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Review

The Yin and Yang of pre-operative screening for meticillin resistant and sensitive *Staphylococcus aureus* (MRSA and MSSA): Does the extra effort and cost of suppression reduce surgical site infections?

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ABSTRACT

The inappropriate use and overuse of antibiotics, together with the demographic changes of an ageing population, chronic diseases such as diabetes mellitus, increased patient contact with healthcare facilities, high bed occupancy rates and the increase in surgical procedures, have all contributed to the rise in prevalence of Healthcare Associated Infections. These are attributable to selection and emergence of multi-resistant organisms. Additionally, there is evidence that this surveillance programme considerably underestimates true rates of SSI.

Strategies for prevention of SSIs are still in development and both MSSA and MRSA surveillance/suppression are likely to be considered as a plausible strategy for identifying at-risk patient prior to surgery, but a pertinent question remains: which surgical patients are likely to benefit most from this intervention?

Contents

1. Epidemiology of staphylococcal infections in the hospitalized patient population

The overuse and inappropriate use of antibiotics, together with the increasing demographics of an ageing population, chronic diseases such as diabetes mellitus, increased patient contact with healthcare facilities, high bed occupancy rates and the increase in surgical procedures, have all contributed to the rise in prevalence of Healthcare Associated Infections (HCAIs). These are attributable to selection and emergence of multi-resistant organisms. Infections caused by meticillin resistant *Staphylococcus aureus* (MRSA) have had extensive media coverage and have challenged medical practice. Although now dramatically falling, the UK had one of the highest recorded MRSA rates in Europe when measured by the surrogate use of mandatory reporting of bacteraemias caused by MRSA [1].

When translated into the cause of surgical site infections (SSIs), in which MRSA was implicated, the consequences were catastrophic both for patients and for the use of health care resources. SSIs caused by MRSA led to a longer postoperative stay, higher treatment costs and a poorer prognosis [2–4]. For example, the management of MRSA-infected hip and knee prostheses is associated with considerable mortality; and morbidities which include prosthetic joint removal and even amputation. Since 2004 the Health Protection Agency (HPA), now Public Health England (PHE), has coordinated mandatory surveillance of SSIs after major

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implant, orthopaedic operations [5] with an initial finding that almost half the SSIs were attributable to *S. aureus* with almost two thirds of these being due to MRSA (the severity of infection being related to type MRSA15 (ST 20) and MRSA 16 (ST 36)). However, there is evidence that this surveillance programme considerably underestimates true rates of SSI as it depends on in-patient and readmission data [6]. Although the proportion of SSIs, relating to MRSA, has fallen in line with reductions in bloodstream infection, sensitive forms of *S. aureus* have not fallen at a similar rate.

2. Microbial ecology of staphylococcal colonization of the skin

Currently, three patterns of nasal carriage can be recognized in healthy individuals: persistent carriers, intermittent carriers and non-carriage [7]. Persistent carriers have been found to have a higher nasal load of *S. aureus* and can be viewed therefore as being at a higher risk for developing endogenous infection [8]. The range of individuals who are persistent carriers is between 12% and 30%, whist intermittent carriage is estimated as being between16% and 70% [9,10]. Individuals who have a persistent nasal carriage of *S. aureus* also have also been found to have a higher rate of *S. aureus* colonization (2–3 times) at distant anatomical sites [7]. As a general rule nasal carriage of MRSA lies somewhere between 3% and 6%; the risk is higher in patients who have recently been resident in health care facilities, are living in long-term care facilities and those who have co-morbidities resulting in frequent healthcare contacts such as renal failure [11]. *S. aureus* colonization, including Meticillin sensitive *S. aureus* (MSSA) as well as MRSA, increases the risk of an HCAI by at least six times and by 15 times when nosocomially acquired MRSA colonization is present. When admitted to secondary health care, patients who are colonized with MRSA are also at greater risk of SSI, with a significantly increased risk of morbidity and mortality.

Person-to-person transmission of MRSA has been documented and is considered to be a driver for the requirement for rapid detection and suppression if patients are to be protected. Some individuals are intermittent carriers of MSSA but person-to-person transmission of MSSA is less well documented. However, once an infection occurs, the cost of treating patients infected with *S. aureus* is considerable, especially when an implant is implicated, as the presence of biofilm necessitates removal of the affected implant and an extended course of antibiotic therapy. The need to isolate infected patients in secondary care is also resource-intensive and can affect a patient's quality of life, particularly when an elderly patient is deprived of the associated loss of social interaction [12]. In addition, antibiotics such as vancomycin, needed for prophylaxis and treatment of MRSA, cost more and can only be administered intravenously [13,14].

