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Nasal decolonization of *Staphylococcus aureus* with mupirocin: strengths, weaknesses and future prospects

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Staphylococcus aureus **in the nose is a risk factor for endogenous staphylococcal infection. UK guidelines recommend the use of mupirocin for nasal decolonization in certain groups of patients colonized with methicillin-resistant *S. aureus* (MRSA). Mupirocin is effective at removing *S. aureus* from the nose over a few weeks, but relapses are common within several months. There are only a few prospective randomized clinical trials that have been completed with sufficient patients, but those that have been reported suggest that clearance of *S. aureus* from the nose is beneficial in some patient groups for the reduction in the incidence of nosocomial infections. There is no convincing evidence that mupirocin treatment reduces the incidence of surgical site infection. New antibiotics are needed to decolonize the nose because bacterial resistance to mupirocin is rising, and so it will become less effective. Furthermore, a more bactericidal antibiotic than mupirocin is needed, on the grounds that it might reduce the relapse rate, and so clear the patient of MRSA for a longer period of time than mupirocin.**

Keywords: antimicrobials, infection control, MRSA, nosocomial, surgical

Nasal decolonization of methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) is currently used in some countries for specific patient groups. For example, in the UK it is recommended[1] that carriers of MRSA, who are receiving prophylaxis for an operation, should undergo nasal decolonization with mupirocin. Mupirocin is effective at removing *S. aureus* from the nose over a few weeks, but nasal relapses are common within several months.[2] There are few prospective randomized clinical trials (RCTs) with sufficient patients to achieve statistical significance that have been completed in this field.[3] Taken together, these trials suggest that clearance of *S. aureus* from the nose is beneficial in some patient groups.[4] This paper describes the risks, benefits and importance of patient selection in the use of mupirocin to decolonize the anterior nares.

S. aureus strains

MSSA lives on the skin of humans as a commensal. In developed countries ~30%[5–7] of the general adult population are colonized, although the data range from as low as 15%[8] up to 100%, in specific populations, such as those with MSSA skin infections.[9] Nasal colonization (stable colonization is defined as *S. aureus* in the nose detected from nasal swabs taken several days apart) with strains such as MRSA is much lower, at ~1% of the total population,[10] and is more frequent in certain subgroups of patients such as frequently hospitalized people, those of advancing age, patients on dialysis, AIDS patients and diabetics.[1,11]

Colonization with MRSA has been shown to increase the risk of infection with MRSA both immediately after colonization[12] and in long-term carriers, of whom 23% develop MRSA infections in the year following the identification of their carriage status.[13] Patients who have had contact with healthcare facilities such as hospitals may be colonized in the nose with healthcare-associated (HA) MRSA. A different set of MRSA strains affects patients who have not had recent contact with healthcare units, and these strains are called community-associated (CA) MRSA. HA-MRSA usually causes diseases such as bacteraemia and infective endocarditis that tend to be more multiresistant. In contrast

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CA-MRSA tends to affect younger, healthy people, causing skin and soft tissue infections and other infections such as the serious necrotizing pneumonia.[11] It is currently less multiresistant than HA-MRSA and is usually susceptible to commonly used antibiotics such as tetracyclines, but is more virulent, e.g. it invades tissue more readily, partly as a result of some strains that carry the Panton-Valentine leucocidin toxin gene.[14]

Methicillin resistance of MRSA is determined by carriage of the *mecA* gene that encodes a variant of the penicillin binding protein 2A, which has a low affinity for β-lactam antibiotics. The *mecA* gene is found on the staphylococcal cassette chromosome (SCC). Different strains of MRSA have SCC*mec* numbered I to VI. SCC*mec* types I to III are typically found in HA-MRSA,[15] while CA-MRSA characteristically carries the two smallest SCC*mec*, types IV[16] and V.[17] CA-MRSA grows faster *in vitro* than HA-MRSA, indicating a greater genetic fitness in the absence of the selection pressures from the widespread use of antimicrobials that shaped the genetic background of HA-MRSA strains.[14] CA-MRSA is thought to be currently using some of the more 'successful' genetic lineages from MSSA such as ST30 (Oceania clone) or ST8 (USA 300 clone).[15] Around the world CA-MRSA is presenting with changing resistance profiles[14] and outbreaks outside hospitals have been reported from close communities such as prisons,[18] military barracks,[19] rafting guide companies[20] and American football teams.[21] This evolution towards communicability and toxicity is likely to present new challenges for infection control.

