Background

Healthcare-associated infection (HAI) is recognized as a preventable cause of patient morbidity and mortality. Elimination of HAI is an important public health issue with nationally established reduction targets designed to improve patient safety and contribute to antibiotic stewardship efforts to combat emergence of antibiotic resistance. An estimated 1.7 million of these infections occur annually with a multistate HAI prevalence survey conducted in 2011 finding that one of every 25 inpatients in US acute care hospitals had at least one HAI. Nearly 50% of the point-prevalence HAIs were surgical site infections (21.8%) and device-associated infections (25.6%) and Staphylococcus aureus (S. aureus) was identified as the second most common HAI pathogen. A summary of pathogen data associated with HAIs reported to the National Healthcare Safety Network (NHSN) from 2011 – 2014 found S. aureus to be a leading cause of HAIs, with 42 – 52% of these isolates resistant to methicillin. Therefore S. aureus has been a target for HAI reduction efforts due to its prevalence in healthcare settings, virulence, and multidrug-resistance, and importantly, the propensity for S. aureus nasal carriage to lead to infection when host defenses are breached.

Nasal carriage of SA

The anterior nares is the primary reservoir for S. aureus carriage and approximately 20% - 30% of healthy individuals are persistently colonized. Since the 1950’s, it has been recognized that endogenous strains of S. aureus are associated with the pathogenesis of serious staphylococcal infection. The increased risk of S. aureus infection for nasal carriers has been demonstrated among patients undergoing surgery, continuous ambulatory peritoneal dialysis, hemodialysis and those with immunosuppression. In several of these studies, molecular typing demonstrated that the colonizing strain of S. aureus was recovered from the infected site. In a multicenter study of S. aureus bacteremia, 82% of blood isolates were identical to those from the anterior nares. These studies provided evidence that an important strategy for the prevention of serious staphylococcal infections is the elimination of S. aureus nasal carriage. The eradication of S. aureus nasal carriage has also been shown to have immense value in controlling transmission of the organism from patient to patient and from healthcare worker to patient, most notably with methicillin-resistant Staphylococcus aureus (MRSA). Approximately 1 – 3% of healthy adults are colonized with MRSA although higher carriage rates have been reported among hospitalized and long-term care patients. Nasal carriage of S. aureus leads to hand carriage and environmental contamination contributing to endemic levels of the organism and potential outbreaks in healthcare settings.

Decolonization as an HAI prevention strategy

The goal of decolonization is to lower the microbial bio-burden on patient body sites to reduce 1) the risk that endogenous colonization will lead to infection when host defenses are altered e.g. surgery, insertion of invasive devices and 2) the risk of exogenous colonization from other patients and/or the environment e.g. poor hand hygiene practices by healthcare workers, contaminated equipment. Decolonization is a component of the vertical approach to HAI prevention which targets specific pathogens, such as MRSA, and is generally bundled with active surveillance screening for the pathogen and the use of contact isolation precautions. Nasal decolonization through the application of a topical antibiotic or antiseptic agent and skin decolonization through the application of an antiseptic during bathing are common methods and frequently are used together. Persistent S. aureus carriers tend to have higher nasal microbial loads and high load counts of MRSA in the nose was associated with colonization at other body sites.
Patients with a short-term risk of infection, such as surgical patients and short-stay intensive care unit patients, are more likely to have success with decolonization as *S. aureus* is known to rapidly re-colonize body sites within weeks to months.\(^{11}\)