The cost of all SSIs, not only after orthopaedic surgery but also after paediatric and head and neck surgery, operative procedures on patients on renal and intensive care units and open cardiac procedures (all mostly related to *S. aureus* infections), is a burden to healthcare systems in addition to the effect on postoperative morbidity and mortality.

3. MRSA/MSSA screening and decolonization from an evidence-based perspective

The 2010 national prevalence of methicillin-resistant *S. aureus* (MRSA), in US healthcare in-patient facilities, was reported in 2012. This national APIC-led study found that the prevalence of MRSA (66.4 per 1000 inpatients) had actually increased from the 2006 rate (46.3 per 1000 inpatients) [15,16]. In part, these findings have stimulated the accelerated interest in the preoperative identification of MRSA colonization in surgical patients, followed by active suppression as a pre-emptive strategy for reducing the risk of postoperative surgical site infection [16]. In England, in response to the rising trend of MRSA bacteraemias, the Department of Health initiated an MRSA screening programme for patients undergoing elective surgery in April 2009, which extended to all admissions in 2010. Together with other infection protection initiatives and the growth of "zero tolerance" (Winning Ways, 2003; Clean Your Hands Campaign, 2004; Clean, Safe Care, 2007; High Impact Interventions on SSI, 2011) the incidence of MRSA bacteraemia has shown a steep decline across all countries of the UK [17–20]. The decline has also been attributed to MRSA clonal changes and may be independent of these initiatives [21]. Nevertheless, it has been suggested that the cost-effectiveness of expensive and universal MRSA screening should be re-examined [22,23]. The evidence that screening and suppression for MRSA has been of benefit, let alone the screening strategy, implementation and the actual suppression methods used has also been questioned in the United States [24,25].

Several studies have suggested that suppression of the MRSA carrier state is effective in reducing SSIs caused by MRSA in selected surgical disciplines. In a study conducted in 2007, patients admitted to a tertiary medical center for elective surgery were screened (nasal) for MRSA. Positive patients were treated with 2% mupirocin (twice a day for 5 days) and, in addition, were instructed to take three 4% chlorhexidine gluconate (CHG) showers prior to surgery. Whilst a reduction was seen in MRSA infections, in patients undergoing selective cardiac procedures and hysterectomies, the findings were not statistically significant. However, a significant reduction in MRSA SSIs was observed in patients undergoing knee and hip (prostheses) procedures ($p < 0.04$) [26]. In a further study, published in 2010, an active surveillance programme (PCR-based) was implemented to detect *S. aureus* nares colonization (MSSA and MRSA) in elective orthopaedic surgery patients. A total of 1588 patients were identified as being *S. aureus* carriers (22.6%); 309 (4.4%) were characterized as MRSA. All positive (MRSA and MSSA) patients had suppression therapy with 2% mupirocin (twice a day for 5 days) and instructed to take 2% CHG total body-showers for 5 days prior to surgery. At admission, the initial MRSA colonized patients were re-screened by PCR and repeat positives were flagged for contact isolation. While the reduction in MSSA surgical site infections did not approach significance ($p = 0.094$), a significant reduction in MRSA infections ($p < 0.032$) was observed compared to a baseline pre-intervention control group [27]. A prospective Swiss study, which included 21,754 surgical patients, found no significant reduction in nosocomially acquired MRSA infections after implementing of a PCR-based universal surveillance programme in surgical wards [28]. However, this study has been highly criticized because only 43% of the patients, known to be MRSA carriers before surgery, received effective perioperative antimicrobial prophylaxis against MRSA. It is also worth noting that 31% of the MRSA carriers undergoing elective surgery were actually identified after surgery had taken place because of the emergent nature of the intervention and delays in reporting screening results [28]. In 2011, two large institutional studies were published, one conducted in a critical care patient population and the other in the US Veterans Affairs Hospital system, and added to the ambiguity surrounding the benefit of active surveillance in medical and surgical patient populations [29,30]. In the first study, which targeted ICU patients ($n = 5435$ admissions), surveillance cultures (nasal) were obtained on admission and processed in a remote laboratory. The study emphasized an expanded use of barrier precautions, in addition to contact precautions, but did not use nasal mupirocin in culture positive patients or attempt to reduce the density of body site contamination using CHG body-wash or cleansing. Consequently, merely identifying carriers and expanding the use of barrier precautions did not effectively reduce MRSA transmission [29]. The

