Nasal decolonization of \textit{Staphylococcus aureus} with mupirocin: strengths, weaknesses and future prospects

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

\textbf{\textit{S. aureus} strains}

MSSA lives on the skin of humans as a commensal. In developed countries \textasciitilde30\%\textsuperscript{5–7} of the general adult population are colonized, although the data range from as low as 15\%\textsuperscript{8} up to 100\%, in specific populations, such as those with MSSA skin infections.\textsuperscript{9} Nasal colonization (stable colonization is defined as \textit{S. aureus} in the nose detected from nasal swabs taken several days apart) with strains such as MRSA is much lower, at \textasciitilde1\% of the total population,\textsuperscript{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.\textsuperscript{1,11}

Colonization with MRSA has been shown to increase the risk of infection with MRSA both immediately after colonization\textsuperscript{12} and in long-term carriers, of whom 23\% develop MRSA infections in the year following the identification of their carriage status.\textsuperscript{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. It is currently less multi-resistant 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 leukocidin toxin gene.

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 SCCmec numbered I to VI. SCCmec types I to III are typically found in HA-MRSA, while CA-MRSA characteristically carries the two smallest SCCmec, types IV and V. 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. 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). Around the world CA-MRSA is presenting with changing resistance profiles and outbreaks outside hospitals have been reported from close communities such as prisons, military barracks, rafting guide companies and American football teams. 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 that S. aureus in the USA in 2005 was responsible for 478,000 nosocomial infections, 58% from MRSA, that progressed to cause 10,800 deaths overall with 5,500 from MRSA. Although MRSA has been associated with higher infection rates than MSSA, it is thought that at least some of this effect is due to differences in the severity of co-morbid illness. The cost to health services of controlling and treating S. aureus infections on society as a whole is harder to quantify. The density at which the anterior nares are colonized may be a further risk factor; a 3-fold increase in surgical patients with MRSA, that progressed to cause 10,800 deaths overall with 5,500 from MRSA. Although MRSA has been associated with higher infection rates than MSSA, it is thought that at least some of this effect is due to differences in the severity of co-morbid illness. The cost to health services of controlling and treating 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, and of habitual nose-picking, to nasal carriage. Aerial transmission is an alternative route and may be particularly important in instances of colonized patients with allergies who tend to release higher S. aureus loads. 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.

**Mupirocin removes MRSA and MSSA from the nose**

Mupirocin is established as the best topical antimicrobial available for Gram-positive bacteria, 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. 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%. Under everyday working conditions, poor patient compliance may reduce the effect further. For example, in one case, mupirocin only decolonized 6% of patients.
Mupirocin resistance

Mupirocin acts on isoleucyl tRNA synthetase to inhibit protein synthesis. It is this enzyme that is the focal point of resistance. Emergence of bacterial resistance to mupirocin, in many cases, is rising. Interestingly though, significant increases in resistance to mupirocin have been reported in one hospital with only light mupirocin usage, while regular usage in another was not sufficient to increase the mupirocin resistance. 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. 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 ≥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. An estimated 6.6% of patients who carry *S. aureus* are colonized with multiple strains, so presenting an opportunity for horizontal gene transfer both for developing new strains and perpetuating the resistance genes themselves. The plasmid can be incorporated into other species such as *Staphylococcus epidermidis* to act as a potential reservoir. The mutation behind LL-MR is readily inducible by exposure to mupirocin *in vitro*. 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*.

In one study 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.

Does nasal decolonization benefit the patient?

There are only a few 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%. A recent study, 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., 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 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 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. and Kalmeijer et al., but not for those found in the later studies (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. in 1989, and may have led the investigators in the smaller trials to underestimate the number of subjects needed to contract disease. 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 suggested that these three trials, together with one other, 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, 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 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. 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%. 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 and, therefore, nasal decolonization with mupirocin may be useful in ICUs. In a prospective, randomized double-blinded study it was suggested that the inclusion of mupirocin, intranasally and in an oral paste, significantly reduced MRSA lung infections (73.2% 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.
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 ² ² It has been established that significant increases in resistance to mupirocin can occur after repeated or extended courses of mupirocin and, in order to maximize the potential therapeutic benefits of mupirocin, it is recommended that 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.² ³ 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 colonization 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, chlorhexidine 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 Ila 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 integrity⁸³ and has shown potent clearance of MRSA on *ex vivo* porcine skin samples.⁸⁴ Phico Therapeutics⁸⁵ 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 Therapeutics⁸⁶ has developed the compound HT61, which showed a bactericidal effect against MSSA and MRSA in the nose in a Phase Ila 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 report⁸⁷ 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 trials⁵⁵ 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 SSI. 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 \textit{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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References

