AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews

Decolonization in Prevention of Health Care-Associated Infections

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SUMMARY

Colonization with health care-associated pathogens such as *Staphylococcus aureus*, enterococci, Gram-negative organisms, and *Clostridium difficile* is associated with increased risk of infection. Decolonization is an evidence-based intervention that can be used to prevent health care-associated infections (HAIs). 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, bacitracin, retapamulin, povidone-iodine, alcohol-based nasal antiseptic, tea tree oil, photodynamic therapy, omiganan pentahydrochloride, and lysostaphin. Mupirocin is still the gold standard agent for *S. aureus* nasal decolonization, but there is concern about mupirocin resistance, and alternative agents are needed. Of the other nasal decolonization agents, large clinical trials are still needed to evaluate the effectiveness of retapamulin, povidone-iodine, alcohol-based nasal antiseptic, tea tree oil, omiganan pentahydrochloride, and lysostaphin. Given inferior outcomes and increased risk of allergic dermatitis, the use of bacitracin-containing compounds cannot be recommended as a decolonization strategy. Topical decolonization agents reviewed included chlorhexidine gluconate (CHG), hexachlorophane, povidone-iodine, triclosan, and sodium hypochlorite. Of these, CHG is the skin decolonization agent that has the strongest evidence base, and sodium hypochlorite can also be recommended. CHG is associated with prevention of infections due to Gram-positive and Gram-negative organisms as well as *Candida*. Conversely, triclosan use is discouraged, and topical decolonization with hexachlorophane and povidone-iodine cannot be recommended at this time. There is also evidence to support use of selective digestive decontamination and selective oropharyngeal decontamination, but additional studies are needed to assess resistance to these agents, especially selection for resistance

Published 27 January 2016

Citation Septimus EJ, Schweizer ML. 2016. Decolonization in prevention of health care-associated infections. Clin Microbiol Rev 29:201–222. doi:10.1128/CMR.00049-15.

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among Gram-negative organisms. The strongest evidence for decolonization is for use among surgical patients as a strategy to prevent surgical site infections.

INTRODUCTION

Health care-associated infections (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 "Antibiotic Resistance Threats in the United States, 2013" highlights that at least two million Americans acquire severe antibiotic-resistant infections each year, which results in 23,000 deaths annually. Most deaths occur in health care settings such as hospitals. That CDC report recommends attempting to prevent these infections through appropriate antibiotic use and infection prevention practices (1). HAIs are now the fifth leading cause of death in U.S. acute-care hospitals (2). 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 (3–5). 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.

Over the past several years, 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 (6). Second, there are now coordinated efforts among federal agencies aimed at HAI prevention (7), including public reporting of hospital-specific HAI rates (8) 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) among intensive care unit (ICU) patients 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, *Clostridium difficile* infections (CDI), catheter-associated urinary tract infections (CAUTIs), and influenza vaccination among health care workers. In addition, starting in 2015, CLABSIs and CAUTIs must be reported hospital wide. These 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 (7, 8). Therefore, hospitals now have a financial incentive to implement prevention strategies to control HAIs. One such prevention strategy is bacterial decolonization.

Bacteria have been part of the normal human microflora for eons and usually do not cause signs or symptoms of infection (9). This 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 colonize the pharynx (11, 12). Other organisms, such as enterococci, *C. difficile*, and Gram-negative organisms (e.g., *Enterobacteriaceae*), commonly colonize the gastrointestinal tract (13).

TABLE 1 Vertical and horizontal approaches[a]

Approach
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)
CHG bathing
Selective digestive tract decontamination

[a] Based on data from reference 27. HH, hand hygiene; PPE, personal protective equipment; SCIP, surgical care improvement project.

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 (14–17). Hospitalized patients and long-term-care facility residents are at high risk of colonization with health care-associated pathogens. In 2012, a survey of 143 Canadian hospitals found that among their inpatients, 4.5% were colonized or infected with MRSA, 2.7% were colonized or infected with vancomycin-resistant enterococci (VRE), 1.4% were colonized or infected with *C. difficile*, 1.3% were colonized or infected with an extended-spectrum β-lactamase (ESBL)-producing organism, and 0.1% were colonized or infected with carbapenem-resistant *Enterobacteriaceae* (CRE) (18).

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, and HIV-infected patients (19–21). Similarly, gastrointestinal colonization with VRE is associated with increased risk of VRE infection (22–24). Even less-harmful bacteria that colonize the skin, such as CNS, can lead to infections among immunosuppressed patients and patients undergoing surgery (25, 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 (27) (Table 1). 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 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) is another horizontal decolonization strategy to prevent hospital-acquired respiratory tract infections.

Horizontal decolonization approaches have the potential to eradicate multiple pathogens from a cocolonized patient. Cocolonization with more than one type of bacteria is common because some risk factors for colonization are common to multiple MDROs (30). One recent study found that among nursing home residents with indwelling devices, those colonized with multidrug-resistant *Acinetobacter baumannii* had a high likelihood of also being colonized with another antibiotic-resistant Gram-negative pathogen (31). Similarly, other studies have found that ICU patients colonized with VRE are often cocolonized with ESBL-producing bacteria or with MRSA (30, 32). Colonization of multiple body sites is also seen frequently. One study found that the likelihood of developing an MRSA infection increases as more body sites are MRSA colonized (19).