VA study, which was published in the same journal, is a remarkable contrast in design and execution. Over a 3 year period 1,934,598 patients were enrolled in an "MRSA bundle" that included universal nasal surveillance (PCR-based), contact precautions for colonized or infected patients, enhanced hand hygiene practices and a change in "institution culture" surrounding aseptic practices. The mean prevalence of MRSA was 13.6%, and the incidence of MRSA–HCAIs declined in their ICUs from 1.64 per 1000 patient days to 0.62 per 1000 patient days ($p < 0.001$) [30]. The take-home message from this study suggests that the risk-reduction benefit derived from an active staphylococcal surveillance programme is dependent on two factors, a "robust" prospective surveillance programme and an institutional commitment to evidence-based interventional strategies which are triggered upon positive (MSSA or MRSA) surveillance findings.

Whilst very few, well-designed, clinical studies exist in current medical and surgical literature, selected peer-reviewed evidence suggests that active surveillance does play a role in reducing risk in selective patient populations. However, applying this strategy across the broad scope of surgical practice appears to be less warranted since mandating universal surveillance would likely pre-empt local assessment of risk and prioritization of healthcare resources. Another unresolved issue involves whether a single-site (nasal) culture has sufficient power to detect the maximum number of colonized (MRSA and MSSA) patients. Another, cross-sectional study has shown that while nasal screening may be viewed as the "gold standard" for assessing patient colonization, it only identifies66% of true MRSA carriers. The combination of nasal and perineal screening identified 82% of colonized patients [31]. A systematic review, of over 4281 abstracts and 735 manuscripts, extracted 23 papers (n = 39,479 patients) which met the criteria for analysis and found that extranasal screening increased MRSA recovery by approximately one-third (33%) compared to nares culture alone. Cultures from the oropharynx were found to increase MRSA detection by 21% over nares alone; perineum by a factor of 20%; wound by 17% and axilla by 7% [32]. While extranasal *S. aureus* detection is likely to increase the overall yield of MRSA detection, the additional cost associated with increased site surveillance would probably be cost prohibitive for many healthcare facilities. Whilst eradication of the carrier state, in selected at-risk patient populations, has been suggested to decrease the risk of postoperative infection, routine screening (nasal or a combination of sites) to identify persistent carriers is still viewed by many practitioners as controversial [33].

There is considerable opportunity here for research; the patho-geography and mapping of clones might help with molecular genomic surveillance within the next 5–10 years, if all these isolates could be examined in central, appropriately resourced, laboratories. It has been shown that, by using rapid MSSA PCR screening and suppression within 24 h of admission [34], there can be statistically significant reductions in MSSA-related SSIs and in hospital stays. A paper, published in the New England Journal of Medicine [35], included almost 7000 patients and made a case for MSSA screening and suppression. However, there were several flaws in the methodology which included structural problems, only a small proportion of patients were randomized for example, with a substantial possibility of bias. The publication should probably be considered as presenting grade II evidence and further studies are needed to evaluate the strength of the authors' conclusions. *S. aureus* is still the most common organism retrieved from SSIs and remains heavily implicated in other HCAIs but, despite the fall in MRSA bacteraemias, there has been little change in the prevalence of MSSA bacteraemia. In addition, SSI rates are greatly influenced by the adequacy of surveillance and definitions as well as adoption and compliance with NICE guidelines or High Impact Intervention care bundles [14,36].

Nasal mupirocin has been widely used for the suppression of *S. aureus* (MSSA and MRSA) in surgical patients or high risk patients for well over 25 years [37,38]. However, many of the clinical studies documenting the benefit of nasal application of mupirocin in surgical patients are often poorly designed, lack adequate controls and are generally of poor scientific quality. In one prospective study, involving 614 orthopaedic operations, patients were randomized to mupirocin compared with a placebo. The eradication rate was significantly more effective in the treatment group compared to control (27.8% vs. 83.5%, $p < 0.05$). However, no significant difference was noted in either the SSI rate between the mupirocin treatment and placebo or in the length of stay between study groups [39]. In another prospective study, nasal mupirocin suppression was used prior to open heart procedures. Overall, nasal mupirocin was effective in reducing the sternal wound infection rate (2.7% vs. 0.9%, $p < 0.005$) and shortening postoperative stay (12.1 vs. 38.4 days, $p < 0.004$) compared with a control (untreated) group. The authors concluded that mupirocin was safe, inexpensive and effective in reducing the overall risk of sternal wound infections [40].