1. Coia JE, Duckworth GJ, Edwards DI \textit{et al.} Guidelines for the control and prevention of methicillin-resistant \textit{Staphylococcus aureus} (MRSA) in healthcare facilities. \textit{J Hosp Infect} 2006; 63 Suppl 1: S1–44.

2. Doebbeling BN, Reagan DR, Pfaffer MA \textit{et al.} Long-term efficacy of intranasal mupirocin ointment. A prospective cohort study of \textit{Staphylococcus aureus} carriage. Arch Intern Med 1994; 154: 1505–8.

3. Perl TM, Cullen JJ, Wenzel RP \textit{et al.} Intranasal mupirocin to prevent postoperative \textit{Staphylococcus aureus} infections. \textit{N Engl J Med} 2002; 346: 1871–7.

4. van Rijen MM, Bonten M, Wenzel RP \textit{et al.} Intranasal mupirocin for reduction of \textit{Staphylococcus aureus} infections in surgical patients with nasal carriage: a systematic review. \textit{J Antimicrob Chemother} 2008; 61: 254–61.

5. Kluytman J, van Belkum A, Verbrugh H. Nasal carriage of \textit{Staphylococcus aureus}: epidemiology, underlying mechanisms, and associated risks. \textit{Clin Microbiol Rev} 1997; 10: 505–20.

6. Wertheim HF, Mellers DC, Vos MC \textit{et al.} The role of nasal carriage in \textit{Staphylococcus aureus} infections. \textit{Lancet Infect Dis} 2005; 5: 751–62.

7. Gorwitz RJ, Kruzon-Moran D, McAllister SK \textit{et al.} Changes in the prevalence of nasal colonization with \textit{Staphylococcus aureus} in the United States, 2001–2004. \textit{J Infect Dis} 2008; 197: 1226–34.

8. Anwar MS, Jaffery G, Rehman Bhatti KU \textit{et al.} \textit{Staphylococcus aureus} and MRSA nasal carriage in general population. \textit{J Coll Physicians Surg Pak} 2004; 14: 661–4.

9. Nahmias AJ, Lepper MH, Hurst V \textit{et al.} Epidemiology and treatment of chronic staphylococcal infections in the household. \textit{Am J Public Health Nations Health} 1962; 52: 1828–43.

10. Tenover FC, McAllister S, Fosheim G \textit{et al.} Characterization of \textit{Staphylococcus aureus} isolates from nasal cultures collected from individuals in the United States in 2001 to 2004. \textit{J Clin Microbiol} 2008; 46: 2837–41.

11. Boucher HW, Corey GR. Epidemiology of methicillin-resistant \textit{Staphylococcus aureus}. \textit{Clin Infect Dis} 2008; 46 Suppl 5: S344–9.

12. Coelho R, Glynn JR, Gaspar C \textit{et al.} Risk factors for developing clinical infection with methicillin-resistant \textit{Staphylococcus aureus} (MRSA) amongst hospital patients initially only colonized with MRSA. \textit{J Hosp Infect} 1997; 37: 39–46.

13. Datta R, Huang SS. Risk of infection and death due to methicillin-resistant \textit{Staphylococcus aureus} in long-term carriers. \textit{Clin Infect Dis} 2008; 47: 176–81.

14. Tristan A, Ferry T, Durand G \textit{et al.} Virulence determinants in community and hospital methicillin-resistant \textit{Staphylococcus aureus}. \textit{J Hosp Infect} 2007; 65 Suppl 2: 105–9.

