Decolonization to Prevent Healthcare-Associated Infections 2024 State-of-the-Art Review

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ABSTRACT

Colonization with health care-associated pathogens such as *Staphylococcus aureus*, enterococci, Gram-negative organisms, and *Clostridioides difficile* is associated with increased risk of infection. Decolonization is an evidence-based intervention that can be used to prevent health care-associated infections. This review evaluates agents used for nasal topical decolonization, topical (e.g., skin) decolonization, oral decolonization, and selective digestive or oropharyngeal decontamination. Although the majority of studies performed to date have focused on *S. aureus* decolonization, there is increasing interest in how to apply decolonization strategies to reduce infections due to Gram-negative organisms, especially those that are multidrug resistant. Nasal topical decolonization agents reviewed include mupirocin, povidone-iodine, alcohol-based nasal antiseptic, and photodynamic therapy.

Topical decolonization agents reviewed included chlorhexidine gluconate, and povidone-iodine. Of these, CHG is the skin decolonization agent that has the strongest evidence base. There is also evidence to support the use of selective digestive decontamination and selective oropharyngeal decontamination, but additional studies are needed to assess resistance to these agents, especially selection for resistance. Small studies have shown some effect of fecal microbiota transplant against multidrug resistant gram-negative organisms. Some of the strongest evidence for decolonization is to prevent surgical site infections in high-risk procedures primarily cardiac and orthopedic procedures.

Keywords: nasal decolonization, skin decolonization, healthcare-associated infections, selective digestive decontamination.

Introduction

Healthcare-associated infections (HAIs) are a leading cause of preventable harm in hospitals. HAIs burden patients, complicate treatments, prolong hospital stays, increase costs, and can be life-threatening. Up to 15% of patients develop an infection while hospitalized. The Centers for Disease Control and Prevention (CDC) report recommends attempting to prevent these infections through appropriate antibiotic use and infection prevention practices. HAIs are now the fifth leading cause of death in United States (U.S.) acute-care hospitals[1]. The human suffering and financial burden associated with these infections are significant. Recent reports have estimated that U.S. health care system direct costs that can be attributed to HAIs range from $9.8 billion to $45 billion per year[2]. Beyond direct financial costs, HAIs also contribute significantly to increased patient length of stay in the hospital, which results in both financial costs and patient dissatisfaction. HAIs are not only a threat for patients and healthcare systems, but also the antimicrobial use associated with their treatment can accelerate antimicrobial resistance and increase adverse events. HAIs also represent one quarter of sepsis cases in hospitals[3].

Over the past few decades, large changes in U.S. health care have had an impact on HAI prevention. First, we now know that a significant percentage of HAIs can be prevented by use of evidence-based strategies[4]. Second, there are now coordinated efforts among federal agencies aimed at HAI prevention, including public reporting of hospital-specific HAI rates and linking hospital-specific HAI performance measures to financial reimbursement in order to stimulate HAI prevention efforts. Since 2011, hospitals have been required to report to the CDC's National Healthcare Safety Network (NHSN) all of their central-line associated bloodstream infections (CLABSIs) in order to qualify for annual payment updates. The Centers for Medicare and Medicaid (CMS) also requires hospitals to report new data to NHSN, including surgical site infection (SSI) rates for colon surgery and abdominal hysterectomy, methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections, *Clostridioides difficile* infections (CDI), catheter-associated urinary tract infections (CAUTIs), and influenza vaccination among health care workers. This data, as well as other quality metrics, will be used to determine CMS reimbursement levels for each hospital as a component of value-based purchasing, thus creating performance-driven reimbursement[5]. Therefore, hospitals now have a financial incentive to implement prevention strategies to control HAIs.

In the U.S. each day, approximately one in 31 U.S. patients and 1 in 43 nursing home residents contracts at least one HAI. In the last point-prevalence survey a total of 12,299 patients in 199 hospitals were surveyed. Fewer patients had HAIs in 2015 (394 patients [3.2%; 95% confidence interval, 2.9 to 3.5]) than in 2011 (452 [4.0%; 95% CI, 3.7 to 4.4]) (P<0.001), largely owing to reductions in the prevalence of SSIs and UTIs. Pneumonia, gastrointestinal infections (most of which were due to CDI), and SSIs were the most common health care-associated infections[6].

In 2022–2023, 28 European Union/European Economic Area (EU/EEA) countries and three Western Balkan countries (Kosovoi, Montenegro and Serbia) participated in the third European CDC (ECDC) point prevalence survey (PPS) of HAIs and antimicrobial use in European acute care hospitals[7]. The prevalence of patients with at least one HAI in the EU/EEA sample was 7.1%. When extrapolated to the average daily number of occupied beds per country, the weighted HAI prevalence was 6.3%. After adjustment for the one non-participating EU/EEA country (Denmark), this corresponded to an estimated total of 93,305 patients with at least one HAI on any given day, 4.3 million (95% CI: 3.1–5.8 million) patients with at least one HAI and 4.8 million (95% CI: 3.1–5.8 million) HAIs (infection episodes) per year in the period 2022 to 2023 in acute care hospitals in the EU/EEA.

Of a total of 22,806 reported HAIs in the European Union/European Economic Area EU/EEA, the most

frequently reported types of HAI were respiratory tract infections (29.3% of the total, including pneumonia 19.0%, COVID-19 7.0% and other lower respiratory tract infections 3.3%), urinary tract infections[UTIs] (19.2%), SSIs (16.1%), bloodstream infections[BSIs] (11.9%) and gastro-intestinal infections (9.5%), with CDIs accounting for 62.1% of the latter and 5.9% of all HAIs. The microorganisms most frequently isolated from HAIs were, in decreasing order, *Escherichia coli* (12.7%), *Klebsiella spp.* (11.7%), *Enterococcus spp.* (10.0%), SARS-CoV-2 (9.5%), *S. aureus* (9.0%), *C. difficile* (8.0%), *P. aeruginosa* (7.9%), coagulase-negative staphylococci (5.8%), *Candida spp.* (4.7%), *Proteus spp.* (3.2%), *Acinetobacter spp.* (3.2%) and *Enterobacter spp.* (3.0%).

Up until the COVID-19 pandemic, there was significant progress in reducing HAIs. However, the pandemic resulted in extraordinary challenges for infection prevention in hospitals. Increased HAIs were observed throughout 2020 and 2021 as hospitals responded to increased patient volumes, increased patient acuity levels, and staffing challenges[8]. However, in the 2022 National and State Healthcare-Associated Infections Progress Report showed an improvement. The report demonstrated about 9% decrease in CLABSI between 2021 and 2022, an overall, 12% decrease in CAUTI between 2021 and 2022, a 19% decrease in ventilator associated events (VAE) between 2021 and 2022, and no significant changes in SSI related to 9 of the 10 select procedures tracked in the report between 2021 and 2022. However, hip arthroplasty SSIs increased 8%. There was a 16% decrease in hospital onset MRSA bacteremia between 2021 and 2022, There was a 3% decrease in hospital onset CDI infections between 2021 and 2022[9].