Although mupirocin is viewed as the "gold-standard" for "short-term" suppression of MRSA, it has been less effective as a "long-term" suppression agent. The efficacy of a 7-day combined course of topical and systemic agents has been evaluated, which included 2% CHG body-cleansing, 2% mupirocin topical application to the anterior nares (twice daily), rifampicin (300 mg twice daily) and doxycycline (100 mg twice daily), in a hospitalised patient population. Combination therapy was initiated within 4-days of a positive (MRSA) culture result and the comparator group was "no treatment". Follow-up cultures were obtained from the anterior nares, perineum, skin lesion site, vascular access sites and other sites that may have initially yielded MRSA. At 3 and 8 months, 74% and 54% of treated patients respectively were culture negative for MRSA compared to the non-treatment group ($p < 0.0001$). This study suggests that in hospitalized patients, MRSA can be successfully suppressed (long-term) using a 7-day combination therapy of CHG cleansing, topical mupirocin and oral rifampicin/doxycycline [41]. However, the implication of this approach for surgical patients undergoing elective surgery is unknown. A final cautionary consideration is warranted, in an effort to reduce risk while practicing within a realm of fiscal conservatism, as some practitioners are invoking the empirical practice of using nasal mupirocin in the absence of appropriate surveillance studies. While there is some ambiguity concerning the risk associated with development of mupirocin resistance, when used for short-term or long-term empiric use, this type of utilization would appear to violate our current mandate for "antibiotic stewardship" or appropriate antibiotic use policies [42]. At present, and for the foreseeable future, mupirocin is the only topical agent which has been documented to have a benefit in suppressing both MRSA and MSSA carriage; therefore institutional policies preserving its use as an effective suppression agent are warranted.

4. MRSA/MSSA surveillance: laboratory strategies

Whilst MRSA may be in decline in some selective clinical environments, it is possible that some current limited resources could be re-directed towards funding for MSSA screening and suppression [43]. A screening/suppression protocol would be similar for all *S. aureus* as the current, universally implemented MRSA protocols but would be targeted only at risk patient groups [44–49].

Rapid PCR MSSA screening offers a real time tool for the implementation of interventions but a health economist's involvement is required to evaluate a programme aimed at targeting at-risk groups. Nevertheless, the expansion of screening to include MSSA may not, at the laboratory level, result in a drastic escalation

in costs. In practical terms the same patient swab could be used for testing MRSA and MSSA. The PCR test for MRSA costs approximately £10, and expanding this to include all *S. aureus* would cost an additional £1. However, higher costs would necessarily be borne at the intervention/suppression aspect of the patient pathway because of the higher carriage rates of MSSA and numbers of patients identified to require suppression (adding labour costs of up to £20 per patient). For this reason a robust cost-effectiveness assessment is required.

For MSSA screening there is some agreement that nose-only swabbing and processing using PCR, or conventional culture method using chromogenic plates, would be cost effective (only 5–10% of carriers being missed by leaving out throat/groin screening). This could be offered as the minimum intervention with the need for local interpretation for the special needs of higher risk patients having cardiac, paediatric or head and neck surgery for example. The swabbing of additional, more intrusive, sites might be left to clinical judgement and based on local epidemiology. The use of PCR or chromogenic agar also needs similar local interpretation. Unlike MRSA, there are no data indicating which screening site is preferential for the determination of carriage rate of MSSA and therefore it is difficult to prescribe a 'gold standard'.

If MRSA screening can be rationalized to patients most at risk of infection from the risk factors identified from prospective studies then, with the savings made, it may be possible to introduce targeted MSSA screening with little extra overall cost. Screening for all *S. aureus* colonization would not materially increase laboratory costs as PCR or chromogenic assays can be performed on the same samples. However, screening for MRSA in high-risk patients misses up to a third of carriers of *S. aureus*, and patients negative to MRSA screening alone still experience *S. aureus* infections. Thus, screening for MRSA alone in high risk patients is not without error, and current molecular techniques cannot predict the severity of *S. aureus* infections. Once suppression has ceased, MRSA recolonization can be rapid and colonization with MRSA increases the risk of transmission of MRSA. However, MSSA suppression does appear to have the potential to reduce infection in carriers.