15. de Lencastre H, Oliveira D, Tomasz A. Antibiotic resistant \textit{Staphylococcus aureus}: a paradigm of adaptive power. \textit{Curr Opin Microbiol} 2007; 10: 428–35.

16. Daum RS, Ito T, Hiramatsu K \textit{et al.} A novel methicillin-resistance cassette in community-acquired methicillin-resistant \textit{Staphylococcus aureus} isolates of diverse genetic backgrounds. \textit{J Infect Dis} 2002; 186: 1344–47.

17. Ito T, Ma XX, Takeuchi F \textit{et al.} Novel type V staphylococcal cassette chromosome mec driven by a novel cassette chromosome recombinase, \textit{ccrC}. \textit{Antimicrob Agents Chemother} 2004; 48: 2637–51.

18. David MZ, Mennella C, Mansour M \textit{et al.} Predominance of methicillin-resistant \textit{Staphylococcus aureus} among pathogens causing skin and soft tissue infections in a large urban jail: risk factors and recurrence rates. \textit{J Clin Microbiol} 2008; 46: 3222–7.

19. Campbell KM, Vaughn AF, Russell KL \textit{et al.} Risk factors for community-associated methicillin-resistant \textit{Staphylococcus aureus} infections in an outbreak of disease among military trainees in San Diego, California, in 2002. \textit{J Clin Microbiol} 2004; 42: 4050–3.

20. Decker MD, Lybarger JA, Vaughn WK \textit{et al.} An outbreak of staphylococcal skin infections among river rafting guides. \textit{Am J Epidemiol} 1986; 124: 969–76.

21. Bowers AL, Huffman GR, Sennett BJ. Methicillin-resistant \textit{Staphylococcus aureus} infections in collegiate football players. \textit{Med Sci Sports Exerc} 2008; 40: 1362–7.

22. Klein E, Smith DL, Laxminarayan R. Hospitalizations and deaths caused by methicillin-resistant \textit{Staphylococcus aureus}, United States, 1999–2005. \textit{Emerg Infect Dis} 2007; 13: 1840–6.

23. Salda Dar, Bradley EA. The risk of infection after nasal colonization with \textit{Staphylococcus aureus}. \textit{Am J Med} 2008; 121: 310–5.

24. Shurland S, Zhan M, Bradham DD \textit{et al.} Comparison of mortality risk associated with bacteraemia due to methicillin-resistant and methicillin-susceptible \textit{Staphylococcus aureus}. \textit{Infect Control Hosp Epidemiol} 2007; 28: 273–9.

25. Noskin GA, Rubin RJ, Schentag JJ \textit{et al.} The burden of \textit{Staphylococcus aureus} infections on hospitals in the United States: an analysis of the 2000 and 2001 Nationwide Inpatient Sample Database. \textit{Arch Intern Med} 2005; 165: 1756–61.

26. Doebbeling BN. Nasal and hand carriage of \textit{Staphylococcus aureus} in healthcare workers. \textit{J Chemother} 1994; 6 Suppl 2: 11–7.

27. Wertheim HF, van Kleef M, Vos MC \textit{et al.} Nose picking and nasal carriage of \textit{Staphylococcus aureus}. \textit{Infect Control Hosp Epidemiol} 2006; 27: 963–7.

28. Wilson RD, Huang SJ, McLean AS. The correlation between airborne methicillin-resistant \textit{Staphylococcus aureus} with the presence of MRSA colonized patients in a general intensive care unit. \textit{Anaesth Intensive Care} 2004; 32: 202–9.
Review

29. Bischoff WE, Wallis ML, Tucker BK et al. "Gesundheit!" sneezing, common colds, allergies, and Staphylococcus aureus dispersion. J Infect Dis 2006; 194: 1119–26.

30. Bischoff WE, Tucker BK, Wallis ML et al. Preventing the airborne spread of Staphylococcus aureus by persons with the common cold: effect of surgical scrubs, gowns, and masks. Infect Control Hosp Epidemiol 2007; 28: 1148–54.

31. Emonts M, Uitterlinden AG, Nouwen JL et al. Host polymorphisms in interleukin 4, complement factor H, and C-reactive protein associated with nasal carriage of Staphylococcus aureus and occurrence of boils. J Infect Dis 2008; 197: 1244–53.