HAIs are frequently due to endogenous pathogens, originating from the patients' own microbial flora. This fact promotes innovative approaches to HAIs prevention including decolonization of HAIs pathogens carriers and optimizing skin preparation. The main aim of this paper is to review decolonization strategies to prevent bacterial HAIs and to address challenges in their development and use in target populations. This review will include agents used for nasal topical decolonization, topical (e.g., skin) decolonization, selective digestive and oropharyngeal decontamination. (Table 1)

Table 1 Decolonization Strategies to Prevent Health Care-Associated Infections

Nasal Decolonization
Mupirocin
Povidone-Iodine
Nasal alcohol antiseptic
Photodynamic Therapy

Skin Decolonization
Chlorhexidene
Povidone-Iodine

Selective Digestive Decontamination
Polymyxin
Tobramycin
Amphotericin B

Selective Oropharyngeal Decontamination
Polymyxin
Tobramycin
Amphotericin B
Cefotaxime IV

Fecal Microbiota Transplant

Bacteria is part of the normal human microflora and usually do not cause infection. Colonization is most common in body sites such as the nose, skin, and gastrointestinal tract. The body sites of colonization are usually specific to the type of bacteria. *S. aureus* and other commensal Gram-positive organisms (e.g., coagulase-negative staphylococci [CNS]) most commonly colonize the skin and mucosal membranes of the nose[10]. Both Gram-positive (e.g., *Streptococcus pneumoniae*) and Gram-negative organisms can colonize the pharynx[11,12]. Other organisms, such as enterococci, *C difficile*, and Gram-negative organisms (e.g., *Enterobacterales*), commonly colonize the gastrointestinal tract[13].

Bacterial colonization can occur among both healthy and ill populations. Between 15 and 30% of healthy adults are nasally colonized with methicillin-susceptible *S. aureus* (MSSA), and 1% to 3% are nasally colonized with MRSA[14,15]. *S. aureus* colonization at other body sites, including the pharynx, groin, perianal region, or axilla, is also associated with development of *S. aureus* infections. This is most common among high-risk groups such as ICU patients, men who have sex with men, HIV-infected patients, insulin dependent diabetes mellitus, and certain chronic skin conditions[16,17]. Similarly, gastrointestinal colonization with VRE is associated with increased risk of VRE infection[18,19]. Recent studies have highlighted the role of rectal colonization with carbapenem-resistant gram-negative bacteria as an important

source of HAIs[20]. MDRO colonization in solid organ transplants is also associated with increased risk of infection and death. The risk on mortality was higher with carbapenem resistant Enterobacteriaceae (CRE) colonization among liver transplant recipients[21].

Hospitalized patients and long-term-care facility residents are at higher risk of colonization with health care-associated pathogens especially MDROs. There is clearly an increased risk of colonization and infection with multidrug resistant organisms (MDROs) in long term care in the range of 40% to as high as 80%[22,23]. This is far higher than the typical hospital with a prevalence of 10%-15%. Infections caused by MDROs are estimated to cause over 35,000 deaths in the U.S. every year and increase medical costs by $4.6 billion[24]. Efforts to reduce spread of MDROs has focused on infection prevention primarily in acute care facilities and more recently in long-term care as well[25]. Decolonization has emerged as an important strategy across the continuum of care. The goal of decolonization is to reduce or eliminate the bacterial load on the body. Carriers with high bacterial loads are at higher risk of infection and are more likely to transmit the bacteria to their environments[15,26].

Since colonization often leads to infection, two overarching approaches to HAI prevention have emerged: (i) horizontal strategies to broadly reduce the burden of all pathogens and (ii) vertical approaches to reduce colonization or infection due to specific pathogens (Table 2)[27].

Table 2 Vertical and horizontal approaches

Vertical (substantially reduces one pathogen; is pathogen specific)
Active surveillance (e.g., for MRSA, VRE, *C. difficile*, Gram-negative MDROs)
Contact precautions (e.g., for MRSA/VRE colonization or MRSA/VRE infection, *C. difficile infection*
Gram-negative MDROs)
Decolonization (e.g., for MRSA)

Horizontal (substantially reduces all infections; is not pathogen specific)
Standard precautions (HH, cough etiquette, PPE, universal gloving)
Bundles of care (e.g., CLABSI, SCIP, ventilator bundle)
CHG bathing
Selective digestive tract decontamination
Fecal Microbiota Transplant

HH, hand hygiene; PPE, personal protective equipment; SCIP, surgical care improvement project.

Vertical approaches are directed at a single pathogen and often utilize active surveillance testing. This is important because multidrug-resistant organisms (MDROs), such as VRE, multidrug-resistant Gram-negative organisms, MRSA, and *C. difficile*, are similar in that colonization often precedes infection, transmission occurs by direct or indirect contact, and there are many more asymptomatic patients than infected patients. In addition, unrecognized colonized patients can serve as a source of transmission[28].

Horizontal decolonization approaches can target all clinically meaningful health care-associated bacteria, including *S. aureus*, enterococci, *Candida*, and Gram-negative bacteria. Chlorhexidine gluconate (CHG) skin decolonization of all high-risk patient populations is an example of a horizontal strategy. Since CHG has broad-spectrum activity, it has been shown to reduce infections due to Gram-positive, Gram-negative, and *Candida* organisms. Reducing the bioburden through the use of CHG can also prevent blood culture contamination caused by skin commensals (e.g., coagulase-negative staphylococci), which may reduce the additional costs and unnecessary antibiotic treatment associated with blood culture contamination[29]. Selective digestive tract decontamination (SDD) and fecal microbiota transplant (FMT) are additional horizontal decolonization strategies to prevent HAIs to be discussed later.

Decolonization is the most effective among patient populations who are at risk of infection for only a short period of time[30]. These include populations such as surgical patients, who may be at a lower risk of infection after surgical closure and surgical wound healing, and ICU patients, who are at a much lower risk once they are discharged from the ICU. This window of time is important because of concern regarding both recolonization and resistance to colonizing agents. Thus, patient populations who are at risk for only short periods of time can achieve short term success with decolonization.

This is important since studies have found that patients tend to become recolonized with *S. aureus* within weeks or months of being decolonized[31,32]. In fact, *S. aureus* recolonization rates at 1 year approached 50% for health care workers and 75% for patients on peritoneal dialysis[33]. Similarly, one study found that the *S. aureus* recolonization rate at 4 months was 56% in patients on hemodialysis[34]. The goal of this paper is to review the current evidence for different decolonization strategies on preventing HAIs.

Nasal topical decolonization strategies

MUPIROCIN
Nasal mupirocin is the most widely used topical antibacterial agent. Mupirocin inhibits synthesis of bacterial proteins by reversibly binding to bacterial isoleucyl-tRNA synthetase. It has excellent activity against staphylococci, most streptococci, and some gram-negative organisms, including *Neisseria gonorrhoeae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*[35]. There are two different formulations of mupirocin, depending on the vehicle. The first is a nasal ointment in petrolatum. The second is a generic topical ointment that utilizes a polyethylene glycol vehicle. Both have been used for nasal decolonization; however, the generic topical ointment may be used more frequently due to its lower cost. Side effects are uncommon and are mostly local site reactions such as stuffy nose or burning or stinging of the nose.

A randomized control trial (RCT) comparing mupirocin against a placebo found that 83% of the mupirocin group were decolonized, compared with only 27% of the placebo group (*P* =0.001). That trial also found that 81% of carriers who received three to five doses of mupirocin were decolonized, compared with 93% of carriers who received six or more doses of mupirocin (*P* =0.001)[36]. Currently, mupirocin is recommended to be applied to the anterior nares twice daily for 5 days.

A systematic literature review evaluated 23 clinical trials, including 12 trials that evaluated topically applied antibiotics. The authors concluded that

short-term nasal mupirocin was the most effective treatment for MRSA decolonization, with success rates of 90% at 1 week after treatment and approximately 60% after a longer follow-up time[10]. The effectiveness of mupirocin was similar for both MSSA and MRSA carriers. A Cochrane review aimed to determine whether the use of mupirocin among *S. aureus* carriers reduced *S. aureus* infections. Only RCTs comparing a mupirocin group with a control group that received either no treatment, placebo, or an alternative nasal treatment were included. The authors found that mupirocin was associated with a significant reduction in *S. aureus* infections (relative risk [RR] 0.55; 95% confidence interval [CI], 0.43 to 0.70)[37]. Lastly, two systematic literature reviews and meta-analyses of published studies found a protective effect of mupirocin decolonization against surgical site infections (SSIs), especially among nongeneral surgery such as cardiac surgery, orthopedic surgery, and neurosurgery[38,39].