**Nasal decolonization with Mupirocin**

The introduction in the mid-1980's of intranasal mupirocin calcium ointment, a topical antibacterial agent produced from the bacterium *Pseudomonas fluorescens*, led to its widespread use as the decolonization agent of choice for preventing SA infection and transmission. Mupirocin has excellent in vitro activity against staphylococci and most streptococci, is rapidly metabolized, and has minimal side-effects.\(^{12}\) In a systematic review of 23 clinical trials published from 1977 – 2008 which evaluated the effectiveness of oral and/or topical antibiotics for the eradication of MRSA carriage, short-term use of mupirocin was concluded to be the most effective in eradicating MRSA with an estimated success probability of 90% one week after treatment, was equally effective against methicillin-sensitive *S. aureus* (MSSA) and MRSA carriage and was safe for use.\(^{13}\) Mupirocin was successful in eradicating both nasal and hand carriage of *S. aureus* among hemodialysis patients with 87% of the patients carrying the same strain at both sites, suggesting that self-inoculation of vascular access sites may contribute to the occurrence of *S. aureus* bacteremia.\(^{14}\) A placebo-controlled trial with hemodialysis patients found the incidence of *S. aureus* carriage and infections was significantly lower among the mupirocin treated patients.\(^{15}\) Multiple studies among other high-risk patients have demonstrated that mupirocin is effective in eradicating *S. aureus* nasal colonization, resulting in decreased infections, specifically for those patients undergoing surgery or receiving care in an intensive care unit (ICU).

**Reducing risk of endogenous infection: Decolonization to prevent surgical site infections (SSIs)**

An estimated 157,500 SSIs resulting in more than 8,000 deaths occur annually in the US healthcare system.\(^{1,2}\) The estimated excess length of hospital stay (LOS) for these infections is 11 days with a cost of $20,785; if MRSA is the causative pathogen, the LOS and cost increases to 23 days and $42,300, respectively.\(^{16}\) Since *S. aureus* is the top ranked pathogen for surgical site infections (SSI)\(^{2}\) and *S. aureus* carriers are two to nine times more likely than noncarriers to have SSIs\(^{6}\), perioperative nasal decolonization has been instituted and studied as an SSI prevention strategy. The Mupirocin and the Risk of *Staphylococcus aureus* (MARS) Study, a double-blinded, randomized controlled trial involving more than 4,000 patients, found that among the patients with nasal carriage of *S. aureus*, 4.0% of those that received mupirocin had nosocomial *S. aureus* infections compared with 7.7% of those who received placebo (OR 0.49; P=0.02).\(^{17}\) A meta-analysis of randomized clinical trials or prospective before-after trials concluded that perioperative intranasal mupirocin decreased the incidence of SSI when used as prophylaxis in nongeneral (orthopedic, neurosurgery, and cardiothoracic) surgery but the reduction was not seen with general (gastrointestinal, other general) surgery trials.\(^{18}\) There has been wide adoption by both the orthopedic and cardiothoracic surgical communities of decolonization protocols. A systematic review of 19 studies examining the ability of the decolonization protocol to reduce SSIs for elective orthopedic and trauma patients found a range of SSI reduction from 29% – 57% in total SSIs for the studies that used mupirocin alone and 13% – 81% in total SSIs, 56% – 200% reductions in *S. aureus* carriers are two to nine times more likely than noncarriers to have SSIs\(^{6}\), perioperative nasal decolonization has been instituted and studied as an SSI prevention strategy.
SSIs, and 29% – 100% reductions in MRSA SSIs for studies that used mupirocin and chlorhexidine. A before-after trial involving cardiac surgery patients with institution of an intervention of pre-operative nasal screening for MSSA and MRSA, decolonization of carriers with mupirocin twice daily and chlorhexidine daily bathing for 5 days, and modification of prophylactic antibiotics to vancomycin and cefazolin for MRSA carriers found a 42% reduction in SSIs.

Reducing risk of exogenous infection: Decolonization to reduce/prevent transmission of MRSA