Colonization can lead to infections in the colonized person and transmission from person to person via direct or indirect contact. Colonizing bacteria can be transmitted from healthy carriers to uncolonized people, such as between members of the same household or the same long-term-care facility. They can also be transmitted between sick patients via the hands of health care workers and shared hospital environments such as bed rails (33). Illness that leads to immunodeficiency, invasive procedures such as surgery or central lines, and high-risk activities are associated with the transition from harmless colonization to harmful infection (22, 34). Decolonization strategies aim to decrease the bacterial burden in order to prevent transmission and infection. Often, these strategies are vertical strategies in which patients are screened for certain pathogens of interest (e.g., MRSA or VRE) and decolonized if they are found to carry those pathogens. This may prevent both endogenous and exogenous infections.

Endogenous infections occur when a colonizing isolate enters a different body site on the same person and causes an infection. These infection sites include open cuts or wounds, surgical sites, and device sites. Patients who are nasally colonized with *S. aureus* are more than twice as likely to develop an *S. aureus* infection as noncolonized patients (10, 22, 34). Bacterial colonization can be categorized as persistent carriage, intermittent carriage, or noncarriage (14). One study of nursing home residents with indwelling devices found that of the 15% who were colonized with multidrug-resistant *Acinetobacter baumannii*, nearly half of those colonizations recurred over time (31). Other studies have shown that among *S. aureus* nasal carriers, approximately 40% are persistently colonized and 60% are intermittently colonized (14). Those who are persistently colonized with *S. aureus* are at a higher risk of infection than intermittent carriers or noncarriers (35). One study found that among *S. aureus* carriers who were decolonized and then exposed to a mixture of *S. aureus* strains, persistent carriers preferentially reselected the same strain with which they were previously colonized (36).

Exogenous infections occur when the infecting bacteria does not come from a patient's own flora but rather comes from another person or the surrounding environment. This can occur in hospitals, in long-term-care facilities, or in the community. Close quarters, open wounds, devices, and suboptimal health care worker hand hygiene and environmental cleaning are risk factors for exogenous infections (33, 34).

Increasing antibiotic resistance among health care-associated pathogens and the lack of new antibiotics in the developmental pipeline have led to a focused effort to prevent, rather than solely treat, HAIs. Many interventions to prevent HAIs, such as isolation, protect only against exogenous infections. However, decolonization is a potentially useful prevention strategy against both endogenous and exogenous infections (37). Thus, the colonized patient and, potentially, the surrounding patients both benefit. The two most common methods of decolonization are application of antimicrobial ointment to the nose and of antimicrobial body washes to the skin. These have been shown to reduce infections in specific subsets of patients, such as surgical, dialysis, long-term-care, and ICU patients, although results vary depending on the pathogen and the host (26, 38–44).

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 (14, 45). Persistent *S. aureus* carriers have been found to carry a greater quantity of *S. aureus* in their noses (measured in $\log_{10}$ CFU per nares culture) than intermittent carriers (46). Average *S. aureus* bacterial loads among nasal carriers tend to range between 1.8 and 2.9 $\log_{10}$ CFU per nares culture (47, 48). One study found that this load increased among MRSA carriers when patients received antibiotics that did not have activity against MRSA (e.g., beta-lactams or fluoroquinolones) (48). They hypothesized that this may be due to either suppression of normal flora such as CNS, leading to overgrowth of MRSA, or an increase in the expression of MRSA adherence factors that promote colonization (48). Another study found that higher log counts of MRSA in the nose were associated with an increased likelihood of colonization at other body sites and a greater likelihood of high log counts at those body sites (49). That study found that mean extranasal MRSA loads ranged from 0.87 $\log_{10}$ CFU per culture in the axilla to 1.65 $\log_{10}$ CFU per culture in the perineum to 1.70 $\log_{10}$ CFU per culture in the groin (49). Some decolonizing agents claim to completely eliminate the bacterial load from their application sites, while others claim to only decrease the load. Yet, there are few data on the level to which the bacterial load must be reduced in order to prevent transmission and infections.

Decolonization is the most effective among patient populations who are at risk of infection for only a short period of time (50). 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 (50).

Studies have found that patients tend to become recolonized with *S. aureus* within weeks or months of being decolonized (51, 52). In fact, *S. aureus* recolonization rates at 1 year approached 50% for health care workers and 75% for patients on peritoneal dialysis (53). Similarly, one study found that the *S. aureus* recolonization rate at 4 months was 56% in patients on hemodialysis (54). The goal of this paper is to review the evidence for different

TABLE 2 Characteristics of representative studies that have contributed to the evidence base[a]