Although mupirocin appears to be an effective topical agent, resistance among *S. aureus* has now been identified in multiple studies, especially with widespread use over prolonged periods[40,41]. More importantly, studies have shown that high-level mupirocin-resistant (HL-MR) *S. aureus* results in decolonization failure. The association between low level mupirocin (LL-MR) and failure of mupirocin decolonization is unclear. Walker et al.[42] published a prospective study to determine the efficacy of nasal mupirocin in decolonizing patients with mupirocin-susceptible MRSA (MS MRSA) and mupirocin resistant MRSA, both LL-MR MRSA and HL-MR MRSA. Patients received 2% mupirocin nasally twice daily for 5 days. They were then cultured at day 3 and weeks 1, 2, and 4 after treatment. Nares cultures at day 3 posttreatment were negative for 79% of patients who had MS MRSA, 80% of patients who had LL-MR MRSA, and 28% of patients who had HL-MR MRSA. However, at the follow-up 1 to 4 weeks later, the sustained decolonization for patients with HL-MR MRSA and LL-MR MRSA was low (25% each, compared to 91% in patients colonized with MS MRSA). This result

suggests that mupirocin probably temporally suppresses growth of LL-MR MRSA but does not result in sustained decolonization. Posttreatment cultures usually had the same genotype and susceptibility phenotypes as the corresponding baseline cultures. This appears to show endogenous recolonization rather than exogenous acquisition.

Perl et al. treated over 2,000 patients with mupirocin, performed mupirocin susceptibility testing, and found that only 6 of the 1,021 isolates (0.6%) were mupirocin resistant[36]. Another study described the results of repeated point-prevalence surveys over 4 years to determine if mupirocin resistance had emerged in surgical units using preoperative prophylaxis with 5 days of nasal mupirocin. They found no evidence of sustained emergence or spread of mupirocin resistance. No HL-MR strains were identified[43]. Finally, a Dutch study evaluated over 20,000 patients who received mupirocin prophylaxis for major cardiothoracic surgery. No mupirocin resistance emerged[37]. Despite these promising results, all these studies were done over a decade ago. More recently Hayden et al.[44] evaluated mupirocin susceptibility of MRSA in the REDUCE-MRSA Trial. Isolates from the baseline and intervention periods were collected and tested for susceptibility to mupirocin by Etest. At baseline, 7.1% of MRSA isolates expressed low-level mupirocin resistance, and 7.5% expressed high-level mupirocin resistance. The study found the odds of mupirocin-resistance were no different in the intervention versus baseline periods across arms, but confidence limits were broad and therefore, results should be interpreted with caution. However, a recent meta-analysis described a global increase in the prevalence of high-level mupirocin resistance among clinical *S. aureus* isolates over time[45]. In another study Semret et al. found topical mupirocin was able to interrupt colonization of 52% and 68% of methicillin-resistant Staphylococcus aureus (MRSA)-colonized patients carrying mupirocin-resistant and -sensitive strains, respectively, including 44.4% and 85.7% of those colonized only in the nares[46]. Although a trend to

decreased effectiveness was seen for clearing mupirocin-resistant MRSA, this agent can still decolonize many patients with resistant strains. They used higher doses of mupirocin, four times daily for 2 weeks, or until discharge.

In a new large-scale pragmatic study, the Mupirocin-Iodophor ICU Decolonization Swap Out Trial, the investigators compared nasal mupirocin to nasal iodophor along with universal CHG bathing[47]. In this noninferiority, cluster-randomized trial of 801,668 admissions at 137 hospitals, exposure to nasal mupirocin significantly reduced *S aureus* clinical cultures by 18.4% compared with iodophor in adult ICUs in the setting of universal daily chlorhexidine bathing. The sustained effectiveness of mupirocin plus CHG bathing over 7 years of use since the REDUCE MRSA trial[48], even in the setting of reports of rising and high rates of mupirocin resistance is reassuring. In summary, although mupirocin currently may be the best option for topical *S. aureus* nasal decolonization, the use of mupirocin may lead to mupirocin resistance and treatment failures. Thus, alternatives to mupirocin for eradication of patients colonized with *S aureus* may be needed, however, mupirocin remains the gold standard.

POVIDONE-IODINE

Povidone-iodine (PI) is a complex of polyvinylpyrrolidine and tri-iodine ions that has been widely used as an antiseptic on skin, wounds, and mucous membranes. PI has activity against both gram-positive and gram-negative bacteria. Specifically, PI has activity against both MSSA and MRSA. Hill and Casewell[49] assessed the *in vitro* activity of 5% PI as an alternative to mupirocin for the nasal decolonization of *S. aureus*. In that study, PI was able to eliminate 11 test organisms, including both mupirocin sensitive and mupirocin-resistant MRSA. The results suggested that PI may be a good decolonizing agent for the prevention of infections due to *S. aureus*, including MRSA and mupirocin-resistant strains, however, the addition of nasal secretions *in vitro* reduced the PI activity. This concern was confirmed by Rezapoor et al.[50]

who published a randomized, placebo-controlled study comparing 10% off-the-shelf PI, 5% PI-based nasal antiseptic (PINA), or saline (placebo) for nasal decolonization. Four hundred and twenty-nine patients undergoing primary or revision total joint arthroplasty, femoroacetabular osteoplasty, pelvic osteotomy, or total shoulder arthroplasty were included. Baseline nasal cultures were taken immediately preoperatively, followed by treatment of both nares twice for 2 minutes with 4 applicators. Reculturing of the right nostril occurred at 4 hours and the left at 24 hours. Ninety-five of the 429 patients (22.1%) had a positive culture result for *S. aureus*. Of these 95, 29 were treated with off-the-shelf PI, 34 with PINA, and 32 with saline swabs. At 4 hours post-treatment, *S. aureus* culture was positive in 52% off-the-shelf PI patients, 21% PINA patients, and 59% saline patients. After 24 hours posttreatment, *S. aureus* culture was positive in 72% off-the-shelf PI patients, 59% PINA patients, and 69% saline group. PINA was significantly more effective at decolonizing *S. aureus* over the 4-hour time interval (P = .003). The authors concluded off-the-shelf PI swabs may not be as effective at 4 hours as the specifically manufactured product for nasal *S. aureus* decolonization. There are now currently 3 nasal iodophor antiseptics (5% and 10%) with properties which enable better adherence to nasal mucosa.

Phillips et al. performed a prospective, open-label trial of twice-daily nasal mupirocin for 5 days before surgery compared to two applications of a 5% nasal PI solution within 2 hours of surgical incision in patients undergoing arthroplasty or spine fusion surgery. Both groups also received CHG baths, with 2% cloths, the night before and the morning of surgery. If the preoperative nasal culture was positive for *S. aureus*, another nasal culture was obtained within 1 to 3 days after surgery. The proportion of postoperative negative nasal cultures was 92% (78 of 85 patients) for those assigned to mupirocin versus 54% (45 of 84 patients) for those assigned to PI[51]. In a recent study Saidel-Odes et al. showed that when there is preoperative scant *S aureus* nasal colonization, nasal PI application on

the evening before and the morning prior to surgery was very effective in achieving *S aureus* eradication. However, when there was a high *S aureus* nasal colony count preoperatively, nasal PI application on the evening before and the morning prior to surgery was less effective in achieving *S aureus* eradication[52]. In the study discussed under mupirocin, exposure to nasal mupirocin significantly reduced *S aureus* clinical cultures by 18.4% compared with iodophor in adult ICUs in the setting of universal daily chlorhexidine bathing. However nasal iodophor was better than no intranasal intervention[47]. Lastly, in a proof-of-concept study, the investigators set out to determine whether nasal decolonization with PI diminishes the utility of polymerase chain reaction (PCR)–based nasal MRSA screening. All baseline PCR-positive results were confirmed via culture. Follow-up MRSA PCR tests were obtained after 4–6 days, immediately prior to intranasal PI application, or at least 8 hours after the most recent application. All follow-up samples also underwent confirmatory culture. PCR remained highly sensitive for nasal MRSA colonization even after multiple applications of PI and most patients remained culture positive after 4–13 applications raises concerns that PI may be less effective than mupirocin for clearing nasal colonization[53]. In summary, PI may be an alternative to mupirocin, but PI may not be as effective as mupirocin at eradicating intranasal *S aureus.*