HAIs caused by MRSA are common in healthcare settings and account for a high proportion of the S. aureus infections. Data from the National Healthcare Safety Network (NHSN) for 2014 reports that 50.7% of S. aureus central line-associated bloodstream infections (CLABSSIs), 52% of S. aureus catheter-associated urinary tract infections and 42.6% of S. aureus SSIs were caused by MRSA. MRSA has been associated with higher morbidity and mortality rates than MSSA which has been attributed to delays in initiation of effective antimicrobial therapy and higher severity of illness among individuals with resistant strains rather than increased virulence of the strains. MRSA is primarily transmitted by direct contact – patient to patient via the hands of healthcare providers – or through indirect contact via contaminated equipment and environmental surfaces. Standardized practices or a horizontal approach to prevent transmission include hand hygiene, use of gowns and gloves, environmental hygiene, antimicrobial stewardship and with high-risk patients, decolonization with chlorhexidine bathing to reduce microbial bioburden on the skin. The pathogen-specific or vertical approach to prevent transmission may include the use of MRSA active surveillance testing (AST) to target carriers with or without supplemental decolonization but the effectiveness of this strategy remains controversial. A comparison of approaches was studied by Huang and colleagues in a cluster-randomized clinical trial conducted in 74 adult ICUs comparing outcomes associated with 3 MRSA control strategies: active surveillance for MRSA with isolation of colonized patients, active surveillance with targeted decolonization of MRSA carriers with topical chlorhexidine and intranasal mupirocin for 5 days and universal decolonization of all ICU patients with intranasal mupirocin for 5 days and topical chlorhexidine daily for the entire ICU stay without AST. The authors found a 37% reduction in MRSA-positive clinical cultures attributed to the ICU, a significant reduction in overall BSIs and a statistically non-significant reduction in MRSA BSIs in the universal decolonization group.

Mupirocin resistance

Mupirocin resistance occurs in two phenotypes: low-level with minimal inhibitory concentrations (MIC) between 8 and 64 mg/ml, which occurs through point mutations in the isoleucyl-tRNA synthetase (ileS) gene that may reduce the binding ability of mupirocin, and high-level with MICs of >512 mg/ml mediated by plasmids carrying the mupA gene. In the late 1990’s, mupirocin resistance began to emerge. In a large public teaching hospital that implemented universal decolonization with nasal mupirocin as an adjunct to infection control measures to address an endemic MRSA problem, mupirocin resistance among MRSA isolates increased from 2.7% to 65% over a 3-year period. More recent surveillance studies have reported mupirocin-resistant (MupR) MRSA strains in up to 13% of surgical ICU patients in the absence of routine use of mupirocin and 23.7% MupR among MRSA clinical isolates in a facility where mupirocin was routinely used to decolonize MRSA-positive patients. More recent surveillance studies have reported mupirocin-resistant (MupR) MRSA strains in up to 13% of surgical ICU patients in the absence of routine use of mupirocin and 23.7% MupR among MRSA clinical isolates in a facility where mupirocin was routinely used to decolonize MRSA-positive patients.

MRSA in these studies, 8.6% and 5.1% respectively, exhibited high-level resistance. Mupirocin resistance was highly prevalent in MRSA isolates from a pediatric population and MRSA was a strong risk factor for resistance to mupirocin. A strong association has been found between prior mupirocin use and subsequent mupirocin-resistant in MRSA. Utilizing MRSA isolates as part of mandatory screening and clinical sampling
at two London teaching hospitals where mupirocin was used to
decolonize MRSA-positive patients on general wards only, the
estimated transmission probability of a mupirocin-susceptible
(MupS) strain was 2.16 times that of a mupirocin-resistant
(MupR) strain in the absence of mupirocin usage. A 5-year
simulation model found the total prevalence of MupR among
MRSA patients was 9.1% with a “screen and treat” mupirocin
policy which increased to 21.3% with universal mupirocin
use.30 The authors concluded that long-term increases in the
prevalence of MupR is likely with universal use of mupirocin.
Currently, mupirocin susceptibility testing is infrequently
performed and therefore, the prevalence of MupR MRSA
strains is unknown in many clinical settings. The concern about
resistance from selective pressure and treatment failure with
increasing widespread use of mupirocin has led to the use of
antiseptics as alternative decolonization agents. One such
alternative, povidone-iodine, is gaining popularity due to its
efficacy in eradicating S. aureus, safety, patient satisfaction
and cost.