Category and treatment	First author, yr (reference)	Study design	Decolonization[b]	Study population	Sample size	Methodology utilized for testing
Nasal						
Mupirocin	Perl, 2002 (56)	RCT	Universal	Surgical patients	3,864	"Nasal culture"
	Mody, 2003 (43)	RCT	Targeted	Long-term-care facility residents (persistent *S. aureus* carriers)	127	Standard culture, susceptibility testing using E-tests
	Schweizer, 2015 (152)	QE time series design	Targeted	Surgical patients	42,534	Varied
Retapamulin	Naderer, 2008 (82)	RCT	Targeted	Persistent *S. aureus* carriers	43	Not stated
Nasal povidone-iodine	Phillips, 2014 (84)	RCT	Universal	Surgical patients	1,697	"Nasal culture"
	Bebko, 2015 (85)	QE	Universal	Surgical patients	709	Not stated
Topical						
Topical chlorhexidine gluconate	Climo, 2013 (26)	Cluster randomized trial	Universal	ICU patients	7,727	Either standard culture-based or molecular-based (PCR) methods
	Huang, 2013 (40)	Cluster randomized trial	Universal and targeted	ICU patients	74,256	Varied
	Milstone, 2013 (109)	Cluster randomized crossover study	Universal	Pediatric ICU patients	4,947	Not stated
	Derde, 2014 (110)	QE/cluster randomized trial	Universal	ICU patients	8,976	Varied
Sodium hypochlorite	Fritz, 2011 (125)	RCT	Targeted	Patients with *S. aureus* CA-SSTI	300	Standard culture and susceptibility testing
SDD/SOD	de Smet, 2009 (140)	Cluster randomized crossover study	Universal	Mechanically ventilated ICU patients	5,939	Cultures with selective media and susceptibility testing
	Saidel-Odes, 2012 (146)	RCT	Targeted	CRKP carriers	40	Chromogenic agar plus susceptibility testing with Hodge test and E-tests
	Huttner, 2013 (145)	RCT	Targeted	ESBL-E carriers	54	Chromogenic agar confirmed by MALDI-TOF MS plus susceptibility testing with double-disc synergy test
	Oostdijk, 2014 (142)	Cluster randomized crossover study	Universal	ICU patients	9,800	"Surveillance culture"

[a] Abbreviations: RCT, randomized controlled trial; QE, quasi-experimental; ICU, intensive care unit; CHG, chlorhexidine gluconate; PI, povidone-iodine; RET, retapamulin; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci; HRE, highly resistant *Enterobacteriaceae*; ESBL-E, extended-spectrum β-lactamase-producing *Enterobacteriaceae*; MALDI-TOF MS, matrix-assisted laser desorption ionization–time of flight mass spectrometry; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CA-SSTI, community-associated skin and soft tissue infection.
[b] Targeted decolonization was defined as only colonized patients receiving the decolonizing agent; universal decolonization was defined as all patients receiving the decolonizing agent regardless of colonization status.

decolonization strategies on preventing HAIs. Most studies of decolonization have reported only on *S. aureus* decolonization; thus, much of this review will focus on *S. aureus* decolonization.

NASAL TOPICAL DECOLONIZATION STRATEGIES

Mupirocin

Mupirocin is a topical antibacterial agent made up of pseudomonic acids produced by the bacterium *Pseudomonas fluorescens*. This agent inhibits synthesis of bacterial proteins by reversibly binding to bacterial isoleucyl-tRNA synthetase. It has excellent activity against staphylococci, most streptococci, and Gram-negative organisms, including *Neisseria gonorrhoeae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (55). 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 controlled 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 mupi-

TABLE 2 (Continued)

Body site(s) screened	Pathogen(s) screened for	Duration of follow-up	Other interventions	Decolonization/recolonization assessed
Nose (but all patients decolonized regardless)	MRSA, MSSA	30 days	CHG shower (cardiac patients only)	Yes; 93% decolonized in mupirocin group, 27.4% decolonized in placebo group
Nose and wounds	MRSA, MSSA	6 mo	None	Yes; at 90 days 61% of mupirocin group and 18% of the placebo group were still decolonized; at 6 mo too few residents remained to draw conclusions
Nose	MRSA, MSSA	90 days	CHG bathing, vancomycin for MRSA carriers	No
Nose	*S. aureus*	28 days	None	Yes; 28 days later 75% decolonized in 3-day RET group, 86% decolonized in 5-day RET group, 31% decolonized in placebo group
Nose (but all patients decolonized regardless)	MRSA, MSSA	3 mo (7–31 days for colonization)	CHG bathing, vancomycin for MRSA carriers	Yes; 7–31 days later 92% decolonized in mupirocin group and 54% decolonized in PI group
Nose (but all patients decolonized regardless)	MRSA	30 days (day after surgery for colonization)	CHG bathing, oral rinse	Yes; the day after surgery 469 patients were tested, 2.2% of PI group carried MRSA and 5.7% of control group carried MRSA
Nose, perirectal area (but all patients decolonized regardless)	MRSA, VRE	Hospitalization	None	No
Nose	MRSA	Hospitalization	Intranasal mupirocin	No
None	None	Hospitalization	None	No
Perineum, nose, wounds (but all patients decolonized regardless)	MRSA, VRE, HRE	Hospitalization	Hand hygiene improvement	No
Nose, axilla, inguinal folds	MRSA, and MSSA	4 mo	Education and intranasal mupirocin	Yes; at 4 mo *S. aureus* was eradicated from 48% of controls and 71% of the bleach-mupirocin group
Throat, rectum, sputum	Gram-negative bacteria, MRSA, VRE	28 days (8 for colonization)	None	Yes; rate cultures positive for Gram-negative bacteria declined from day 2 to day 8 for both SDD and SOD patients
Rectum, urine, groin, throat	CRKP	6 wk	None	Yes; 6 wk later 33% in placebo group and 58% in SDD group had negative rectal cultures
Rectum, urine, groin	ESBL-E	28 days	None	Yes; 52% of treatment group and 37% of placebo group had eradicated ESBL-E carriage
Rectum, oropharynx, endotracheal aspirates	Gram-negative bacteria, VRE	28 days	None	Yes; over time the prevalence of highly resistant microorganisms increased during SOD and SDD