32. Dall’Antonia M, Coen PG, Wilks M et al. Competition between methicillin-sensitive and -resistant Staphylococcus aureus in the anterior nares. J Hosp Infect 2005; 61: 62–7.

33. Andersson DI, Levin BR. The biological cost of antibiotic resistance. Curr Opin Microbiol 1999; 2: 489–93.

34. Hurdle JG, O’Neill AJ, Ingham E et al. Analysis of mupirocin resistance and fitness in Staphylococcus aureus by molecular genetic and structural modeling techniques. Antimicrob Agents Chemother 2004; 48: 4366–76.

35. Davis KA, Stewart JJ, Crouch HK et al. Methicillin-resistant Staphylococcus aureus (MRSA) nares colonization at hospital admission and its effect on subsequent MRSA infection. Clin Infect Dis 2004; 39: 762–8.

36. Munoz P, Hortal J, Giannella M et al. Nasal carriage of S. aureus increases the risk of surgical site infection after major heart surgery. J Hosp Infect 2008; 68: 25–31.

37. Kalmeijer MD, van Nieuwland-Bollen E, Bogaers-Hofman D et al. Nasal carriage of Staphylococcus aureus is a major risk factor for surgical-site infections in orthopaedic surgery. Infect Control Hosp Epidemiol 2000; 21: 319–23.

38. Garrouste-Orgeas M, Timsit JF, Kallel H et al. Colonization with methicillin-resistant Staphylococcus aureus in ICU patients: morbidity, mortality, and glycopeptide use. Infect Control Hosp Epidemiol 2001; 22: 867–92.

39. Yu VL, Goetz A, Wagener M et al. Staphylococcus aureus nasal carriage and infection in patients on haemodialysis. Efficacy of antibiotic prophylaxis. N Engl J Med 1986; 315: 91–6.

40. Nouwen J, Schouten J, Schneeberger P et al. Staphylococcus aureus carriage patterns and the risk of infections associated with continuous peritoneal dialysis. J Clin Microbiol 2006; 44: 2233–6.

41. Nguyen MH, Kauffman CA, Goodman RP et al. Nasal carriage of Staphylococcus aureus in HIV-infected patients. Ann Intern Med 1999; 130: 221–5.

42. Chang FY, Singh N, Gayowski T et al. Staphylococcus aureus nasal colonization and association with infections in liver transplant recipients. Transplantation 1998; 65: 1169–72.

43. von Elff C, Becker K, Machka K et al. Nasal carriage as a source of Staphylococcus aureus bacteraemia. N Engl J Med 2001; 344: 11–6.

44. Wertheim HF, Vos MC, Ott A et al. Risk and outcome of nosocomial Staphylococcus aureus bacteraemia in nasal carriers versus non-carriers. Lancet 2004; 364: 703–5.

45. Kalmeijer MD, Coertjens H, van Nieuwland-Bollen PM et al. Surgical site infections in orthopaedic surgery: the effect of mupirocin nasal ointment in a double-blind, randomized, placebo-controlled study. Clin Infect Dis 2002; 35: 353–8.

46. Gould JC, Smith JH, Moncur H. Mupirocin in General Practice: a placebo controlled trial. In: Wilkinson DS, Price JD, eds. International Congress and Symposium Series. Number 80. Mupirocin, A Novel Topical Antibiotic: London: Royal Society of Medicine, 1984: 85–93.

47. Casewell MW, Hill RLR, Duckworth GJ. The effect of mupirocin (pseudomonic acid) on the nasal carriage of Staphylococcus aureus. In: Dobson RL, Leyden JJ, Noble W et al., eds. Excerpta Medica–Current Clinical Practice Series No. 16. Bactroban (mupirocin). Proceedings of an International Symposium. Amsterdam: Elsevier, 1985; 47–53.

48. Konvalinka A, Errett L, Fong IW. Impact of treating Staphylococcus aureus nasal carriers on wound infections in cardiac surgery. J Hosp Infect 2006; 64: 162–8.

