1.5. PREVENTION: RISK MITIGATION, LOCAL FACTORS

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QUESTION 1: Is preoperative methicillin-resistant *S. aureus* (MRSA) decolonization effective at reducing surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing orthopaedic procedures? If so, is preoperative MRSA decolonization cost-effective?

RECOMMENDATION: No definitive recommendation can be made regarding the routine implementation of preoperative S. aureus screening and decolonization protocols due to conflicting literature. Additionally, no definitive recommendation can be made about selective or universal treatment, although the universal treatment strategy seems to be the most cost-effective strategy and easiest to implement. Alternatives to mupirocin such as povidone-iodine nasal ointment may obviate the concern for antibiotic resistance raised by universal treatment protocols.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 86%, Disagree: 7%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

There is evidence in the literature that patients colonized with *Staphylococcus aureus* in their nasal or skin flora are at increased risk of SSIs and PJIs after total joint arthroplasty (TJA) [1–3]. SSIs resulting from *S. aureus* are significantly higher among TJA patients compared to other orthopaedic surgeries [4]. It is not clear whether this increased risk is exclusively due to the carrier state or the association of *S. aureus* colonization with other medical risk factors for PJI such as diabetes, obesity, renal insufficiency, inflammatory arthritis or immunosuppression [2,5,6]. For example, Maoz et al. [7] analyzed data from 3,672 primary and 406 revision hip arthroplasties and found that *S. aureus* colonization was associated with higher PJI rates but was not an independent risk factor in a multivariate analysis.

That said, the existence of an endogenous contamination pathway has long been recognized among PJI cases [8]. While the concordance between wound and nasal isolates among carriers is high, *S. aureus* infections can also be found in non-carriers [2,9,10]. The actual preponderance of the endogenous route over the traditional exogenous mode of infection acquisition is not constant and may be based on geography and institution, depending on the epidemiological setting. It has been shown that institution-wide MRSA endemics do not necessarily lead to a high MRSA infection risk after elective hip and knee arthroplasty [11]. However, many institutions have attempted to minimize this potentially modifiable source of contamination by instituting preoperative screening and decolonization protocols in *S. aureus* carriers to reduce infection rates.

Several different approaches have been described. A perfect screening test has a high sensitivity to identify all *S. aureus* carriers at a reduced cost, and a perfect treatment regimen would be easy to administer and cost-effective, while achieving preoperative *S. aureus* eradication without short- or long-term or patient- or population-based adverse effects. Standard culture techniques are often used, but their sensitivity is highly variable depending on the number of samples taken for each patient and the method of sampling. Naturally, screening multiple body sites is more sensitive for identifying carriers and using nasal swabs as a surrogate for colonization testing may only identify two-thirds of true MRSA carriers [12,13]. Molecular polymerase chain reaction (PCR) based screening techniques may provide results in a shorter time frame, but this technique is more expensive, and there is conflicting evidence regarding the theoretical advantage of PCR over traditional cultures [14,15].

Treatment of *S. aureus* carriers has traditionally been achieved utilizing nasal mupirocin ointment twice a day with whole-body chlorhexidine once a day for the five days preceding surgery [16,17]. The biggest criticism of this treatment regimen is that increased use of mupirocin, an antibiotic, can potentially increase the risk for antibiotic resistance.

Other decolonization alternatives use antiseptics, such as povidone-iodine, rather than antibiotics (i.e., mupirocin) to achieve *S. aureus* eradication. It is relevant to acknowledge that not all povidone-iodine products are equally effective in eliminating nasal *S. aureus* [18]. A specific povidone-iodine product for nasal use that contains excipients which protect the solution against deactivation by nasal secretions was developed and tested favorably in vitro against traditional products such as mupirocin [19]. This povidone-iodine treatment rapidly achieves a significant reduction in bacterial counts after one hour of treatment, and a prospective, open-label, randomized clinical trial demonstrated that preoperative decolonization resulted in significantly fewer *S. aureus* infections compared to five days of mupirocin for patients undergoing primary or revision TJA or spinal fusion [19,20].

These treatment regimens are effective for reducing *S. aureus* colonization in patients, but *S. aureus* colonization persists in approximately 20% of patients despite adequate treatment [3,21–24]. There is also a lack of long-term decolonization even after successful preoperative eradication [25,26]. The risk of infection after decolonization, especially among MRSA carriers, is not lowered to baseline of a non-colonized patient [2,21,24,27–29]. Nevertheless, there is moderate evidence derived from several retrospective studies suggesting that either universal preoperative treatment or universal screening and treatment of identified carriers may be beneficial for reducing overall SSIs [24,30–32] and specifically for *S. aureus* and MRSA after elective orthopaedic surgery [24,33–36].