Morbidity, mortality and economic impact of *S. aureus* disease

It has been estimated[22] that *S. aureus* in the USA in 2005 was responsible for 478000 nosocomial infections, 58% from MRSA, that progressed to cause 10800 deaths overall with 5500 from MRSA. Although MRSA has been associated with higher infection[23] rates than MSSA, it is thought that at least some of this effect is due to differences in the severity of co-morbid illness.[24] The cost to health services of controlling and treating *S. aureus* infections is high with one study in the USA suggesting $9.7 billion in 2001.[25] The impact of *S. aureus* infections on society as a whole is harder to quantify.

S. aureus transmission and adhesion

The ways in which *S. aureus* is transmitted and the mechanisms behind its survival in the nasal environment are important factors in colonization. It is likely that transmission from one individual to another is mediated by hand-to-nose contact, indicated by the association of hand carriage,[26] and of habitual nose-picking,[27] to nasal carriage. Aerial transmission[28] is an alternative route and may be particularly important in instances of colonized patients with allergies who tend to release higher *S. aureus* loads.[29,30] Having reached the anterior nares, the next step towards successful colonization is for the bacteria to effectively adhere to the nasal epithelial cells. Interactions between humans and *S. aureus* determine the nature of the nasal carriage and are influenced by the genotypes of both the host and microbe.[31]

Competition between staphylococci for colonization in the anterior nares

The 'ecological niche' of the anterior nares has a finite area that can be colonized and there is competition between different genotypes for this space. One study[32] observed nasal colonization with MSSA in 17% of patients and 8% with MRSA. However, only 0.6% were co-colonized with both and so the investigators concluded that, whilst different organisms can compete for the same niche, in this case MSSA has greater fitness, which suggests that it may prevent colonization by MRSA. The fitness advantage of MSSA over MRSA can be accounted for by the added resistance mechanism(s) of MRSA that incur viability and competitiveness costs.[33,34]

Does nasal colonization with *S. aureus* matter?

Nasal colonization as a risk factor for S. aureus disease

S. aureus (including MRSA) colonization of the nose is an endemic risk factor for infectious diseases such as bacteraemia and skin and soft tissue infections in many patient populations,[6] e.g. the general hospital population,[35] patients undergoing general,[5] thoracic[36] and orthopaedic[37] surgery, patients being treated in intensive care units (ICUs),[38] non-surgical patients (including those on haemodialysis),[39] continuous ambulatory peritoneal dialysis (CAPD) patients,[40] HIV-positive patients[41] and liver transplant patients.[42]

It seems that most *S. aureus* disease is caused by the patient's own bacteria. The rates of *S. aureus* autoinfection, where the *S. aureus* strain detected from the wound matches that swabbed from the nose, are high both in observational studies and in RCTs. Autoinfection rates tend to lie between 76% and 86%.[3,43–45] The density at which the anterior nares are colonized may be a further risk factor; a 3-fold increase in surgical site infections (SSIs) has been reported in surgical patients with high concentrations of nasal *S. aureus*.[37] These associations do not necessitate causality and both could conceivably be produced by a third party such as immunological changes influencing bacterial activity. Crucially though, evidence that nasal *S. aureus* decolonization leads to a decreased incidence of *S. aureus* infection in certain cases, is an important indication that nasal colonization is implicated in autoinfection.[3,4]

Mupirocin removes MRSA and MSSA from the nose

Mupirocin is established as the best topical antimicrobial available for Gram-positive bacteria[1,46] and has been applied to the task of nasal decolonization since the 1980s to target nasal *S. aureus* carriage on the grounds that *S. aureus* carriage is a risk factor for *S. aureus* disease.[47] It is a relatively potent decolonizing agent; immediately after completion of nasal mupirocin treatment, 81.5% to 100% of patients are successfully decolonized compared with spontaneous or vehicle-mediated decolonization rates of 0% to 46%.[3,48–50] Under everyday working conditions, poor patient compliance may reduce the effect further. For example, in one case, mupirocin only decolonized 6% of patients.[50]