ALCOHOL-BASED NASAL ANTISEPTIC

Alcohols are antimicrobial by denaturing proteins. Alcohol has bactericidal activity against most gram-positive and gram-negative bacteria, including MDROs. Alcohol concentrations between 60 and 90% are most effective, but duration of activity is short. Most alcohol-based hand antiseptics contain either isopropanol or ethanol[54]. Steed et al. published a double-blinded, placebo controlled RCT testing the effectiveness of an alcohol-based nasal antiseptic in reducing *S. aureus* nasal colonization in colonized health care workers. Health care workers testing positive for nasal *S. aureus* colonization were treated three times during the day with a nasal alcohol-based antiseptic

or placebo. The antiseptic formulation contained 70% ethanol combined with natural oil emollients and the preservative benzalkonium chloride. Nasal *S. aureus* and total bacterial colonization levels were determined before and at the end of a 10-hour shift. Antiseptic treatment reduced *S. aureus* colony forming units (CFUs) from baseline by 82% (mean) and 99% (median) (P= 0.001)[55].

In research brief Kanwar et al. conducted 2 nonblinded trials to determine effectives of single application of two different doses of a commercially available alcohol product (Nozin® Nasal Sanitizer) to reduce nasal MRSA in colonized patients[56]. In the first trial a single application was applied in each nostril. In the second trial 3 separate applications were applied intranasally over 3 minutes. The control group received intranasal saline. For all participants cultures were collected from the nares prior to and 10 minutes, 2 hours, and 6 hours after application. Cultures were also collected for MRSA from the clothing and skin of 23 participants. They also applied 3-single dose applications at 0, 4, and 8 hours. Nares cultures were collected at baseline and 2 hours after the third dose. The single-dose application was associated with a nonsignificant trend toward reduced mean MRSA concentrations in the treatment group versus the control group at 10 minutes and at 2 hours after dosing. The triple-dose application significantly reduced mean MRSA concentrations in comparison to controls at 10 minutes and at 2 hours after dosing, but not at 6 hours after dosing. MRSA was frequently recovered from the clothing (19 of 23, 83%) and skin (17 of 23, 74%) of participants. For repeated dosing of the alcohol-based nasal sanitizer over 8 hours there was no reduction in MRSA 2 hours after the final dose in comparison to baseline (mean ±SE, 2.3 ±0.43 vs 2.3 ±0.78 log$_{10}$ colony forming units per swab; P > .05). Bottom line: single-dose application of alcohol-based sanitizer did not significantly reduce nasal MRSA and triple-dose application only transiently reduced MRSA.

The manufacturer recommends triple-dose application for preoperative treatment and twice-

daily application of single dose postoperatively and for ICU decolonization. Based on the Kanwar study, it may be possible that frequent high dose alcohol may be adequate to suppress *S aureus.* Therefore, more studies are needed to determine the optimal concentration and frequency to eradicate colonization of *S. aureus.*

PHOTODYNAMIC THERAPY (PDT)

The use of a light source, such as a laser, has been suggested as an alternative method to eliminate *S aureus* nasal carriage. Photodynamic therapy (PDT) consists of the combination of a light-activated chemical and UV or infrared wavelengths. This combination creates free radicals that damage bacterial cell walls and membranes. In preliminary human testing, PDT eradicated nasal MRSA, with total treatment times of less than 10 min[57]. In a small cohort study, Bryce et al.[58] found that the colonization rates for MSSA and MRSA were 24.4% and 0.9%, respectively, before PDT therapy. Of those who received PDT (0.1% methylene blue plus laser), 85% had a reduced *S. aureus* burden in the anterior nares as measured by semiquantitative colony counts. Street and colleagues used a methylene blue- and CHG-based photosensitizer formulation[57]. That study evaluated the efficacy of using PDT for nasal MRSA decolonization at the preclinical and clinical levels. Preclinical testing was done in a custom nasal reservoir model and on human skin cultures colonized with MRSA. Human clinical testing was also performed. Using full-thickness skin cultures, they performed photodynamic treatment comparisons with either methylene blue or CHG alone or the combination of methylene blue and CHG. They found that the combination formulation using both methylene blue and CHG was much more effective than either methylene blue or CHG alone. Application of methylene blue or CHG alone with illumination led to some reduction in MRSA viability compared with that for the control (0.2-log10 and 1.1-log10 reductions, respectively) immediately posttreatment. In contrast, PDT treatment using a combination of methylene blue and CHG produced a statistically significant 5.1- log10 reduction compared with the nontreated control and a rapid antibacterial effect. In addition, the combination produced sustained decolonization that persisted for up to 5 days. Embleton et al. demonstrated that a monoclonal antibody conjugate targeting MRSA, when exposed to red light, selectively eliminated MRSA in all growth phases while not harming *Escherichia coli* and *Staphylococcus epidermidis.* This suggested that PDT may protect normal nasal microbiota while eliminating the target organism[59]. Lastly in a small study, patients on maintenance hemodialysis who were nasal carrier of *S aureus* were randomly assigned to decolonization with a single application of PDT or with a topical mupirocin regimen (twice a day for 5 days)[60]. Nasal swabs were collected at time 0, directly after treatment completion, 1 month after treatment, and 3 months after treatment. Participants receiving photodynamic therapy (71%) and participants treated with mupirocin (77%) had cultures that were negative for *S aureus* (P=0.9). Of the patients who had negative cultures directly after completion of photodynamic therapy, 67% were recolonized within 3 months and 54% of mupirocin patients were recolonized after 3 months. PDT is another promising approach for nasal *S aureus* decolonization, but larger clinical trials are needed to evaluate the impact on clinically significant infections.

Topical Agents

CHLORHEXIDINE GLUCONATE

Chlorhexidine, a topical antiseptic, has been used throughout the world for decades. Chlorhexidine gluconate (CHG) is a cationic biguanide that works by binding to bacterial cell walls, which alters the osmotic equilibrium of the bacterial cell. CHG has activity against Gram-positive and Gram-negative bacteria and yeasts. CHG has an excellent safety record. Adverse events associated with CHG are mild skin irritation and rare serious allergic reactions[61].

CHG efficacy has been documented for diverse indications, including handwashing, procedure skin preparation, vaginal antisepsis, gingivitis treatment, and body washes for infection prevention. CHG is available in a wide range of concentrations (0.5%

to 4%) and formulations. CHG can be used on its own or combined with ethanol or isopropyl alcohol. Some CHG products are also sold over the counter. This review focuses only on the use of CHG to prevent HAIs.

In 1991, a study demonstrated that CHG alcohol disinfection of the central line site before insertion was associated with a significant reduction in central-line-associated infections compared with 10% PI or 70% alcohol[62]. The use of CHG alcohol has now become the standard of care for site preparation and maintenance.

