**Title**

Is the use of mupirocin beneficial for clearance of methicillin-resistant *Staphylococcus aureus* from newly admitted patients in the healthcare setting?

**Abstract**

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the more prevalent forms of healthcare associated infection (HCAI) and is responsible for global morbidity and mortality. A number of strategies have been employed to reduce the prevalence of this pathogen in the healthcare setting including improved hand hygiene, screening of healthcare workers and/or new admissions and decolonisation using the antibiotic mupirocin. However, there is much debate surrounding the use of mupirocin and it is not universally utilised due to concerns over resistance. In this article, I compared two studies and explored the associated literature to assess whether mupirocin was indeed beneficial in the clearance of MRSA from newly admitted patients in the healthcare setting. Using the CASP appraisal methodology, I compared papers by Milstone *et al.* (2010) and Cadilla *et al.* (2010) for their scientific rigour. Both papers used different methodologies and had their respective deficiencies and strengths but after appraisal, the findings of both studies appeared to suggest that decolonisation with mupirocin was of benefit but only if antibiotic screening of swabs was conducted beforehand. Failure to adhere to such recommendations has implications for increased drug resistance and selection of MDR-MRSA strains with inevitable results for those infected.

**Keywords**

Mupirocin; methicillin-resistance; *Staphylococcus aureus*; infection; prevention.

**Introduction**

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the more prevalent forms of healthcare associated infection (HCAI) and is responsible for premature morbidity and mortality (Saiman *et al.,* 2003). A number of strategies have been employed to reduce the prevalence of this pathogen in the healthcare setting including improved hand hygiene, screening of healthcare workers and/or new admissions and decolonisation using the antibiotic mupirocin (Gerber *et al.* 2006). While strategies such as rigorous attention to hand hygiene have been shown to have demonstrable benefit for the patient experience by reducing nosocomial rates of infection with MRSA (Gagne *et al.,* 2010), decolonisation using mupirocin is still not universally practiced (APIC, 2010). However, mupirocin has been used for decolonisation of MRSA carriers for a number of years (Wagenlehner *et al.,* 2007) and has been postulated as being a cost-effective adjunct to surveillance against MRSA colonisation and nosocomial transmission (Nelson *et al.,* 2010). While other studies have corroborated these cost-effective findings, caution has been noted since the level of mupirocin efficacy is critical to the cost-effectiveness of the strategy (Young & Winston, 2006).

Mupirocin, or pseudomonic acid, has been approved for the decolonisation of *S. aureus* nasal carriage in patients who are older than 12 years of age (Patel *et al.,* 2009). Resistance among isolates of *S. aureus* varies considerably and there have been many studies documenting this (Rotger *et al.,* 2005; Babu *et al.,* 2009). Mupirocin resistance in *S. aureus* is mediated through the acquisition of plasmid containing the *mupA* gene and has been associated with an increased use of mupirocin in the clinical setting (Coates *et al.,* 2009). Furthermore, the removal of *S. aureus* from patients and healthcare workers appears to be transient, with relapse rates being noted (Doebbeling *et al.,* 1994). Therefore, it is crucial that the effectiveness of mupirocin in preventing nosocomial MRSA infection is examined closely and a number of recent studies have attempted to elucidate the epidemiology of this particular strategy (Milstone *et al.,* 2010; Cadilla *et al.,* 2010). I have chosen these two studies to highlight the different approaches taken in attempting to understand

the epidemiology of mupirocin resistance in MRSA in new admissions to the healthcare setting.

**Methods**

Using the main tenets of the critical appraisal skills programme (CASP, 2010) as summarised by Burls (2009), I applied the same questions and methodological critique to articles on mupirocin resistance by Milstone *et al*. (2010) and Cadilla *et al.* (2010). The questions are as follows:

1. Did the study address a clearly focused area?
2. Was the methodology used appropriate for answering the question of interest?
3. Is there evidence of selection bias from the cohort?
4. Was there any measurement or classification bias?
5. Have the authors accounted for the confounding factors?
6. Was there appropriate follow-up of patients/cases?
7. What were the results and was correct statistical analysis used?
8. Are the results plausible and can they be ratified when bias and confounding is taken into consideration i.e. are the results 'real'?
9. Can the results be applied to the local population and do they agree or disagree with the current evidence?

Once the two studies have been subjected to robust critical appraisal in this fashion, then appropriate inferences can be made concerning the articles' claims.

**Results**

***Did the study address a clearly focused area?***

Both studies were clear in their focus. The Milstone study attempted to assess whether decolonisation using mupirocin was an important adjunct to an existing strategy aimed at reducing MRSA infections in a single hospital, while the Cadilla study aimed to confirm a hypothesis i.e. high-level resistance of

MRSA to mupirocin was associated with multi-drug resistance to other antibiotics.

***Was the methodology appropriate for the question of interest?***

The Milstone study assessed an intervention-based methodology, which was introduced in response to a cluster of MRSA infections in an intensive care unit whereas the Cadilla study was a prospective molecular analysis of isolates from patients who had been admitted to hospital in order to confirm a hypothesis. The Milstone study could be best described as a retrospective observational cohort study while the Cadilla study was a molecular analysis of patient isolates. Neither of these study methodologies is particularly robust and are prone to various forms of bias and confounding.