Mupirocin resistance

Mupirocin acts on isoleucyl tRNA synthetase to inhibit protein synthesis.[51] It is this enzyme that is the focal point of resistance. Emergence of bacterial resistance to mupirocin, in many cases, is rising.[52,53] Interestingly though, significant increases in resistance to mupirocin have been reported in one hospital with only light mupirocin usage,[54] while regular usage in another was not sufficient to increase the mupirocin resistance.[55] There are two phenotypes of mupirocin-resistant *S. aureus*, 'low-level' and 'high-level' (LL-MR and HL-MR, respectively), and both are able to cause treatment failure.[56] The working definition of LL-MR is a mupirocin MIC of 8–256 mg/L and the working definition of HL-MR is a mupirocin MIC of $\geq$512 mg/L. The LL-MR genotype is a mutation of the chromosomal gene *ileS-2 (mupA)*, which encodes a resistant version of isoleucyl tRNA synthetase, while HL-MR's genotype is a plasmid-transferrable alternative version of the same gene.[34] An estimated 6.6% of patients who carry *S. aureus* are colonized with multiple strains,[57] so presenting an opportunity for horizontal gene transfer both for developing new strains[58] and perpetuating the resistance genes themselves. The plasmid can be incorporated into other species such as *Staphylococcus epidermidis*[59] to act as a potential reservoir.[60] The mutation behind LL-MR is readily induced by exposure to mupirocin *in vitro*.[61] This resilience of *S. aureus* resistance mechanisms means that mupirocin resistance is unlikely to be eradicated on the removal, or restriction, of mupirocin use, particularly as LL-MR mutations are not associated with a significant fitness burden over mupirocin-susceptible *S. aureus*.[34]

In one study[56] decolonization was achieved on day 3 after mupirocin treatment in 78.5% of mupirocin-susceptible MRSA, 80% of LL-MR MRSA and 27.7% of HL-MR MRSA. At 4 weeks, 91% of the mupirocin-susceptible MRSA group were still culture-negative, whilst only 25% of both the LL-MR and HL-MR MRSA groups were culture-negative. This 75% LL-MR MRSA persistence suggests even low-level resistance is sufficient to lead to treatment failure. If mupirocin-susceptible MRSA and LL-MR MRSA can be considered to have similar exogenous infection rates, then this result indicates that LL-MR MRSA recolonization is due to endogenous relapse rather than exogenous recolonization. The endogenous relapse may be attributable to latent bacterial sub-populations that may be difficult to detect by culture methods.[62]

Does nasal decolonization benefit the patient?

There are only a few[3,45,48] prospective RCTs that have been completed with sufficient patients, assessing the benefits of nasal decolonization, but those that have been reported suggest that the clearance of *S. aureus* from the nose is beneficial in some patient groups.

Surgery

In clean elective surgery in developed countries, the baseline rate for SSI is 1%–5% of which S. *aureus* causes 30%–50%.[63] A recent study,[48] with strong methodology and the only prospective RCT assessing SSIs performed with blinding during the data analysis, found that, despite clearing 81.5% of nasal *S. aureus*, no significant effect of mupirocin on the outcome of SSIs caused by *S. aureus* occurred (total *S. aureus* infections: 3.8% mupirocin, 3.2% placebo; $P=1.00$, CI = 0.32–4.69). Another large RCT, by Perl *et al*.,[3] concluded that mupirocin did not significantly reduce *S. aureus* SSIs, but that it did significantly reduce the total number of nosocomial *S. aureus* infections among the *S. aureus* carriers. A third study[45] found that mupirocin did not significantly reduce the *S. aureus* SSI rate even though there were 5-fold fewer endogenous *S. aureus* SSIs in the mupirocin group than in the control group.