Culture-based screening methods are, in general, inexpensive and do not require skilled molecular technologists to perform the analysis. The primary advantage of the currently available molecular screening methods is high sensitivity and rapid turn-around time. When compared to direct culture, current molecular methods are up to 13% more sensitive and have limits of detection as low as 100 bacteria per swab [50,51]. However, the current array of commercially available chromogenic media has been developed for high-throughput MRSA screening from nasal swabs. These media contain a concentration of oxacillin or cefoxitin which is inhibitory to *mecA*-negative staphylococci. A chromogenic substrate, utilized specifically by *S. aureus*, gives these media specificity for MRSA which appear as pigmented colonies. The sensitivity and specificity of these screening media are high, ranging from 88 to 98% and 98% to 100%, respectively when compared to standard culture methods [52–54]. Therefore, use of chromogenic media is a viable option for those institutions which are unable to support automated molecular technology.

5. Final considerations: should MSSA and MRSA screening and suppression be viewed as a critical intervention for "at risk" patient groups and be included in national guidelines?

(i) The incidence of MRSA bacteraemia has fallen but MSSA bacteraemia has not, and there is a continued need to reduce the incidence of invasive staphylococcal infections in hospital patients. The Bode et al. [35] publication has its limitations but makes a case for the introduction of MSSA screening and suppression to reduce SSI incidence and the length of hospital stay. However, without further, more scientifically convincing studies this cannot be supported. In addition, the use of a clinical risk assessment tool (CRA) needs to be established with assessment of cost benefits which needs cooperation with a specialist health economist.

(ii) If it is to be implemented, MSSA screening and suppression should be focussed on patients who are most prone to serious *S. aureus* infections. This specifically includes patients on renal units or ICUs and those undergoing high-risk surgery such as operations where implants are implicated (orthopaedic and vascular in particular) and cardiac operations involving sternotomy.

(iii) The "sheep dip" approach of decolonizing patients most at risk of *S. aureus* infections, without prior screening, needs careful consideration because of fears of developing wide resistance, specifically to mupirocin. There is some evidence that new strains with high-level resistance to mupirocin are gaining a foothold, particularly in France [55]. If this is likely to be a significant issue suppression ought to be specifically kept for patients who have screened positively for MRSA/MSSA, and who are at higher risk of *S. aureus* infections or when the consequences of an SSI are more catastrophic or life-threatening. The decision needs to be taken and in line with local epidemiology.

(iv) If a national screening strategy is to be introduced it would be both judicious to undertake pilots in specific groups of patients, allowing some local flexibility and incorporating a pre-determined review point. The results from this type of audit/research might be used to determine whether screening should include a wider group of patients, or even be introduced universally, or nationally.

(v) Improved acceptance and use of agreed definitions of SSI and the quality of surveillance probably needs enhancing in primary and secondary care, together with consideration and bolstering of compliance with guidelines and care bundles on SSIs, before widespread MSSA screening/decolonization is introduced. Compliance with this best practice should be ensured before engaging on a new national screening/suppression programme.

(vi) Reference laboratory patho-geography and mapping of MSSA isolates may be possible. The referral criteria for strain typing by reference laboratories would need to be used to inform changes in the screening programme. There are many research opportunities, which could involve the study of stored isolates to indicate whether infections are endogenous or exogenous; sharing of isolates with reference laboratories could ascertain the origin of specific clones; monitoring could be used to prove the value of screening/suppression; risk of SSI could be minimized and used to aid the measurement of compliance (with a reduction of litigation risk if undertaken satisfactorily); and all isolates could be archived for resistance patterns (outbreaks, clusters and national surveillance).

The US Centers for Disease Control and Prevention's guidelines for prevention of SSIs is currently in its final stages of development and both MSSA and MRSA surveillance/suppression are likely to be considered as a plausible strategy for identifying at-risk patient prior to surgery, but a pertinent question remains: which surgical patients are likely to benefit most from this intervention? In general the following guidelines are warranted:

- A targeted approach should be directed towards cardiac, total joint arthroplasty, vascular and other device-related surgical procedures.
- Surveillance for both MSSA and MRSA is warranted, while a single nasal swab meets current criteria, extranasal surveillance

improves recovered of both MSSA and MRSA in high-risk surgical patient populations.

- Patients who are positive for MSSA or MRSA should receive mupirocin twice daily for 5 days prior to surgery and also take daily a minimum of 2–3 CHG showers/cleansing prior to surgery.
- Empirical use of mupirocin should be avoided as it may be viewed as being inappropriate under current "antibiotic stewardship" practices.

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