***Was there evidence of selection bias?***

The Milstone study assessed a cohort of neonates from a single hospital unit. Unfortunately, it is probably not possible to extrapolate the findings from this cohort to the general population since neonates are unlikely to have prior exposure to antibiotics therefore it would have been better to include other subjects such as cases from paediatric and adult intensive care as this sample would have more representative of the general population. In comparison, the Cadilla study assessed MRSA isolates from a single hospital in a given year and did not stratify by age. Furthermore, the number of samples studied was relatively large and therefore the inferences gained from this study, may be generalisable to the population. In addition, non-MDR samples were randomly selected.

***Was there any measurement or classification bias?***

Milstone and colleagues actually admit that one of the limitations to their study was that there was potential for misclassification bias i.e. classification could have been subjective. However, the study by Cadilla was a molecular analysis of isolates and therefore the methodology for assigning whether isolates were

resistant to mupirocin were completely objective and had been validated in a previous study (Cadilla *et al.,* 2009).

***Did the authors account for the confounding factors?***

Both studies are relatively simplistic in nature but the Cadilla design should not be prone to significant confounding. However, in the Milstone study, the authors again admit that clinicians, who were involved in treating patients who were enrolled into the study, may have been decolonised based on clinician factors. Undoubtedly, these could be classified as potential confounders of the results.

***Was there appropriate follow-up of patients/cases?***

The Milstone study followed patients up for 615 days, which is a very long time–frame and were able to identify cases of MRSA infection from those who were decolonised with mupirocin and those who were not. This could be considered a robust methodology with regard to this criterion. In contrast, there was no aspect of follow-up for the Cadilla study.

***What were the results and were the correct analyses used?***

In both studies, multi-variate regression analysis was conducted – linear (Milstone) and logistic (Cadilla) and these analyses are appropriate for the pertinent study methodologies. Milstone and colleagues' main finding is that decolonisation as part of a wide infection control strategy is an important factor in reducing nosocomial MRSA transmission based on the relative risk (0.08), confidence intervals (0.002-1.03) and p-value (0.04). While $p < 0.05$ and the IRR were statistically significant i.e. mupirocin treatment reduced the number of MRSA infections, the small sample size is shown in the confidence interval i.e. it breaches 1.00. Thus, the results are strongly suggestive that mupirocin treatment is beneficial in preventing MRSA infection as part of an overall infection prevention and control strategy.

The main findings from the Cadilla study were that MDR MRSA is more likely to be isolated from a different site on the body than a non-MDR MRSA strain ($p<0.0001$). Furthermore, there was a strong statistical association between resistance to mupirocin and resistance to other beta-lactam antibiotics for those MRSA isolates (odds ratio = 9.8, confidence intervals 4.04 - 23.9 and $p< 0.001$).

***Can the results be considered real when bias and confounding is taken into consideration?***

It is not possible to corroborate the findings of Milstone and colleagues who argue for inclusion of mupirocin in an infection control regimen since the cohort was based on neonates and therefore is not directly applicable to the general population. However, as the results suggest statistical significance, it would be appropriate to repeat a similar study but with a larger sample size, which was more representative of the population. In contrast, the results of Cadilla and colleagues appear to be irrefutable and are also plausible – if MRSA is resistant to many antibiotics, it is likely to be resistant to mupirocin.

***Are the results applicable to the general population and do they refute or agree with the current evidence?***

The study by Cadilla appears to confirm the findings of others and is applicable to other areas of the USA and probably continental Europe. The authors suggest that unless sensitivity testing is conducted, that treatment of patients with mupirocin for decolonisation may result in an increase in prevalence of MDR-MRSA (David *et al.,* 2008; Simor *et al.,* 2007).
The study by Milstone appears to confirm other studies, which have looked at the role of mupirocin decolonisation as part of an infection control strategy (Ridenour *et al.,* 2007; Sandri *et al.,* 2006; Lessa *et al.,* 2009). However, the authors note that larger studies are required to truly confirm the role of mupirocin decolonisation in infection control.

**Discussion**

It is clear from these studies that the role of mupirocin in decolonising new patients is beneficial in preventing nosocomial MRSA infections. However, it is also clear that if such practices are continued and anti-microbial resistance surveillance of nasal swabs is not included, that MDR MRSA is much more likely to increase in prevalence (McDougal *et al.,* 2010). The findings of the studies have relevance to other countries in the world but only for those countries, where MRSA could be considered a major problem i.e. the prevalence is high. In countries such as the Netherlands, where the prevalence of MRSA is considered to be low, guidelines have been produced on decolonisation treatment of either uncomplicated or complicated carriage (Tacconelli & Johnson, 2011). This has resulted in an increased treatment rate and eradication of MRSA from the nares of newly admitted patients. However, there are obvious caveats, which must be considered.

Although not all strains of MRSA are resistant to mupirocin, a number of aforementioned studies suggest that indiscriminate use of mupirocin will result in an increase in the prevalence of MDR-MRSA (David *et al.,* 2008; Simor *et al.,* 2007). It may be that while decolonisation appears to be important in infection control strategies, that it is the monitoring of mupirocin resistance, which is actually more important (Caffrey *et al.,* 2010). While much of the focus of the essay has been on the effect of mupirocin resistance, it is important to acknowledge that MRSA is an organism, which can quickly mutate and become resistant to other forms of antibiotic including mupirocin. Therefore, it is antibiotic stewardship, which is fundamental to this aspect of the infection control process. A recent study suggests that the strategy against MRSA in Europe may be reaping rewards in that the incidence has decreased but pertinently this has been due to a multi-factorial approach, which includes hand hygiene, screening, isolation of infected cases and regulatory changes in healthcare (Struelens & Monnet, 2010).

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