49. Doebbling BN, Breman DL, Neu HC et al. Elimination of Staphylococcus aureus nasal carriage in health care workers: analysis of six clinical trials with calcium mupirocin ointment. The Mupirocin Collaborative Study Group. Clin Infect Dis 1993; 17: 466–74.

50. Hansen D, Patzke PI, Werfel U et al. Success of MRSA eradication in hospital routine: depends on compliance. Infection 2007; 35: 260–4.

51. Hughes J, Mellows G. On the mode of action of pseudomonic acid: inhibition of protein synthesis in Staphylococcus aureus. J Antimicrob Chemother 1978; 31: 330–5.

52. Simor AE, Stuart TL, Louie L et al. Mupirocin-resistant, methicillin-resistant Staphylococcus aureus strains in Canadian hospitals. Antimicrob Agents Chemother 2007; 51: 3880–6.

53. Fujimura S, Watanabe A. Survey of high- and low-level mupirocin-resistant strains of methicillin-resistant Staphylococcus aureus in 15 Japanese hospitals. Chemotherapy 2003; 49: 36–8.

54. Jones JC, Rogers TJ, Brookmeyer P et al. Mupirocin resistance in patients colonized with methicillin-resistant Staphylococcus aureus in a surgical intensive care unit. Clin Infect Dis 2007; 45: 541–7.

55. Fawley WN, Parnell P, Hall J et al. Surveillance for mupirocin resistance following introduction of routine peri-operative prophylaxis with nasal mupirocin. J Hosp Infect 2006; 62: 327–32.

56. Walker ES, Vasquez JE, Dula R et al. Mupirocin-resistant, methicillin-resistant Staphylococcus aureus: does mupirocin remain effective? Infect Control Hosp Epidemiol 2003; 24: 342–6.

57. Cespedes C, Said-Salim B, Miller M et al. The clonality of Staphylococcus aureus nasal carriage. J Infect Dis 2005; 191: 444–52.

58. Diep BA, Carleton HA, Chang RF et al. Roles of 34 virulence genes in the evolution of hospital- and community-associated strains of methicillin-resistant Staphylococcus aureus. J Infect Dis 2006; 193: 1495–503.

59. Janssen DA, Zarins LT, Schaberg DR et al. Detection and characterization of mupirocin resistance in Staphylococcus aureus. Antimicrob Agents Chemother 1993; 37: 2003–6.

60. Bastos MC, Mondino PJ, Azevedo ML et al. Molecular characterization and transfer among Staphylococcus aureus strains of a plasmid conferring high-level resistance to mupirocin. Eur J Clin Microbiol Infect Dis 1999; 18: 393–8.

61. Casewell MW, Hill RL. In vitro activity of mupirocin ('pseudomonic acid') against clinical isolates of Staphylococcus aureus. J Antimicrob Chemother 1985; 15: 523–31.

62. Coates A, Hu Y, Bax R et al. The future challenges facing the development of new antimicrobial drugs. Nat Rev Drug Discov 2002; 1: 895–910.

63. Trautmann M, Stecher J, Hemmer W et al. Intranasal mupirocin prophylaxis in elective surgery. A review of published studies. Chemotherapy 2008; 54: 9–16.

64. French GL, Cheng AF, Wong SL et al. Repeated prevalence surveys for monitoring effectiveness of hospital infection control. Lancet 1998; ii: 1021–3.

65. Garcia AM, Villa MV, Escudero ME et al. [Use of nasal mupirocin for Staphylococcus aureus: effect on nasal carriers and nosocomial infections]. Biomedica 2003; 23: 173–9.

66. Kallen AJ, Wilson CT, Larson RJ. Perioperative intranasal mupirocin for the prevention of surgical-site infections: systematic review of the literature and meta-analysis. Infect Control Hosp Epidemiol 2005; 26: 916–22.
67. Klevens RM, Edwards JR, Tenover FC et al. Changes in the epidemiology of methicillin-resistant Staphylococcus aureus in intensive care units in US hospitals, 1992–2003. Clin Infect Dis 2006; 42: 389–91.

