zealand showed a resistance rate of 28 per cent to mupirocin.

Resistance was also found to occur significantly more frequently ($p<0.05$) among community acquired *S. aureus* (30.2 per cent) than among hospital-acquired isolates (19.8 per cent).[9]

Collated national resistance data from New Zealand laboratories showed that 19.3 per cent of nearly 15,000 *S. aureus* isolates tested were mupirocin-resistant in 1999.14 The resistance mechanism is thought to be due to the production of modified IRS enzymes or to an alteration in membrane permeability.[7]

**Australia reverses the trend**

That this inexorable pattern of increasing resistance can be reversed was demonstrated by Australia. As in New Zealand, mupirocin was being used empirically and frequently in the north of Western Australia to treat infected skin

lesions, resulting in the emergence, selection and amplification of a mupirocin-resistant strain of MRSA. This peaked in 1993 with 18 per cent high-level resistance found.[13]

As a result of this finding, the Health Department of Western Australia proposed guidelines restricting the use of mupirocin, making it available by prescription only. Since then mupirocin resistance has fallen to 0.3 per cent in 1997.[13]

It was this irrefutable evidence that the trend could be reversed, along with the publication of the increasing prevalence of resistance,8 which led the Ministry of Health to reverse the OTC status of mupirocin and return it to prescription only status a few months ago.

**Resistance to other topical antibiotics**

At the time of decline in mupirocin resistance in Australia there was a corresponding progressive increase in fusidic acid resistance that rose from 4.6 per cent of Western Australian isolates in 1994 to 12.4 per cent in 1997.[13] Fusidic acid resistance is based on the presence of either fusA (the gene that controls ribosomal protection) or fusB (a gene causing decreased permeability into the bacteria).[1]

The prevalence of fusidic acid resistance in New Zealand is also increasing (but so far without the corresponding drop in mupirocin). In a national survey in 1982 the resistance rate was 2.4 per cent but by 1999 this had increased to 17 per cent.[14]

There is also clear evidence in acne patients that antibiotic resistant staphylococci are selected by antibiotic use, and are transferable between patients and close contacts.[11]

Conventional treatment of acne uses both topical and systemic broad-spectrum antibiotics. Treatment is for a minimum of three months and often for several years. *Proprionibacterium acnes* has developed resistance following both systemic and oral forms of erythromycin and these strains are often also resistant to clindamycin.[1] Tetracyline resistance can also develop during treatment.[1]

After treatment, more than 50 per cent of patients harbour resistant bacteria and it is estimated about one in four acne patients has strains resistant to erythromycin, clindamycin and tetracycline.[12]

The 1999 collated New Zealand antibiotic resistance data show a resistance rate of 11.9 per cent to erythromycin and of 3 per cent to clindamycin among *S. aureus*. (However, clindamycin resistance is often inducible and difficult to detect in the laboratory; it is likely the "true" resistance is closer to erythromcyin resistance rates.)[14]

**Altering public expectations**

So how can these trends be reversed? The first and perhaps the hardest step is addressing that of public expectation.[15]

The need for topical antibiotics or antiseptics for skin lesions, sores and grazes is an area that requires public education more than ever. With so much advertising of products for skin disinfection, and the message to use bacterial soaps because our skin is loaded with bacteria, it is important GPs and other health professionals take

the opportunity, when possible, to educate people on the general concepts of minor wound management.

**Wound management**

Ask yourself at all times: Is anything beyond cleaning the wound and perhaps suturing, required? The basic principle is simple: clean it, cover it, check it.

*Clean it*. If the wound is contaminated or at high risk of contamination an antiseptic wash is necessary, but 48 to 72 hours post-injury the risk of infection is reduced and ongoing disinfectant use is not required unless medical or social conditions such as immunisation or poor nutrition mean the person is more susceptible to infections.[16]

*Cover it.* There are a number of wound coverings but for a basic wound a non-adhesive dressing should be adequate.

*Check it*. The person should check the wound, being aware of the signs of wound infection and have an action plan if infection is suspected.

**When should topical therapy be used?**

For a small, *localised* spot of impetigo and superficial wound infections a topical agent may be suitable. Although chronic wounds may also benefit from topical applications, this is a more specialised area too extensive to discuss here.

If there is reason for concern such as for an abscess, more extensive skin infections (eg, cellulitis), or in a diabetic, an oral antibiotic may be required; making a concurrent topical antibiotic superfluous.

In some situations it may be necessary to treat extensive impetigo with an oral antibiotic, but remember the issue of early reinfection or cross infection of other family members, and the possibility these potential situations would be adequately treated early with a topical therapy in future. Providing a topical therapy for this "just in case" purpose of one small spot of impetigo seems reasonable, but do so at the risk that this topical medicine may be used around the home for general cuts and sores. Hence it is preferable to prescribe a medicine with the lowest risk of resistance.

**Antiseptic *v* antibacterial**

Povidone iodine (Betadine®, Biocil®) is available in a number of different preparations – ointment, solution or cream. It is well tolerated, effective against a range of organisms – fungi, viruses and bacteria, including MRSA – and has little or no resistance even after extensive clinical use for 150 years.[17,18] It has been used for skin disinfection, superficial skin infections, burns and chronic wounds.[18-20]

Povidone iodine is a water soluble complex of elemental iodine and synthetic polymer with a protracted release of iodine which appears to reduce the incidence of iodine sensitivity.[17,19] The mechanism of action of iodine is diverse and this may be why bacterial resistance has not been apparent. Resistance would probably have to occur through excretion of inactivating compounds or novel permeability resistance.[17]

These properties make povidone iodine a suitable topical antiseptic when topical therapy is required. Three to four times daily application is recommended.

Fusidic acid is an alternative topical therapy, and while it was considered that short courses are unlikely to be epidemiologically harmful with respect to resistance patterns,21 this has been disproved,[13,14] as noted above. Fusidic acid is a useful antibiotic valuable for systemic and ocular use, and the risk of developing resistance should be minimised by strict limiting of topical use.

**Summary**

Salient lessons have been learnt about the development of bacterial resistance to topical antibiotics through the mupirocin story. In making an informed decision about a policy regarding a switch of topical anibiotic from prescription to OTC status the potential for harm needs to be considered carefully.

We should use any topical antibiotic with care and consider how essential its use is when a topical antiseptic may be adequate and have less risk of bacterial resistance developing.

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