Recently, multiple studies have evaluated the use of CHG bathing to decrease the bacterial burden on the skin of ICU patients to reduce HAIs. CHG bathing can decrease the bioburden of bacteria and yeasts on patients, the hospital environment, and the hands of health care workers[63]. Bleasdale et al. observed a 60% reduction in BSIs among medical ICU patients who were bathed with 2% CHG cloths daily compared with soap and water[64]. Borer et al. examined the association between 4% CHG liquid body wash use and multidrug-resistant *Acinetobacter baumannii* skin colonization and BSIs in the medical ICU. Patients underwent CHG bathing immediately after obtaining initial cultures. Seventeen percent of patients were colonized with *Acinetobacter baumannii* on admission, 5.5% at 24 h, and 1% at 48 h ($P = 0.002$). The prevalence of *Acinetobacter baumannii* BSIs decreased from 4.6 to 0.6 per 100 patients, and the incidence decreased from 7.6 to 1.25 (85% reduction)[65].

In 2013 three randomized cluster trials on the topic of CHG bathing among ICU patients were published. One cluster-crossover study reported that daily 2% CHG cloth bathing in the ICU resulted in a 23% reduction of VRE and MRSA acquisition and a 28% reduction in BSIs[66]. In another study of pediatric ICU patients, Milstone et al. found a significant association between 2% CHG cloth bathing and a decline in BSIs compared with standard bathing[67]. Another trial, called the REDUCE MRSA study, cluster randomized 74 adult ICUs to evaluate three MRSA prevention

interventions: the first cluster implemented MRSA screening and isolation, the second cluster included screening, isolation, and decolonization of MRSA carriers with CHG bathing and nasal mupirocin (i.e., targeted decolonization), and the ICUs in the third cluster did not screen any patients but instead all patients were decolonized with CHG cloth bathing and nasal mupirocin (i.e., universal decolonization). Universal decolonization was found to be associated with the greatest decrease in all-cause BSIs (44%; $P <0.001$) and rates of MRSA clinical cultures (37%; $P = 0.01$)[68]. In a secondary analysis, CHG bathing was also shown to reduce blood culture contamination by 45% ($P = 0.02$), confirming earlier studies[29]. In a follow-up study, implementation of universal decolonization of ICU patients across a large health care system resulted in a decrease rate of CLABSIs by 23.5% ($P<.001$)[69].

In 2014, a European quasi-experimental study evaluated whether universal CHG cloth bathing, in addition to improved hand hygiene compliance, could decrease acquisition of MDROs. That study found that this intervention was associated with a significant decline in MDROs. Then, in a subsequent cluster randomized trial, they found that the addition of rapid screening and isolation did not lead to a further decline in MDROs[70].

In 2015, Noto et al. published a cluster-randomized crossover study of five different ICUs in a single academic institution[71]. ICUs were randomized to bathing with either CHG or nonantimicrobial cloths for 10 weeks, and then there was a 2-week washout period, after which ICUs were crossed over to 10 weeks of the other bathing treatment. The study evaluated a composite outcome of CLABSIs, VAP, CAUTIs, and CDI. This study also evaluated MDRO clinical culture rates, blood culture contamination, and health care-associated BSIs. Unlike in the previous trials, CHG did not reduce the incidence of HAIs. The findings in this study need to be interpreted considering several limitations. For one, the study did not monitor adherence to the bathing protocol, so it is possible that the lack of benefit reflected inadequate bathing. Second, two

of five units were already using CHG. Third, the intervention was only 10 weeks long. It takes a minimum of several weeks to ramp up to ensure adequate training and compliance; thus, many patients may not have received adequate CHG bathing during the intervention periods. Fourth, for two of the HAIs in the composite outcome, VAP and CDI, one would not expect reductions due to the use of CHG. Fifth, the study was conducted at a single center. Lastly, the baseline rates of hospital-acquired infections were low before the study was started, so it may not have been statistically powered to see a difference.

The role of CHG bathing among patients in non-ICU settings has been addressed in two recent studies. The first was the ABATE Infection (active bathing to eliminate infection) trial which was a cluster-randomized trial of 53 hospitals comparing routine bathing to decolonization with universal chlorhexidine and targeted nasal mupirocin in non-critical-care units[72]. They found that universal decolonization did not reduce infection in the overall population, but in post-hoc analyses of patients with medical devices(central lines and midlines) the regimen was associated with significant reductions in all-cause BSIs and MRSA or VRE clinical cultures. In the second trial adults with hematological malignancies hospitalized for chemotherapy in noncritical care units were offered daily 2% CHG bathing[73]. They compared outcomes of patients who chose CHG bathing (CHG group) with outcomes of those who did not choose CHG bathing (usual-care group). The primary outcome was gram-positive cocci-related, skin flora-related, or CLABSIs. The CHG bathing group was associated with a 60% decrease in the primary outcome (adjusted hazard ratio [HR], 0.4; P < .001). However, in a multicenter cluster-randomized controlled trial examining the effect of daily bathing with CHG, octenidine, or soap and water demonstrated a lack of significant preventive effect on CLABSIs in ICUs. However, the trial was underpowered due to a CLABSI rate in the routine care group that was approximately 40% lower than initially assumed[74].

Recently the CDC has proposed a new measure Hospital-Onset Bacteremia and Fungemia (HOB) which would require hospitals to expand surveillance with the intent on broader reduction of BSIs regardless of causative organism or association with a medical device. Investigators have suggested that HOB is a more inclusive measure than CLABSI[75,76]. This is supported by a recent study that demonstrated non-CLABSI HOB events occur in substantially greater numbers than CLABSI events occurring in a 79% to 21% ratio, respectively, in an observational study of patients in 41 acute-care hospitals conducted over a four-year period; additional findings indicated that 68% of the non-CLABSI HOB events were not related to secondary culture sources such as urinary or respiratory sites, and therefore may have attribution to use of vascular access devices[77]. There has been a growing awareness that peripheral IV catheters (PIVCs) can also cause significant morbidity and mortality. In a recent review, investigators identified that more than a third of the hospital onset *S. aureus* BSIs were associated with PIVCs rather than central lines. It is unclear whether CHG bathing with or without an intranasal agent can impact PIVCs BSIs[78]. Just published is a review on prevention of vascular-associate HOB[79]. The review outlines the evidence-based interventions including compliance with appropriate proper skin antisepsis and CHG bathing for high-risk patients.

Based on current evidence, the updated Compendium on "Strategies to Prevent Central Line Associated Bloodstream Infections in Acute-care Hospitals: 2022 Update" continues to recommend CHG bathing in the ICU for patients 2 months and older[80]. The Compendium stated the role of CHG bathing among patients in non-ICU settings was considered unclear despite several good studies discussed above. There is also a need to determine if the widespread use of CHG-based products promotes reduced CHG activity. Testing for CHG susceptibility is currently not standardized and the clinical impact of reduced chlorhexidine susceptibility in bacteria is unknown and not yet well-defined. The future Compendium will hopefully address prevention of HOB not just CLABSI.

POVIDONE-IODINE

PI has broad activity against both Gram-positive and Gram-negative bacteria. PI is applied topically in concentrations from 4% to 10%. It is well tolerated; however, it may cause mild skin irritations and most preparations are inactivated by organic matter. PI has a more rapid bactericidal effect than CHG, but povidone-iodine has not been shown to have a persistent effect like CHG[81]. CHG is recommended over 10% iodine solutions for catheter placement because CHG is associated with a lower risk of infection[62]. Another study compared a CHG preparation to a povidone-iodine preparation for surgical scrub use. The authors found that CHG had more persistent activity than povidone-iodine[82]. In a recent trial patients who were undergoing surgical fixation of a closed fracture of a lower limb or the pelvis, found that the risk of SSIs was lower with skin antisepsis provided by iodine povacrylex in alcohol than with antisepsis provided by chlorhexidine gluconate in alcohol[83]. Iodine povacrylex is an iodophor that is available in alcohol and unique due to its copolymer, povacrylex and is not inactivated by organic matter. In another recent trial PI in alcohol as preoperative skin antisepsis was noninferior to chlorhexidine gluconate in alcohol in preventing SSIs after cardiac or abdominal surgery[84]. The recent Compendium Strategies to Prevent Surgical Site Infections in Acute-care Hospitals: 2022 Update recommended using alcohol-containing preoperative skin preparatory agents if no contraindication exists[85]. Although PI has broad-spectrum properties, it may not be the ideal agent for bathing due to a lack of evidence for persistence, but an iodophor alcohol preparation may be a good alternative agent for preoperative skin site preparation.