rocin ($P < 0.001$) (56) (Table 2). Currently, mupirocin is recommended to be applied to the anterior nares twice daily for 5 days.

Nasal mupirocin is the most widely used topical antibacterial agent. 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 (57). The effectiveness of mupirocin was similar for both MSSA and MRSA carriers.

Multiple studies have shown that mupirocin is effective in eradicating *S. aureus* nasal colonization, resulting in decreased numbers of infections among patients in high-risk settings such as ICUs and hemodialysis, surgical, and long-term-care settings (39, 41, 42, 58). Mody et al. (43) published a double-blinded, placebo-controlled RCT assessing the efficacy of nasal mupirocin in reducing colonization and preventing infections in two long-term-care centers. Twice-daily treatment was given for 2 weeks, and patients were followed for 6 months. After treatment, 93% of residents who received mupirocin were decolonized, compared with only 15% in the placebo group ($P = 0.001$). At 90 days after treatment, 61% of those receiving mupirocin remained decolonized. Additionally, there was a trend, though not statistically significant, toward a reduction in infections. Thus, mupirocin may be effective at eradicating persistent colonization in long-term care.

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, 42). (see Decolonization Prior to Surgery below for additional information) Two other meta-analyses found that decolonization with nasal mupirocin alone or in combination with topical agents such as CHG decreased the odds of *S. aureus* infection by approximately 60% among dialysis patients (39, 44). This was due to a reduction in both exit-site infections and cath-

eter-related bloodstream infections (39). Decolonization was associated with decreased numbers of infections among both hemodialysis patients and peritoneal dialysis patients (39).

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) (58). However, Ellis et al. (59) performed a cluster randomized study to evaluate whether intranasal mupirocin treatment for community-associated MRSA (CA-MRSA)-colonized soldiers could prevent infections in those who received mupirocin and would prevent new colonization and infection in their cluster. Although they found that CA-MRSA was eradicated in colonized soldiers, they failed to show a decrease in infections in the mupirocin-treated soldiers or within their cluster. Furthermore, CA-MRSA decolonization did not prevent new colonization. This study suggests that strategies to prevent CA-MRSA in these populations may require interventions other than mupirocin decolonization, such as hygiene education and CHG bathing (59–61). This may be explained by studies suggesting that nasal colonization may play a less prominent role in pathogenesis and transmission of CA-MRSA. Direct person-to-person and fomite-to-person transmission appears to be an important route for CA-MRSA infections (62). Popovich et al. demonstrated that inguinal and perirectal colonization appears to be more frequent with the USA300 strain (the most common genotype of CA-MRSA as determined by pulsed-field gel electrophoresis [PFGE]) and that patients with clinical CA-MRSA infections appear to be colonized at more than one site (63).

Mupirocin resistance among *S. aureus* has now been identified in multiple studies, especially with widespread use over prolonged periods (64–66). There are two phenotypes of mupirocin resistance: low-level mupirocin resistance (LL-MR), with MICs from 8 to 64 μg/ml, and high-level mupirocin resistance (HL-MR), with MICs of ≥512 μg/ml (67). *S. aureus* isolates with MICs between 64 and 512 μg/ml are uncommon (68). LL-MR results from point mutations in the native chromosomal isoleucyl RNA synthetase gene *ileS* (69, 70). The precise mechanism that confers low-level resistance has not been fully defined, but there are some data to suggest that there are changes in the tertiary structure of the enzyme that may reduce the binding affinity of mupirocin (70). HL-MR results from acquisition of plasmid-mediated *mupA*, which encodes a novel isoleucyl RNA synthetase (69).

Caffrey et al. (71) reported risk factors for mupirocin-resistant MRSA. They matched 40 mupirocin-resistant cases to 270 controls. In their adjusted conditional logistic regression model, they found three risk factors: mupirocin exposure in the prior year (odds ratio [OR] = 9.84; 95% CI, 2.93 to 33.09), infection in the prior year with *Pseudomonas aeruginosa* (OR = 4.85; 95% CI, 1.20 to 19.61), and use of cefepime in the prior year (OR = 2.80; 95% CI, 1.03 to 7.58). A sensitivity analysis found that prior mupirocin exposure was associated with both LL-MR and HL-MR. Thus, prior mupirocin use is associated with mupirocin-resistant MRSA (71).