One shared issue[48] that runs through these trials is that mupirocin has a minimal effect in reducing infections in uncolonized individuals. This dilutes the power of these studies and could contribute to the non-significant results found by both Perl *et al.*[3] and Kalmeijer *et al*.,[45] but not for those found in the later 2006 study[48] (which used data only from colonized patients). Another factor that may have led to the lower than average infection rates in these trials, hence further power dilution, is simply that participation in studies induces healthcare staff to maintain higher standards of hygiene and care, similar to the effect observed by French *et al*.[64] in 1989, and may have led the investigators in the smaller trials to underestimate the number of subjects needed to contract disease.[48] Nonetheless, the results from the two 2002 trials can be combined to increase the power of the trends that were shown to near statistical significance ($P=0.06$, pooled OR = 0.58, 95% CI = 0.33–1.02). A recent meta-analysis[4] suggested that these three trials, together with one other,[65] gave pooled results that, although still failing to substantiate nasal *S. aureus* decolonization with mupirocin as a means of reducing *S. aureus* SSIs, did generate sufficient significance to support mupirocin as an effective means to reduce all postoperative *S. aureus* infections, including SSI. In this study,[4] 3.6% of *S. aureus* infectious diseases occurred in the mupirocin-treated group versus 6.7% in the controls (RR = 0.55, 95% CI = 0.34–0.89, $P=0.02$).

Very large numbers of patients would be needed to confirm intranasal mupirocin's efficacy in reducing SSI with statistical significance. It is estimated that ~14000 patients[66] with a baseline SSI rate of 5% would be needed to demonstrate a 20% reduction in the SSI rate. It is not likely that this study will be undertaken, because of the large investment that would be required in relation to the size of the market.

ICUs

MRSA constitutes >64% of *S. aureus* isolates in US ICUs.[67] One study reported that 8% of admissions to ICUs carried MRSA in the nose and the acquisition of MRSA carriage whilst in the ICU was 10%.[68] The high prevalence of MRSA in ICUs presents a threat to the rest of the hospital population when patients are discharged from the ICU into other hospital wards with their accompanying MRSA[69] and, therefore, nasal decolonization with mupirocin may be useful in ICUs. In a prospective, randomized double-blinded study[70] it was suggested that the inclusion of mupirocin, intranasally and in an oral paste, significantly reduced MRSA lung infections (7 of 104 cases in the placebo group versus 1 of 119 cases in the treatment group; $P<0.05$). Further clinical trials suggest that mupirocin is useful for reducing endogenous MRSA infections in ICUs.[71]

Long-term mupirocin treatment

Studies looking at the long-term efficacy of mupirocin that have focused on nasal decolonization of *S. aureus*, including MRSA, have shown that initial clearance over several weeks is effective but that recolonization after 3 months is high.[2,72] It has been established that significant increases in resistance to mupirocin can occur after repeated or extended courses of mupirocin[73] and, in order to maximize the potential therapeutic benefits of mupirocin, it is recommended this such usage is avoided.[1] In dialysis patients, mupirocin treatment regimens have been described as effectively reducing infection although also increasing the prevalence of resistance to mupirocin.[74] However, it is possible to simply reduce the prevalence of *S. aureus* colonization without altogether eliminating carriage so minimizing the potential for induction of resistance. In care homes, 3 months after effective decolonization, recolonization rates are 39%[75] to 24%.[76] Of these recolonizations, 86% were relapses rather than exogenous recolonization.[75] Another study, in a gastroenterology unit, indicated that mupirocin significantly reduced nasal MRSA colonization and infection rates over 55 months using a single course of mupirocin.[77] In a study on healthy hospital staff, intranasal mupirocin affected a near complete decolonization; 6 months after treatment nasal colonization was 56% (the placebo group maintained 72% colonization) while 1 year after treatment nasal carriage was 53% (the placebo group maintained 76% colonization; RR = 0.70, 95% CI = 0.48–1.02, $P = 0.056$).[2]

What are the alternatives?

New antibiotics are needed to decolonize the nose due to the rise in bacterial resistance to mupirocin and its subsequent reduction in effectiveness. Additionally, a more bactericidal antibiotic than mupirocin is needed on the grounds that it might reduce the relapse rate, so clearing the patient of *S. aureus* for a longer period of time than mupirocin and reducing the associated risks of infection. We have not included other agents that are currently used in some countries, such as neomycin, chlorhexidene or fusidic acid, because, in a limited number of clinical trials, these agents have been shown to be either less effective than mupirocin or are not licensed for nasal decolonization of staphylococci.[78,79]

Drugs coming on to the market

A number of drugs, at varying stages of development, which might be more effective for nasal *S. aureus* decolonization than mupirocin, are on their way to the market. These come from a range of sources, large as well as small pharmaceutical companies (in the case of Replidyne, with inputs from both). The drugs have a diversity of mechanisms.