Povidone-iodine nasal decolonization

Povidone-iodine (PVP-I) is a complex of polyvinylpyrrolidine
and tri-iodine ions which has been used widely for cutaneous
antisepsis prior to the insertion of intravascular devices and
surgical procedures and for wound irrigation. An in vitro study
comparing the activity against S. aureus isolates of 5% PVP-I
cream vs. mupirocin, found PVP-I to be bactericidal against
three MupS S. aureus strains from nasal carriers, and both
MupS and MupR MRSA strains after 1 minute of incubation
but mupirocin did not prevent growth after 180 minutes of
incubation.31 The authors highlighted the rapid bactericidal activity of PVP-I compared with that of mupirocin and the importance of its activity against emerging MupR MRSA strains.

Reducing risk of endogenous infection:
Decolonization to prevent surgical site infections (SSIs)

The use of PVP-I for nasal decolonization in combination with
chlorhexidine bathing to prevent SSIs has revealed promising results. In an open-label, randomized trial of patients
undergoing arthroplasty or spine fusion procedures, deep
SSI rates within 90 days were compared for those individuals
receiving topical 2% chlorhexidine wipes the night before and
morning of surgery in combination with either twice daily
application of nasal mupirocin ointment during the 5 days
before surgery or 2 applications of 5% povidone-iodine solution
into each nostril within 2 hours of surgical incision.32 An
evaluation of 763 surgical procedures in the mupirocin group
and 776 surgical procedures in the povidone-iodine (PI) group
was performed. In the per-protocol analysis, S. aureus deep
SSIs developed in five patients (0.7%) who received mupirocin
and zero patients (0.00%) among those who received PI
(P = 0.03). For patients with a preoperative S. aureus nasal
culture, another nasal culture was obtained within 1 to 3 days
after surgery. The proportion of postoperative negative nasal
cultures was 92% for patients in the mupirocin group vs.
54% for those in the PI group. This was not an unexpected
finding for the authors as mupirocin was intended to eradicate
colonization while PI was intended only to suppress S. aureus
during surgery. The authors concluded that nasal PI may be
considered as an alternative to mupirocin in a multifaceted
approach to reduce SSI. Limitations to this study include lack
of generalizability with use of a single-site, a small sample size
preventing a multivariate analysis and lack of post-discharge
surveillance for patients presenting to other institutions with
late infections.

A recent quasi-experimental, retrospective, nonrandomized
trial compared a preoperative decontamination intervention
– 2% chlorhexidine washcloths and 0.12% chlorhexidine oral
rinse the night before and morning of surgery and the use of
5% PI intranasally once the morning of surgery – to historical
controls without a decontamination protocol to evaluate the impact on SSI rates for patients undergoing elective orthopedic procedures with hardware implantation. Nasal screening for S. aureus before and after decontamination was not performed. A total of 709 patients were analyzed (344 controls and 365 patients who were decolonized) with both groups well matched with no significant differences in age, sex, body mass index, or co-morbidities. There was 100% compliance with completion of the decontamination protocol by patients in the intervention group. Rates of SSIs were statistically significantly lower in the intervention group than in the control group (1.1% versus 3.8%; P= 0.02). These authors point out that, in addition to the more than 50% reduction in SSI rates associated with the intervention, the adherence to and cost of a decontamination regimen is a cardinal factor for its success. They noted that a decolonization protocol containing PI instead of mupirocin could potentially dissipate concerns regarding antibiotic resistance, broaden application beyond S. aureus carriers, and result in cost savings ($35.00 per patient for the PI regimen vs. $54.00 for mupirocin and chlorhexidine). Limitations to this study include the lack of randomization, lack of knowledge of the MRSA carrier status of patients before decontamination which prevented examination of the effect of the protocol on decolonization rates and limited 30-day follow-up for SSI.