More importantly, studies have shown that high-level mupirocin-resistant *S. aureus* results in decolonization failure. The association between LL-MR and failure of mupirocin decolonization is unclear. Walker et al. (72) 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 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 and not exogenous colonization.

The use of mupirocin, especially mupirocin applied repeatedly to dialysis exit sites to prevent infections in chronic dialysis patients, is associated with HL-MR *S. aureus* exit-site infections (65, 73). One study evaluated mupirocin resistance among residents of New Zealand, where mupirocin was available over the counter from the years 1991 to 2000. They reported an increase in mupirocin resistance, reaching 28% by 1999, with the highest rates among community-acquired isolates (74). Resistance has been shown to emerge in facilities with unrestrictive policies in which widespread use of mupirocin is allowed for long periods of time, such as if applied to decubitus ulcers (66). One study reported on mupirocin resistance trends and documented a statistically significant increase in HL-MR isolates. An associated case-control study demonstrated that the presence of a decubitus ulcer was associated with HL-MR isolates ($P < 0.05$) (66).

In contrast to unrestrictive use, short-term use of nasal mupirocin for perioperative prophylaxis to prevent *S. aureus* SSIs has not been associated with increased mupirocin resistance. 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 (56). 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 (75). Finally, a Dutch study evaluated over 20,000 patients who received mupirocin prophylaxis for major cardiothoracic surgery. No mupirocin resistance emerged (41).

To summarize, mupirocin is currently the best option for topical *S. aureus* nasal decolonization. Yet, the use of mupirocin has led to mupirocin resistance and treatment failures, specifically with widespread use over long periods of time. Therefore, alternatives to mupirocin for eradication of MRSA among patients colonized or infected with mupirocin-resistant strains are needed, and it is important to evaluate newer agents or alternative methods of decolonization (76). These alternative agents are described below.

Bacitracin

The topical agent bacitracin is produced from *Bacillus subtilis*. It acts against MRSA and other Gram-positive bacteria by interfering with bacterial cell wall synthesis. Soto et al. performed an RCT

of a 5-day regimen of either mupirocin or bacitracin for *S. aureus* nasal decolonization in health care workers. It was shown that after 30 days, bacitracin was inferior to mupirocin for eradication of *S. aureus* (23% versus 80%; $P < 0.01$) (77).

Bacitracin is also available in combination with polymyxin B (polysporin) and/or neomycin (neosporin). Polymyxin B is derived from *Bacillus polymyxa*. Polymyxins bind to the bacterial cell membrane, which then leads to a modification of the structure. This then creates a permeable cell wall and cell death. Neomycin is an aminoglycoside which binds to the 30S ribosomal subunit and interferes with protein synthesis. Both polymyxin and neomycin have activity against most Gram-negative bacilli. Fung et al. used polysporin ointment in a pilot study without a control group, which evaluated patients who previously failed MRSA decolonization with mupirocin. Of the 11 study patients, nine became decolonized, including three patients who had HL-MR (78). However, in an RCT, investigators compared mupirocin with polysporin triple ointment twice daily along with 2% CHG washes for 7 days to eradicate MRSA colonization. At least half of the patients in each group were colonized in multiple body sites (nasal and extranasal). After 48 h, 65% of the mupirocin group and 31% of the polysporin group were MRSA negative at every body site ($P = 0.001$). At 3 months, patients who received mupirocin were more likely to remain MRSA free than those who received polysporin, but this did not reach statistical significance ($P = 0.22$). The authors concluded that although neither agent performed well, polysporin was significantly less efficacious than mupirocin (79). Rates of allergic dermatitis have also been found to be higher with bacitracin and neomycin than with mupirocin, ranging from 8% to15% (80). Given inferior outcomes and increased risk of allergic dermatitis, the use of bacitracin-containing compounds cannot be recommended as a decolonization strategy.

Retapamulin

Retapamulin belongs to a new antibiotic class called pleuromutilins. Retapamulin acts against Gram-positive and Gram-negative bacteria by interacting at the 50S subunit of the ribosome (81). It is approved for treatment of impetigo due to *Streptococcus pyogenes* or MSSA because it is highly active against *S. aureus* and *S. pyogenes*, with MIC_{90}s of 0.12 μg/ml and 0.03 μg/ml, respectively. It is also active against both MRSA and mupirocin-resistant staphylococci (64).

Although this agent has not been approved by the U.S. Food and Drug Administration (FDA) for nares application, a double-blinded, placebo-controlled RCT of nasal retapamulin was reported at an international conference in 2008. This RCT evaluated 43 patients to determine whether 3- and 5-day nasal applications of retapamulin can eradicate persistent *S. aureus* nasal carriage. Persistent carriers were defined as positive for *S. aureus* on all three screening visits and immediately prior to the initial dose. Retapamulin led to *S. aureus* nasal decolonization in 92% to 94% of patients at 7 days and in 75% to 86% at 28 days. The most common adverse events included sneezing, nosebleed, and headache. Both groups experienced similar rates of nasal discomfort and rhinorrhea (82). There is currently a phase 4 study of nasal decolonization with retapamulin versus placebo to eradicate LL-MR and HL-MR MRSA nasal colonization in adults (https://clinicaltrials.gov/ct2/show/NCT01461668). Additional studies are needed.