Replidyne's REP8839 has a similar mechanism of action to mupirocin, acting on the methionyl tRNA synthetase (MetRS) rather than isoleucyl tRNA synthetase to inhibit protein synthesis. MetRS is thought to be a particularly good target as it takes the first step in translating the methionine required for both the initiation and elongation of peptide chains *in vitro*. REP8839 is active against Gram-positive skin bacteria such as *S. aureus* and *Streptococcus pyogenes*. The drug completed Phase I clinical trials in 2007,[80] but its development has since slowed. Novabay's *N*,*N*-dichloro-2,2-dimethyltaurine is a stabilized analogue of the endogenous *N*-chlorotaurine oxidants synthesized by activated granulocytes.[81] Also known as NVC-422, the oxidant finished, in May 2008, Phase IIa clinical trials as a decolonization spray for nasal *S. aureus*, clearing 88% of colonized subjects.[82] Destiny Pharma is adapting the principles of photodynamic therapy to antimicrobials with its lead compound XF-73. XF-73 is a photosensitive porphyrin derivative that causes a light-dependent disruption of membrane integrity[83] and has shown potent clearance of MRSA on *ex vivo* porcine skin samples.[84]

Phico Therapeutics[85] is developing a bacteriophage approach to eliminate *S. aureus* and, in particular, MRSA. Its lead programme, SASPject™, has completed pre-clinical trials for nasal decolonization. Its *in vitro* activity against different *S. aureus* strains, bar vancomycin-intermediate *S. aureus*/vancomycin-resistant *S. aureus*, is >3 log reduction in viable counts after 6 h. The modified *S. aureus*-specific bacteriophage PTSA1.2/A delivers the complementary α/β-type small acid-soluble spore protein gene from *Bacillus megaterium*, which is then translated into its protein that flips the bacterial DNA A-B resulting in bacterial cell death. The SASPject™ application is focused and confined by the removal of the holin gene from the phage to prevent budding and so viral propagation.

Helperby Therapeutics[86] has developed the compound HT61, which showed a bactericidal effect against MSSA and MRSA in the nose in a Phase IIa clinical trial. HT61 is active against persistent bacteria that are not killed by antibiotics such as mupirocin.

NICE report

The UK's National Institute of Clinical Excellence (NICE) published a report[87] on 22 October 2008 on SSIs, which states: 'There is evidence that nasal decontamination with mupirocin or chlorhexidine administered to all patients undergoing surgery does not affect the overall rate of SSI. There is evidence that nasal decontamination with mupirocin given to *S. aureus* carriers undergoing surgery does not reduce either the incidence of *S. aureus* SSI or the incidence of all-cause SSI.'

NICE does not recommend the routine use of topical antimicrobial agents for nasal decontamination aimed at eliminating *S. aureus* to reduce the risk of SSIs.

We agree with the recommendations of the NICE report, but emphasize that there is evidence that mupirocin treatment reduces the incidence of *S. aureus* nosocomial infections in *S. aureus* carriers. The report does not comment on the use of mupirocin for the prevention of nosocomial infections. Accordingly, we suggest that usage of mupirocin should concentrate on the prevention of nosocomial infections in carriers. The reason for the failure of mupirocin to prevent SSIs is unknown, but may be due to lack of power in the clinical trials[55] or to a lack of efficacy of mupirocin in this patient sub-group.

Conclusions

The evidence suggests that intranasal mupirocin is a useful tool for reducing *S. aureus* autoinfection when patients are at high-risk in the short-term, such as in an ICU. Whilst it reduces the

risk of nosocomial infection, it has not been shown to reduce the risk of SSIs. It is also useful for reducing symptomless spread in hospitals. When patients are at risk of colonization and infection from MRSA, such as those patients on long-term haemodialysis, CAPD and in care homes, its utility is limited by the need to avoid the induction of resistance to it. The rising emergence of *S. aureus* resistance to mupirocin will eventually reach a point at which its benefits are restricted to the extent that its use is no longer economically viable. It is vital that at least some of the new antimicrobial therapies under development reach the market, both to provide a more effective solution to the issue of long-term nasal colonization and to replace mupirocin when it becomes redundant.

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