The cost-effectiveness of *S. aureus* screening/treatment is derived from the cost savings of preventing infections by implementing a screening and decolonization protocol [37]. Therefore, adopting a universal decolonization procedure rather than a screen-and-treat protocol seems to be the most cost-effective approach for treating *S. aureus* colonization based on the prevalence of *S. aureus* carriage, the costs of screening and treatment, and the rate of PJIs and socio-economic costs of dealing with PJI. It is also easier and less resource-consuming to implement a universal decolonization, and, more importantly, no carrier would be left untreated due to screening sensitivity issues or timely identification. However, the treat-all approach is associated with theoretical costs that are often not considered in economic models such as the risk of emerging resistance to topical antimicrobials like mupirocin [38]. Although universal decolonization seems to be the most cost-effective, one or two-swab screen-and-treat strategies also offer cost-effective results. Ultimately, choosing the most appropriate strategy may depend on the baseline PJI risk at each institution and patient subpopulations. In this regard, it is important to stress that although specific medical and demographic risk factors for *S. aureus* (and MRSA) colonization in total joint arthroplasty candidates can be found, there is a large proportion of carriers with no known risk factor(s). Thus, selective

screening of high-risk population subgroups is not an effective approach to accurately identify carriers [5,6,27,39,40]. Definitive evidence evaluating the real value of preoperative *S. aureus* decolonization at reducing PJI after total joint arthroplasty is still lacking, as the evidence demonstrates conflicting reports.

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QUESTION 2: What methods for methicillin-resistant/methicillin-susceptible *S. aureus* (MRSA/MSSA) decolonization exist? What are the benefits and risks associated with the use of each?

RECOMMENDATION: Methods of nasal decolonization include 2% mupirocin ointment, 5% povidone-iodine solution, alcohol-based products and chlorhexidine-based products. Each method has its own advantages and disadvantages related to proven effectiveness, potential for emergence of bacterial resistance and patient compliance. However, no consensus has been reached on the preferred method for decolonization for MRSA, with all products having a potential role.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 3%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

One of the most common organisms responsible for periprosthetic joint infection (PJI) of the hip and knee is MSSA and MRSA. Patients colonized with these organisms have an increased risk of PJI [1–6]. Up to 20 to 30% of the general population are asymptomatic carriers of MSSA and the nares are the main site of colonization [5,7]. Nasal decolonization of such patients to reduce bioburden with MRSA/MSSA has been shown to reduce the rate of PJI but the evidence is limited by underpowered studies [3] or clouded by additional treatment measures in colonized patients [7–17]. Often, decolonization is combined with other prevention measures such as bathing/showering with antiseptic or the use of perioperative vancomycin [1,3,15–18]. Thus, many governing bodies providing recommendations for the prevention of PJI have difficulty agreeing on the best method for decolonization and whether it should be routinely performed [19]. Currently, there are several available options for nasal decolonization, each with its own advantages and disadvantages.

Mupirocin, applied to the nares twice daily for five days preoperatively, has been the most commonly used nasal decolonization strategy for MRSA/MSSA. The medication targets most species of *Staphylococcus* in a safe and reliable manner [20]. The advantage of mupirocin is its low-cost and proven efficacy for decolonization and reduction of PJI based on multiple studies [4,10,13–15]. It leads to a rate of decolonization of 94% at one week and 65% at two weeks [21]. The disadvantage of this agent is the potential for emergence of resistant organisms which has been shown to occur in 3.3% of cases [22], with prior use of the agent increasing the rate of resistance nine-fold [23]. The other disadvantage of the agent is patient non-compliance as application of the ointment to nares twice a day for five days is demanding [24].

Povidone-iodine, applied to the nares as a 5% solution one hour before surgery, has been utilized in an effort to increase patient compliance and to mitigate bacterial resistance. Unlike mupirocin, which is bactericidal and relatively long acting, povidone-iodine provides bacterial suppression for up to 12 hours after application. While this agent has been less intensively studied than mupirocin, it has been shown in some studies to have similar results in terms of reduction of PJIs [25].