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 (83) 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; however, the addition of nasal secretions *in vitro* reduced the PI activity. 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.

Phillips et al. (84) 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 h of surgical incision in patients undergoing arthroplasty or spine fusion surgery. A nasal PI solution was used because it has a film-forming substance which enables better adherence to nasal mucosa. Both groups also received CHG baths, with 2% cloths used, the night before and the morning of surgery. Phillips et al. evaluated 763 surgical procedures 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* during surgery. This study has several limitations. First it was a single-site study, and the results may not be generalizable. Second, the authors could not perform multivariate analysis due to the small sample size. Third, patients were not followed after discharge to identify late infections (84).

Bebko and colleagues (85) recently published 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 against other interventions. Nasal PI has not been studied in other clinical settings. In conclusion, although nasal PI may be a potential alternative to nasal mupirocin for prevention of SSIs, more studies are needed.

Alcohol-Based Nasal Antiseptic

Alcohol has bactericidal activity against most Gram-positive and Gram-negative bacteria, including MDROs. Alcohol concentrations between 60 and 90% are most effective. Alcohols are antimicrobial because they are able to denature proteins. Most alcohol-based hand antiseptics contain either isopropanol or ethanol (86). Steed et al. (87) recently 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* CFU from baseline by 82% (mean) and 99% (median) ($P < 0.001$). A much larger study involving patients colonized with *S. aureus* will be necessary to determine if decolonization with a nasal ethanol antiseptic can reduce *S. aureus* infections.

INVESTIGATIONAL NASAL AGENTS

Tea Tree Oil

Tea tree oil is extracted from the *Melaleuca alternifolia* plant and has broad-spectrum antimicrobial activity. In a pilot study of 30 patients, a combination of 4% tree oil nasal ointment with 5% tree oil body wash was evaluated against 2% mupirocin nasal ointment with triclosan body wash for MRSA decolonization at 48 to 96 h. The tree oil treatment cleared MRSA in 5 of 15 patients (33%), compared to 2 of 15 patients (13%) who received mupirocin with triclosan. Fifty-three percent of patients who received mupirocin with triclosan were still colonized when the treatment ended, compared with 20% of patients who received tea tree oil. The difference was not statistically significant, potentially due to the small sample size (88).

In a larger trial, Dryden et al. (89) compared a tea tree oil regimen with nasal mupirocin ointment, CHG wash, and silver sulfadiazine among hospitalized patients. The tea tree oil regimen comprised application of 10% tea tree cream to the anterior nares three times a day for 5 days and a 5% body wash at least once a day for 5 days plus 10% cream to skin lesions and open wounds. The mupirocin regimen consisted of application of 2% nasal mupirocin ointment to the anterior nares three times a day plus 4% CHG soap over the entire body at least once per day plus 1% sulfadiazine cream to skin lesions and open wounds. Prior to treatment, swabs were collected from each patient's nose, throat, axilla, groin, and any open lesions. These swabs were then tested for MRSA. The same set of cultures was performed after treatment on days 2 and 14. Persistent MRSA colonization at any site was considered to be decolonization failure. A total of 236 patients colonized with MRSA were included in the study. There was no significant difference between the regimens at 14 days. Successful decolonization occurred among 41% of the patients in the tea tree oil group and 49% of patients in the mupirocin treatment group. Interestingly, mupirocin was more successful at decolonizing the nares (78%) than tea tree cream (47%) ($P < 0.01$), yet tea tree treatment was more successful than CHG or silver sulfadiazine at decolonizing the skin. Compliance with treatment regimens was not closely monitored. There were no reports of adverse events. The authors concluded that tea tree preparations may be an effective and safe alternative to mupirocin-containing regimens in eradicating MRSA carriage (89). The optimal concentration of tea tree oil for decolonization is not known. Therefore, more studies are needed to determine the optimal concentration to eradicate colonization of *S. aureus*, to standardize that concentration, and to determine if decolonization with tea tree oil can reduce *S. aureus* infections.

Photodynamic Therapy

The use of a light source, such as a laser, has been suggested as an alternative method to eliminate MRSA nasal carriage. However, studies have shown that laser use alone may not be capable of total bacterial eradication (90). 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. One such chemical is methylene blue, which, when activated by laser light energy, has been shown to kill microbial cells. 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 human flora while eliminating the target organism (91).

A second study used a bacteriophage conjugated with a photosensitizer targeting *S. aureus*. In this study, more than a 3-$\log_{10}$ kill was demonstrated, with little effect on human epithelial cells (92). Street and colleagues (93) used a methylene blue- and CHG-based photosensitizer formulation. 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-$\log_{10}$ and 1.1-$\log_{10}$ reductions, respectively) immediately posttreatment. In contrast, PDT treatment using a combination of methylene blue and CHG produced a statistically significant 5.1-$\log_{10}$ 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 (93).