Selective Digestive or Oropharyngeal Decontamination

SELECTIVE DIGESTIVE DECONTAMINATION AND SELECTIVE OROPHARYNGEAL DECONTAMINATION

Decontaminations of the upper respiratory and digestive tracts are interventions designed to decrease colonization with pathogenic Gram-negative organisms and infections in critically ill patients. These interventions include selective digestive decontamination (SDD) and selective oropharyngeal decontamination (SOD). SDD is performed by application of nonabsorbable antibiotics to the oropharynx and digestive tract. These nonabsorbable antibiotics include tobramycin, polymyxin, and amphotericin, as well as a short course of intravenous antibiotics such as cefotaxime. Oropharyngeal antibiotics are administered as a paste, while the gastric antibiotics are administered as a suspension down the nasogastric tube. SOD consists of the application of topical antibiotics to the oropharynx alone, and intravenous antibiotics are not given.

A 2007 meta-analysis evaluated the association between oral decontamination and the incidence of VAP[86]. It included 11 trials totaling 3,242 mechanically ventilated patients treated with oral application of either antibiotics or antiseptics or standard oral care. When the study results were pooled, it was found that both methods of oral decontamination were associated with decreased risk of VAP (RR 5 0.61; 95% CI, 0.45 to 0.82); however, significant differences for duration of mechanical ventilation, ICU length of stay, or mortality were not seen. In 2009, a cluster randomized crossover study was performed in 13 ICUs located in the Netherlands to evaluate the effectiveness of SDD and SOD[87]. Each ICU was randomized to implement SDD, SOD, and standard care in a random order over a 6-month period. In a logistic regression model, the SOD and SDD groups had lower odds of death at 28 days than the group that received standard care (SOD: OR 5 0.86; 95% CI, 0.740 to 0.99; and SDD: OR 5 0.83; 95% CI, 0.72 to 0.97). For patients receiving SDD or SOD, ICU BSIs were statistically significantly lower for *S. aureus* and nonfermenting Gram-negative organisms, especially *Pseudomonas aeruginosa* and *Enterobacteriaceae*, than with standard care. In another follow-up study, SOD and SDD were also associated with decreased rates of bacteremia and colonization of the respiratory tract

with antibiotic-resistant Gram-negative bacteria among patients admitted to the ICU for greater than 3 days[88]. That study included 47 episodes of acquired BSI that were caused by highly resistant organisms. BSIs acquired in ICUs and caused by highly resistant pathogens were 59% less frequent with SDD than with standard care and 63% less frequent with SDD than with SOD. In a later large trial also in the Netherlands, the authors compared SDD to SOD in regard to antibiotic resistance and patient outcomes[89]. They reported that both SDD and SOD were associated with low levels of antibiotic resistance and that there was no difference in 28-day mortality. Compared with SOD, SDD was associated with decreased rates of BSIs acquired in the ICU and rectal colonization of multidrug-resistant Gram-negative organisms. However, SDD was also associated with an increase in aminoglycoside-resistant Gram-negative organisms. The reduction in BSIs was more pronounced for *Enterobacteriaceae* (OR 5 0.42; 95% CI, 0.29 to 0.60), including aminoglycoside-resistant Gram-negative pathogens (OR 5 0.54; 95% CI, 0.31 to 0.97). Price et al. published a systematic review and meta-analysis evaluating SDD, SOD, and topical CHG compared to standard care or placebo to determine the association with mortality in adult patients in general ICUs[90]. SDD was protective against mortality, with a pooled OR of 0.73 (95% CI, 0.64 to 0.84). SOD was also associated with decreased mortality with a pooled OR of 0.895 (95% CI, 0.74 to 0.97). CHG was associated with higher mortality (OR 5 1.25; 95% CI, 1.05 to 1.5) which in part is why in the recent Compendium update on "Strategies to Prevent Ventilator-associated Pneumonia, Ventilator-associated Events, and Nonventilator Hospital-acquired Pneumonia in Acute-care Hospitals: 2022 Update" states that oral care with CHG is no longer recommended in prevention of ventilator-associated pneumonia (VAP)[91].

There remains concern that SDD or SOD may result in selection of resistant organisms. Daneman et al. published a systematic review and meta-analysis on the effect of select decontamination on antimicrobial resistance[92]. They were unable to detect an association between SDD or SOD and antimicrobial resistance in ICU patients. However, they did admit that the association between decolonization and antimicrobial resistance in the ICU setting needs more research.

More recently, A meta-analysis of 6 cluster randomized trials performed in countries with low levels of antibiotic resistance reported that SOD was associated with a 16% reduction in hospital mortality, and SDD was associated with an 18% reduction in hospital mortality[93]. SDD was more effective than SOD (OR, 0.90; 95% CI, 0.82–0.97 for hospital death).

Finally, a recent systematic review and meta-analysis reviewed the use of SDD in prevention of VAP[94]. Among adults in the ICU treated with mechanical ventilation, the use of SDD compared with standard care or placebo was associated with lower hospital mortality. They do caution that SDD is not recommended in ICUs with high levels of antimicrobial resistance. Based on current level of evidence the Compendium recommends under additional approaches, the use of oral or digestive decontamination to prevent VAP in countries and ICUs with low prevalence of antibiotic-resistant organisms.[91]

On a different note, several studies have examined the role of SDD in reducing colonization, infections, and outbreaks caused by multidrug resistant Gram-negative bacteria. Huttner et al. performed a double-blinded, placebo-controlled RCT to evaluate the efficacy of oral colistin, neomycin, and nitrofurantoin to reduce intestinal colonization with ESBL-producing *Enterobacteriaceae*[95]. This regimen temporarily suppressed ESBL-producing *Enterobacteriaceae* during and immediately after treatment, but the authors documented a rebound only 1 week after ending treatment.

Saidel-Odes et al. performed a blinded RCT comparing placebo to oral gentamicin and oral polymyxin gel plus oral solutions of gentamicin and polymyxin for 7 days to eradicate carbapenem-resistant *Klebsiella pneumoniae* (CRKP)

oropharyngeal and gastrointestinal carriage[96] After 2 weeks, the proportion of rectal cultures that were negative for CRKP was significantly improved in the intervention group (16% in the placebo group versus 61% in the intervention group [OR = 0.13; 95% CI, 0.02 to 0.74; P <0.0016]). A difference was still maintained at 6 weeks (33.3% in the placebo arm and 58.5% in the intervention arm), but it was not statistically significant. Secondary resistance to gentamicin or colistin was not observed in any of the SDD-treated patients. In another study, nonabsorbable oral antibiotics were administered for up to 60 days or until decolonization was documented in patients colonized with CRE[97]. Oral gentamicin or oral colistin was used based on the susceptibility of the isolate. Patients with isolates sensitive to both colistin and gentamicin were randomized to receive either colistin or gentamicin or both. Patients with isolates resistant to both agents were not provided with SDD but were followed to document spontaneous clearance of CRE. Eradication rates in the three treatment groups (gentamicin, colistin, or both) were 42%, 50%, and 37.5%, respectively, each significantly higher than the 7% spontaneous clearance in the control group (P <0.001, P<0.001, and P=0.004, respectively). However, there was no significant difference between the three treatment groups. Mortality in patients who achieved eradication (either spontaneously or by SDD) was significantly lower than that in patients where eradication failed (17% versus 49%, respectively; P = 0.002). Secondary resistance developed in 7 of the 50 SDD-treated patients, gentamicin resistance in 6 of 26 gentamicin-treated patients, and colistin resistance in 1 of 16 colistin-treated patients.