Some newer agents have been introduced recently, namely alcohol-based and chlorhexidine-based solutions, that aim to increase patient compliance and combat emergence of resistance [26]. Nozin is a non-prescription ethyl alcohol-based nasal sanitizer. Such products show promise as an alternative to antibiotic-based treatments [25] with the advantages of preventing antibiotic resistance and administration in a single application [19].

However, larger, well-designed studies will be required to demonstrate that routine screening and decolonization are cost-effective and to determine the optimal method for decolonization. Because of the low prevalence of PJI, any study designed to demonstrate a significant decrease in infection rate must necessarily include a large number of patients. For instance, to demonstrate a significant decrease from 4 to 2%, one would need to include more than 1,100 patients in each group (treated and non-treated), as stated by Sousa et al. [3]. Also, current trials report very limited data on other outcomes such as adverse effects, detection of antibiotic resistance and cost-effectiveness of the various decolonization methods [1,3,15,27,28].

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QUESTION 3: After a patient undergoes methicillin-resistant *Staphylococcus aureus* (MRSA) decolonization, is there a need to re-screen the patient?

RECOMMENDATION: We recognize that a subset of MRSA carriers remains colonized despite preoperative decolonization protocols. Currently, there is no evidence to suggest that re-screening and subsequent repeated MRSA decolonization can change the perioperative prophylactic
antibiotic regimen and reduce the risk of periprosthetic joint infection (PJI) further.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 87%, Disagree: 8%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Colonization with both methicillin-sensitive *Staphylococcus aureus* (MSSA) and MRSA increases the risk of staphylococcal surgical site infections after elective hip and knee arthroplasty [1,2]. In the United States, an estimated 0.6 to 6% of the population are nasal carriers of MRSA [1,3]. For identified carriers of MRSA undergoing hip and knee arthroplasty, standard practice includes decolonization prior to surgery followed by perioperative vancomycin for MRSA coverage.

Previous studies have proven that a protocol of screening and decolonization of MRSA among total joint arthroplasty (TJA) candidates is highly successful in reducing the percentage of MRSA carriers [1,4–8]. However, controversy continues with regard to the ability of *S. aureus* decolonization

protocols to reduce the prevalence of surgical site infections (SSIs) and PJIs in patients undergoing total hip or knee arthroplasty. In a meta-analysis of four studies [9], the use of a prophylaxis protocol for MRSA decolonization reduced SSI cases by approximately 39%. Another meta-analysis of 19 studies [10] suggested a decrease in the rates of SSI with decolonization. However, five of the included studies did not reach significance and were underpowered. Baratz et al. [11] retrospectively described 3,434 patients who underwent elective primary and revision hip and knee arthroplasty over a two year period. Despite successfully obtaining a 78% MRSA decolonization rate at the day of surgery, the incidence of SSI was not decreased compared to an historical control group.

Several studies have re-screened patients on the day of surgery and identified persistent MRSA carriage in as many as 20% of patients, despite preoperative decolonization protocols [8,11,12]. Similarly, MRSA carriers that have been decolonized and later re-screened for future procedures have shown recolonization rates as high as 38% [13,14]. However, no studies have specifically investigated whether persistent MRSA carriage is associated with an increased risk for SSI compared to previous MRSA carriers who remain decolonized. Furthermore, the cost-effectiveness of re-screening and repeated decolonization of MRSA is another important issue to be considered. Slover et al. estimated that the cost of a revision total hip or knee arthroplasty secondary to infection to be $70,000 [15]. The authors then estimated that a screening and decolonization program needed to result in a 35% reduction in revision rates to be cost-effective [15]. More importantly, extended mupirocin use has been shown to increase the risk of mupirocin resistance in MRSA carriers [16].

An important question is whether re-screening a previously identified MRSA carrier will change the clinical management during current and future elective orthopaedic procedures. For nearly all patients with any history of MRSA colonization, the perioperative antibiotic regimen will include vancomycin, regardless of their most recent colonization status. For certain hospital policies, identifying persistent MRSA colonization on the day of surgery may prompt inpatient contact precautions, while those who have been successfully decolonized may not require contact precautions. It is unknown what effect, if any, these perioperative protocols have on rates of surgical site infections.

The cohort most likely to benefit from re-screening are MSSA carriers and previously non-colonized patients after a certain period of time from the initial screening [12,14]. Studies have shown that re-screening can identify new cases of MRSA [12,14]. Re-screening before an additional surgery may be beneficial for these cohorts, as it may identify new MRSA carriage and prompt a change in perioperative antibiotic selection.

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