68. Warren DK, Guth RM, Coopersmith CM et al. Epidemiology of methicillin-resistant Staphylococcus aureus colonization in a surgical intensive care unit. Infect Control Hosp Epidemiol 2006; 27: 1032–40.

69. Gould IM, MacKenzie FM, MacLennan G et al. Topical antimicrobials in combination with admission screening and barrier precautions to control endemic methicillin-resistant Staphylococcus aureus in an intensive care unit. Int J Antimicrob Agents 2007; 29: 536–43.

70. Nardi G, Di Silvestre AD, De Monte A et al. Reduction in gram-positive pneumonia and antibiotic consumption following the use of a SDD protocol including nasal and oral mupirocin. Eur J Emerg Med 2001; 8: 203–14.

71. Muller A, Talon D, Potier A et al. Use of intranasal mupirocin to prevent methicillin-resistant Staphylococcus aureus infection in intensive care units. Crit Care 2005; 9: R246–50.

72. Fernandez C, Gaspar C, Torrellas A et al. A double-blind, randomized, placebo-controlled clinical trial to evaluate the safety and efficacy of mupirocin calcium ointment for eliminating nasal carriage of Staphylococcus aureus among hospital personnel. J Antimicrob Chemother 1995; 35: 399–408.

73. Vasquez JE, Walker ES, Franzus BW et al. The epidemiology of mupirocin resistance among methicillin-resistant Staphylococcus aureus at a Veterans’ Affairs hospital. Infect Control Hosp Epidemiol 2000; 21: 459–64.

74. Tacconelli E, Carmeli Y, Aizer A et al. Mupirocin prophylaxis to prevent Staphylococcus aureus infection in patients undergoing dialysis: a meta-analysis. Clin Infect Dis 2003; 37: 1629–38.

75. Mody L, Kaufman CA, McNeil SA et al. Mupirocin-based decolonization of Staphylococcus aureus carriers in residents of 2 long-term care facilities: a randomized, double-blind, placebo-controlled trial. Clin Infect Dis 2003; 37: 1467–74.

76. Watanakunakorn C, Axelson C, Bota B et al. Mupirocin ointment with and without chlorhexidine baths in the eradication of Staphylococcus aureus nasal carriage in nursing home residents. Am J Infect Control 1995; 23: 306–9.

77. Dupeyron C, Campillo B, Richardet JP et al. Long-term efficacy of mupirocin in the prevention of infections with meticillin-resistant Staphylococcus aureus in a gastroenterology unit. J Hosp Infect 2006; 63: 385–92.

78. Leigh DA, Joy G. Treatment of familial staphylococcal infection—comparison of mupirocin nasal ointment and chlorhexidine/neomycin (Naseptin) cream in eradication of nasal carriage. J Antimicrob Chemother 1993; 31: 909–17.

79. Parras F, Guerrero MC, Bouza E et al. Comparative study of mupirocin and oral co-trimoxazole plus topical fusidic acid in eradication of nasal carriage of methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother 1995; 39: 175–9.

80. Critchley IA, Ochsner UA. Recent advances in the preclinical evaluation of the topical antibacterial agent REP8839. Curr Opin Chem Biol 2008; 12: 409–17.

81. Wang L, Khosrovia B, Najafia R. N-Chloro-2,2-dimethyltaurines: a new class of remarkably stable N-chlorotaurines. Tetrahedron Letters 2008; 49: 2193–5.

82. NovaBay. http://www.novabaypharma.com/company/profile.html (26 April 2009, date last accessed).

83. Maisch T, Bosl C, Szeimies RM et al. Photodynamic effects of novel XF porphyrin derivatives on prokaryotic and eukaryotic cells. Antimicrob Agents Chemother 2005; 49: 1542–52.

84. Destiny Pharma. http://www.destinypharma.com/index.shtml (26 April 2009, date last accessed).

85. Phico Therapeutics. http://www.phicotherapeutics.co.uk (26 April 2009, date last accessed).

86. Helperby Therapeutics. http://helperbytherapeutics.com (26 April 2009, date last accessed).

87. NICE. http://www.nice.org.uk/nicemedia/pdf/CG74FullGuideline.pdf (26 April 2009, date last accessed).