FECAL MICROBIOTA TRANSPLANT

Small studies have shown some effect of fecal microbiota transplant (FMT) for MDRO decolonization. A systematic review in 2021 including found FMT decolonization rates between 20%–90%, and they were slightly higher for carbapenem-resistant *Enterobacteriaceae* than for VRE; this review further found reduced MDRO bloodstream and urinary tract infections[98].

However, they conclude questions remain regarding the true efficacy of FMT and observed decrease in MDRO infections post. They recommend that FMT warrants further research. In 2022 the authors did a systematic review on use of FMT for CRE[99]. FMT was effective to eradicate CRE in 78% of cases and FMT was safe and well tolerated even in immunocompromised patients. They also recommended more studies, especially randomized trials, are needed to validate the safety and clinical utility of FMT for CRE eradication. Huttner and colleagues randomized 39 patients to either 5 days of oral nonabsorbable antibiotics followed by frozen FMT or control in patients colonized with extended-spectrum β-lactamase (ESBL-E) and/or carbapenemase-producing *Enterobacteriaceae* (CPE)[100]. Non-absorbable antibiotics followed by FMT slightly decreased ESBL-E/CPE carriage compared with controls, but this difference was not statistically significant. Study drugs were well tolerated overall but three patients in the intervention group prematurely stopped the study antibiotics because of diarrhea (all received FMT).

Lastly Woodworth et al. conducted a randomized, controlled trial of FMT for MDRO decolonization in renal transplant recipients[101]. Eleven participants were enrolled and randomized 1:1 to FMT or an observation period followed by delayed FMT if stool cultures were MDRO positive at day 36. Participants who were MDRO positive after one FMT were treated with a second FMT. At the last visit, eight of nine patients who completed all treatments were MDRO culture negative. FMT-treated participants had longer time to recurrent MDRO infection versus controls who were not treated with FMT. Bottom line: More studies, especially randomized trials, are needed to validate the safety and clinical utility of FMT for MDRO eradication.

Decolonization to prevent surgical site infections

There is strong evidence that nasal and skin decolonization prior to cardiac and orthopedic

surgery is effective at preventing SSIs especially caused by Gram-positive organisms that are susceptible to mupirocin and CHG. This is because SSIs are often endogenous, spreading from one body site (e.g., nose or skin) to the surgical wound of the same patient. Multiple studies have demonstrated that the genotypes of *S. aureus* colonizing and infecting isolates are identical in 75% to 85% of surgical patients[102]. A meta-analysis of 17 RCTs or quasi-experimental studies that included cardiac and orthopedic surgery patients evaluated the effectiveness of preoperative decolonization[38]. The meta-analysis found that decolonization was significantly protective against Gram-positive SSIs, specifically *S. aureus* SSIs. Decolonization has been effective against both MRSA and MSSA SSIs. One of the larger RCTs included in that meta-analysis was performed in the Netherlands, which has a low incidence of MRSA[102]. That study used PCR to rapidly identify *S. aureus* carriers and randomized 918 carriers to either placebo or nasal mupirocin and CHG. They found a greater than-2-fold decline in *S. aureus* infections and more than a 4-fold decline in *S. aureus* deep SSIs. Another large, quasi-

experimental study included in the meta-analysis prospectively evaluated 992 consecutive open heart surgery patients who did not receive mupirocin prophylaxis in the 22-month preintervention period. They then began providing open heart surgery patients with intranasal mupirocin and CHG bathing on the night before and morning of surgery, as well as mupirocin twice daily for 5 days postoperatively. This intervention group of 854 consecutive patients was followed prospectively for the 16-month intervention period. The rate of sternal wound infections decreased significantly from 2.7% (27 of 992) in the preintervention group to 0.9% (8 of 854) in the intervention group (P = 0.005)[103]. A more recent pragmatic quasi-experimental study implemented a bundled intervention in 20 hospitals in order to prevent complex *S. aureus* SSIs after cardiac surgery and hip and knee arthroplasty[104]. The bundle included CHG bathing for all patients, screening for MRSA and MSSA nasal colonization, nasal mupirocin decolonization for *S. aureus* carriers, and both vancomycin and cefazolin perioperative prophylaxis for MRSA carriers. (Figure 1)
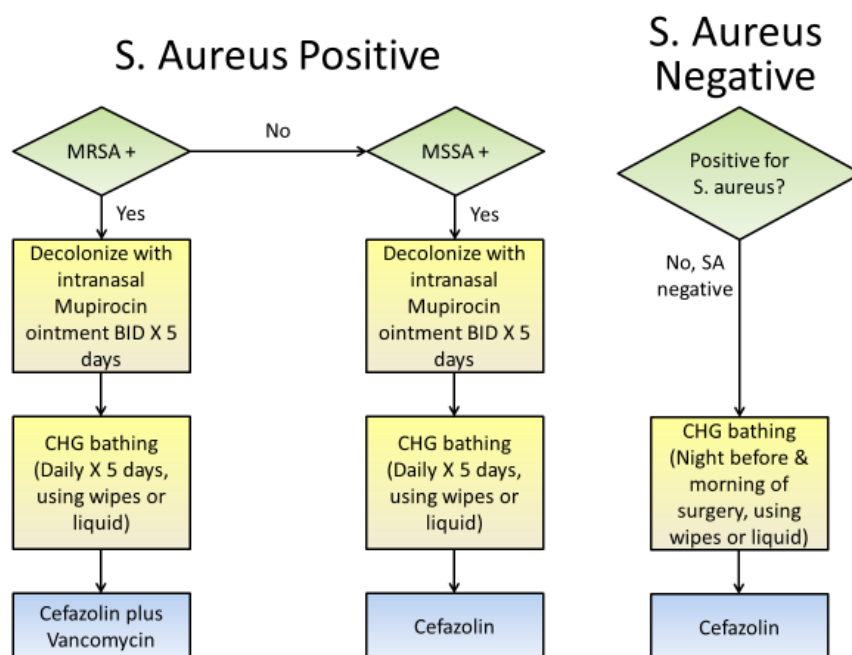
The mean rate of complex *S. aureus* SSIs significantly decreased from 36 infections per 10,000 operations during the baseline period to 21 infections per 10,000 operations during the

intervention period (rate ratio = 0.58; 95% CI, 0.37 to 0.92). A meta-analysis by Kallen et al. aimed to determine whether intranasal mupirocin decolonization could prevent SSIs caused by any

pathogen[39]. They categorized surgery into nongeneral surgery and general surgery. They hypothesized that general surgical procedures, especially those that involve the bowel, would be more likely to be associated with SSIs caused by organisms that are not susceptible to mupirocin (e.g., Gram negative or anaerobic organisms), and thus attenuate the effect of mupirocin. Mupirocin use among non-general surgery patients (e.g., those undergoing cardiothoracic surgery, neurosurgery, or orthopedic surgery) was associated with a reduction in SSIs. Conversely, mupirocin use among general surgery patients (e.g., those undergoing gastrointestinal, oncologic, or gynecologic surgery) did not reduce SSIs. Thus, mupirocin decolonization is recommended for clean nongeneral procedures but not for general surgical procedures that are associated with contamination from the gastrointestinal tract during the operation.