In preliminary human testing, PDT eradicated nasal MRSA, with total treatment times of less than 10 min (93). In a small cohort study, Bryce et al. found that the colonization rates for MSSA and MRSA were 24.4% and 0.9%, respectively, before PDT therapy (94). 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 (95). In a follow-up study, patients undergoing elective cardiac surgery, orthopedic surgery, spinal surgery, vascular surgery, thoracic surgery, or neurosurgery 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. 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). The intention-to-

treat analysis also demonstrated that PDT was associated with a decrease in rates of SSIs. Overall compliance was 94%. However, the study was limited, since the benefits of CHG alone compared to PDT alone were not evaluated (94).

Laser therapy for nasal decolonization could also potentiate antibiotics that were previously ineffective. Bornstein et al. (96) demonstrated the antibiotic-enhancing effect on MRSA with erythromycin cream where erythromycin cream alone did not reduce MRSA. Laser therapy alone produced a 57% reduction in MRSA, versus 97% when laser use was followed by application of erythromycin cream. The authors discussed that one of the mechanisms for erythromycin-resistant *S. aureus* is the use of efflux pumps to transport erythromycin out of the cell. However, inhibitors of ATP synthesis can stop these cellular transport systems. They postulated that the inhibition of energy-dependent efflux mechanisms by sublethal doses of 870-nm/930-nm laser energy contributes to the potentiation of erythromycin against *S. aureus*. In a pilot study, Krespi and Kizhner (97) published the first human study using laser therapy followed by topical erythromycin cream. Among the 14 *S. aureus*-colonized patients who received laser therapy followed by topical erythromycin cream, 13 became decolonized. Decolonization was maintained at 4 weeks.

Photodynamic therapy is a promising approach for topical MRSA decolonization, but larger clinical trials are needed to evaluate different nasal decolonization protocols (including determining the optimal sensitizer) using clinically significant infection as the outcome.

Omiganan Pentahydrochloride

The investigational agent omiganan pentahydrochloride is a unique topical peptide that has *in vitro* activity against Gram-positive and Gram-negative bacteria and yeasts (98). The peptide can depolarize membranes, leading to cell death. In a recent study, omiganan was active against *S. aureus*, including strains that are vancomycin intermediate and vancomycin resistant, even at levels much lower than the clinical formulation (1% gel; 10,000 μg/ml) (99). In a separate study, omiganan was assessed against over 1,000 clinical bacterial isolates as well as 214 clinical yeast isolates. Omiganan was found to be highly active against the bacterial and yeast isolates, including MRSA (98). This agent appears to be promising and merits further clinical studies.

Lysostaphin

The investigational agent lysostaphin is a glycylglycine endopeptidase that is active against staphylococci through cleavage of the cross-linking pentaglycine bridges in staphylococcal cell walls. One study evaluated the *in vitro* activity of lysostaphin against 429 isolates from human blood and nares and found that lysostaphin was active against all 429 isolates, including MSSA and MRSA (100). Kokai-Kun et al. found that lysostaphin was active against all of isolates that they tested and rapidly lyses both growing and stationary-phase *S. aureus* (101). They also found in a cotton rat model that when they compared mupirocin to one application of 0.5% lysostaphin cream, the lysostaphin was more effective at eradicating nasal MRSA, MSSA, and mupirocin-resistant *S. aureus*. In another study, the authors compared the activities of lysostaphin, tea tree oil, and mupirocin against 98 MRSA clinical isolates. Using 24-h time-kill studies, lysostaphin was more effective than either mupirocin or tea tree oil (102). Lysostaphin may offer a therapeutic option, but results need to be validated by well-designed RCTs.

TOPICAL AGENTS

Topical 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 (103).

CHG efficacy has been documented for diverse indications, including handwashing, procedure skin preparation, vaginal antisepsis, oral care for prevention of ventilator-associated pneumonia (VAP), 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 (104). The use of CHG alcohol has now become the standard of care for site preparation and maintenance (105).

Recently, multiple studies have evaluated the use of CHG bathing to decrease the bacterial burden on the skin of ICU patients in an effort 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 (106). Bleasdale et al. observed a 60% reduction in bloodstream infections (BSIs) among medical ICU patients who were bathed with 2% CHG cloths daily compared with soap and water (107). 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 patents 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) (108).

In the year 2013 alone, 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 (26). 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 (109). 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 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%; $P = 0.01$) (40). In a secondary analysis, CHG bathing was also shown to reduce blood culture contamination by 45% ($P = 0.02$), confirming earlier studies (29).

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 (110).

In 2015, Noto et al. (111) published a cluster-randomized crossover study of five different ICUs in a single academic institution. 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 in light of 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 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 (111).

A study of long-term acute-care hospital (LTACH) patients assessed whether the use of daily 2% CHG bathing cloths was associated with lower *Klebsiella pneumoniae* carbapenemase-producing *Enterobacteriaceae* (KPC) skin colonization. That study reported that CHG bathing was associated with decreased KPC skin colonization, especially when CHG skin concentrations were greater than 128 μg/ml. In the study, 35 (56%) of 62 patients had at least one skin site positive for KPC immediately before bathing, versus 20 (32%) of 62 patients after bathing ($P = 0.01$) (112). That study was followed by a stepped-wedge study of LTACHs to test whether an intervention, which included screening for KPC rectal colonization, contact precautions, and daily CHG bathing, would reduce KPC colonization and infection. It was concluded that the intervention was associated with reductions in KPC colonization, blood culture contamination, and BSIs due to all causes (113).