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Despite the need for additional studies which are randomized, multi-center and inclusive of other surgical patient populations, PI decolonization is a promising alternative to mupirocin for the reduction of SSIs and may promote better patient compliance. Maslow and colleagues studied patient experience with preoperative nasal decolonization. The study evaluated and compared patient experiences and satisfaction of patients who were randomized to receive either povidone-iodine (PI) or mupirocin ointment (MO) along with 2% chlorhexidine gluconate wipes. Of 1,679 patients interviewed prior to discharge, a majority of patients in both the PI and MO groups felt that being an active participant in SSI prevention was a positive experience. Those patients assigned to receive PI as nasal decolonization reported significantly fewer adverse events than the nasal MO group (P<.01). Of patients receiving PI, 3.4% reported an unpleasant or very unpleasant experience, compared with 38.8% of those using nasal MO (P<.0001). An assessment of how helpful nasal decolonization was believed to be by the participants, 67% in the MO group felt it to be somewhat or very helpful in reducing SSIs vs. 71% of patients receiving PI (P>.05). The authors noted that despite the shorter course of treatment for PI (5% PI nasal solution in both nostrils by staff within 2 hours of surgical incision vs. MO 2% ointment twice daily for 5 days preoperatively until the morning of surgery) it was perceived by patients to be similarly effective in reducing SSI risk. In addition, 54% of patients reported paying out-of-pocket expenses for MO totaling as much as $115.

Reducing risk of exogenous infection: Decolonization to reduce/prevent transmission of MRSA

MRSA is prevalent not only in acute care healthcare settings but also in nursing home settings where between 26% and 58% of residents are colonized with the organism. Due to the communal environment in nursing homes and the infrequent use of formal contact isolation precautions, preventing transmission of MRSA through healthcare worker hands, shared equipment and the environment is challenging. Concern about the increasing prevalence of MRSA among this patient population at high-risk for infection, as well as the increasing reports of mupirocin-resistant MRSA, has sparked interest in an alternative to mupirocin for nasal decolonization among nursing home residents. Huang recently reported on a CDC – sponsored pilot study – PROTECT – a before-after quasi-experimental study in 3 California nursing homes of universal decolonization with chlorhexidine body washing (daily baths with either 2% CHG-no rinse or 4% CHG showers).
and 5% PI, twice daily, on admit and M-F every other week 2 swabs/nostril, 30 seconds each swab (8 swabs/day) to assess multidrug-resistant organism (MDRO) carriage, including MRSA. Surveillance swabbing of the axilla, groin and nasal was performed on 50 randomly selected residents. MRSA carriage was reduced from 29% to 19%; the adjusted intervention effect found a 59% reduction in all MDROs evaluated. One of the nursing homes continued with the decolonization protocol post-pilot but switched to 10% PI, twice daily, M-F every other week 1 swab/nostril, 30 seconds (at least 3 revolutions/nostril). A comparison between the initial pilot data and the post-pilot data was performed. Both 5% PI (2 swabs/nares) and 10% PI (1 swab/nares) yielded a 40% reduction in MRSA nasal carriage and a 60% reduction in any MRSA carriage when used in combination with CHG bathing. Notably, the nursing feedback from the study was that 2 swabs per nostril seemed redundant and that a 30-second application was impractical and the average application time for PI was 2 – 3 seconds per nostril.

**Summary**

Decolonization is an evidence-based practice to reduce the incidence of healthcare-associated infections. Nasal decolonization, with or without chlorhexidine gluconate bathing, has become an important strategy for reducing SSIs due to *S. aureus* and for the control of MRSA transmission in healthcare settings with endemic prevalence. The gold standard for nasal decolonization has been mupirocin; however, as seen with widespread use of other antibiotics, selective pressure has led to mupirocin-resistant strains of *S. aureus* and treatment failures. As part of an overall approach to antibiotic stewardship, investigators have looked to antiseptics as alternatives for nasal decolonization. The most effective regimen for nasal decolonization will have proven efficacy against organisms, such as *S. aureus*, which cause HAIs, be easy to apply, have minimal adverse reactions, and be a positive experience for patients. The data on povidone-iodine is compelling and has been presented as a promising alternative to mupirocin.

**References**

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