Phillips et al.[51] performed a prospective, open-label trial of twice-daily nasal mupirocin for 5 days before surgery compared to two applications of a 5% nasal PI solution within 2 hours of surgical incision in patients undergoing arthroplasty or spine fusion surgery. Both groups also received CHG baths, with 2% cloths, the night before and the morning of surgery. A total of 763 surgical procedures were evaluated among patients who received mupirocin and 776 surgical procedures among patients who received PI. In the per-protocol analysis, S. aureus deep SSIs developed in five patients (0.66%) who received mupirocin and zero patients (0.00%) among those who received PI ($P < 0.03$). In addition, if the preoperative nasal culture was positive for S. aureus, another nasal culture was obtained within 1 to 3 days after surgery. The proportion of postoperative negative nasal cultures was 92% (78 of 85 patients) for those assigned to mupirocin versus 54% (45 of 84 patients) for those assigned to PI. The authors commented that this was not unexpected, since mupirocin was intended to eradicate colonization while PI was intended only to suppress S. aureus around the perioperative period. This study has several limitations. First the

investigators could not perform multivariate analysis due to the small sample size. Second, patients were not followed after discharge to identify late infections.

Bebko and colleagues[105] published a second study using a preoperative decontamination protocol to reduce SSIs in orthopedic patients undergoing elective hardware implantations. This was a quasi-experimental, retrospective, nonrandomized trial comparing a bundled intervention to historical controls. The intervention consisted of application of 2% CHG and oral CHG the night before and morning of surgery plus an intranasal PI solution the morning of surgery. Patients were evaluated for SSI for the 30 days after their surgery date. Rates of SSIs were statistically significantly lower in the intervention group than in the control group (1.1% versus 3.8%; $P < 0.02$). However, that study was limited because it was not a randomized trial, patients were only followed for 30 days, and information regarding the MRSA carrier status of patients before and after decontamination was not collected; therefore, the study did not allow for evaluation of the effect of nasal decolonization alone versus other interventions.

In a study published earlier this year, Saidel-Odes et al. in a retrospective case control study studied preoperative intranasal PI application in conjunction with CHG bathing to reduce S aureus colonization and SSIs[52]. On admission, the evening before surgery, a nasal swab for S aureus colonization was performed by semiquantitative culture analysis and repeated within 24-hour after surgery. There was a 39.6% eradication of S aureus nasal colonization post PI solution intranasal application similar to the Phillips trial. They did confirm presurgery S aureus nasal colonization was a risk factor for subsequent SSI in orthopedic surgery and they also demonstrated a reduction in SSI rate in the preintervention versus postintervention period for knee arthroplasty, hip arthroplasty, and spine surgery. Of interest patients who were still positive for S aureus on a nasal culture postoperatively were three-fold more likely

to develop an SSI compared to patients who were culture negative postoperatively. Nasal PI application on the evening before and the morning prior to surgery was less effective in achieving *S aureus* eradication if initial nasal presurgery culture demonstrated higher colony counts.

Nasal alcohol products have bactericidal activity against most gram-positive and gram-negative bacteria but have a very short duration of activity. There are only two peer reviewed studies on the use of nasal alcohol in prevention of SSIs. Mullen et al.[106] published a brief report in 2017 using in an alcohol-based nasal antiseptic decolonization to reduce *Staphylococcus* species surgical site infections. All patients scheduled for spine surgery were included in the study. Records from 1,073 spine surgical patients undergoing inpatient or outpatient procedures (400 and 673 in the baseline and intervention periods, respectively) were part of the study. Investigators combined immediate presurgical application of an alcohol-based nasal antiseptic with existing daily CHG bath or wipes in a comprehensive pre and postoperative decolonization protocol. After surgery, patients were expected to follow the regular 3 times daily cycle of staff-applied alcohol-based application in the postsurgical units until discharge, at which time the patient and family coach were instructed to continue applications for an additional 5-7 days with the remaining antiseptic. Mean infection rates were significantly decreased by 81% from1.76 to 0.33 per 100 surgeries during the 15-month trial, when compared with the prior 9-month baseline (P=.036). This is a single-center quasi-experimental intervention. The investigators did comment that their spine population was not sufficiently large to do a randomized control trial so they decided to do a before-and-after trial design. In the second study, Bostian et al. did a retrospective study comparing an 18-month cohort of elective primary total joint arthroplasty patients treated peri-operatively with an alcohol-based nasal agent to historical controls[107]. The alcohol-based agent was administered pre-operatively on the day of surgery and for two weeks after surgery. They reported

patients who used the alcohol-based nasal decolonization had a lower rate of SSI compared with controls not receiving nasal decolonization (0.64% [5/779] vs. 1.55% [10/647]; p = 0.048; odds ratio, 2.43). This study has several imitations. First this was another quasi-experimental retrospective study. Second, the difference found regarding infection rates between groups was found when performing a chai-square analysis, but not when performing regression analysis. Much larger control studies involving patients colonized with *S. aureus* will be necessary to determine if decolonization with a nasal ethanol antiseptic can reduce *S. aureus* infections.

PDT is another promising approach for nasal S *aureus* decolonization. Bryce et al. studied patients undergoing elective cardiac surgery, orthopedic surgery, spinal surgery, vascular surgery, thoracic surgery, or neurosurgery who were asked to bathe with 2% CHG cloths in the 24 h prior to surgery and were given intranasal PDT (0.1% methylene blue plus laser) in the preoperative area[58]. There was a statistically significant decrease in the SSI rate when comparing treated patients to a historical control group (1.6% versus 2.7%; *P* 0.0004; OR 1.73; 95% CI, 1.28 to 2.34). However, the study was limited, since the benefits of CHG alone compared to PDT alone were not evaluated. Larger clinical trials are needed to evaluate the impact on clinically significant infections.

The Compendium on "The Strategies to Prevent Surgical Site Infections in Acute Care Hospitals: 2022 Update" now recommend as an essential practice to decolonize surgical patients with an antistaphylococcal agent in the preoperative setting for high-risk procedures, especially orthopedic and cardiothoracic procedures[85]. This includes patients colonized with either methicillin susceptible *S. aureus* (MSSA) or MRSA. They believe the strongest data recommends up to 5 days of intranasal mupirocin (twice daily) and daily CHG bathing for decolonization. They state there is some preliminary data on intranasal PI administered immediately before surgery. They

admit this approach may have some practical advantages, but more data is needed. There is even less evidence for other alternative strategies such as intranasal alcohol and PDT.

Moving forward, challenges relating to decolonization include expansion of these strategies for additional surgical patient populations, as well as nonsurgical invasive procedures. For example, interventional radiology patients receiving implants such as cardiac implantable electronic devices (CIED) have been associated with significant numbers of postimplant infections, often caused by S aureus[108]. For patients known to be colonized with MRSA or MSSA prior to a CIED procedure, a multigroup British Working Party guideline recommends the use of nasal and topical antimicrobial agents preprocedure in order to suppress carriage[109].

Conclusion

In summary, colonization with health care-associated pathogens such as *S. aureus*, enterococci, Gram-negative organisms, and *C. difficile* is associated with increased risk of infection. Many of these HAIs may be preventable by evidence-based interventions. Based on the evidence described here, decolonization is one such intervention that can reduce rates of HAIs.

Decolonization prevents both vertical and horizontal transmission, depending on the method.

There are several decolonization methods, such as nasal, topical, and oral decontamination, with many different agents. Mupirocin remains the gold standard agent for nasal decolonization of *S. aureus*, but there is concern about mupirocin resistance, and alternative agents are needed. CHG is the skin decolonization agent that has the strongest evidence for reducing HAIs. There is also evidence to support decolonization with SDD and SOD to prevent VAP in countries and ICUs with low prevalence of antibiotic-resistant organisms. FMT may be a new promising intervention in decolonizing patients with gram-negative MDROs, but more studies are needed.

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