Cassir and colleagues recently published a single-center study alternating soap and water bathing with CHG cloths in two divided 6-month periods in the ICU (114). Twenty-nine patients in the CHG group developed HAIs, versus 56 patients in the control group ($P = 0.01$). There were also statistically significant differences in the incidence of community-acquired BSIs, health care-associated VAP, and health care-associated urinary tract infections (UTIs). This effect was greater for HAIs due to Gram-negative organisms. This result may be explained since the authors enrolled only patients who already had a least one episode of suspected sepsis. However, it is unclear how CHG bathing reduced rates of community-acquired BSIs. Huang et al. also demonstrated a 26% reduction in BSIs due to Gram-negative bacteria in the universal decolonization arm of the REDUCE MRSA trial (40). The studies by both Climo et al. and Huang et al. also showed reduced infections due to *Candida* species (26, 40). Further large-scale studies are needed to confirm this result.

Rupp et al. (115) evaluated the effectiveness of hospital-wide CHG patient bathing on rates of HAIs. CHG bathing or showers were given 3 days per week or daily. They reported a significant decrease in infections due to CDI during the intervention period and a statistically significant increase during the washout period. Specifically, the decrease in CDI was statistically significant for both CHG bathing 3 days per week (RR = 0.71; 95% CI, 0.29 to 0.59; $P < 0.001$) and for daily CHG bathing (RR = 0.41; 95% CI, 0.29 to 0.59; $P < 0.001$). The reduction in CDI was unexpected. The authors speculated on some reasons but concluded further studies were needed to validate their observation.

Lastly, appropriate CHG application requires adequate education, training, monitoring, and feedback. Edmiston et al. showed that mean residual CHG concentrations on the skin were much higher in patients given instructions for showering with 4% CHG soap compared with bathing without instructions (116). Finally using a colorimetric assay to determine the CHG on skin, investigators found that CHG application was suboptimal. An intervention which included reeducation and feedback to nurses significantly improved the percentage of skin sites positive for CHG (117).

In summary, with the exception of the study by Noto et al. (111), there is now a body of evidence that in settings of endemicity, horizontal approaches that include universal decolonization with CHG bathing and potentially nasal mupirocin may be more effective than vertical strategies that include active surveillance testing and isolation. These studies support the recently published recommendation that ICU patients over 2 months of age should be bathed with CHG on a daily basis to prevent CLABSIs as basic practice (103). Although the incidence of CHG resistance is currently low and of uncertain clinical significance, resistance to CHG should be monitored with more widespread use.

Hexachlorophane

Hexachlorophane has activity against Gram-positive bacteria but is not effective against Gram-negative bacteria and anaerobes. Hexachlorophane inhibits the electron transport chain of bacteria (118). It is bacteriostatic in the standard 3% liquid concentration and can take multiple days for an effective concentration to be established on the skin. Hexachlorophane is contraindicated for use in neonates because of systemic absorption that may lead to neurotoxicity (119). Given its spectrum and toxicity, hexachlorophane is less clinically useful than CHG and therefore cannot be recommended at this time.

Povidone-Iodine

Povidone-iodine has broad activity against both Gram-positive and Gram-negative bacteria. Povidone-iodine is applied topically in concentrations from 4% to 10%. It is well tolerated; however, it may cause mild skin irritations. Povidone-iodine has a more rapid bactericidal effect than CHG, but povidone-iodine has not been

shown to have a persistent effect like CHG (120). One 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 (121). CHG is recommended over 10% iodine solutions for catheter placement because CHG is associated with a lower risk of infection (122). Although povidone-iodine has broad-spectrum properties, it is not ideal for topical decolonization due to a lack of evidence for persistence and inferior outcomes compared with CHG.

Triclosan

Triclosan has activity against both Gram-positive and Gram-negative bacteria. Triclosan works by targeting many intracellular sites of bacteria. Triclosan resistance develops through a one-step change in enoyl reductase (123). Triclosan is in many liquid soaps, toothpaste, and acne preparations that can be purchased over the counter. These range in concentrations from 0.15% to 1%. However, triclosan has been found in human urine, blood, and breast milk as well as throughout the environment. The U.S. FDA and the U.S. Environmental Protection Agency (EPA) are currently performing scientific and regulatory reviews of the safety of triclosan (124). Giuliano and Rybak recently reviewed the evidence evaluating the use triclosan as an antimicrobial soap and its association with antimicrobial resistance. They concluded that there was no beneficial effect of triclosan over nonantimicrobial soap, and triclosan resistance has been demonstrated. They concluded that the risks outweighs the benefits of triclosan use (124).

Sodium Hypochlorite (Bleach)

Sodium hypochlorite alters cellular metabolism and causes phospholipid destruction. Sodium hypochlorite has been used primarily as part of MRSA decolonization. A recent trial compared no intervention to one of three 5-day interventions: intranasal mupirocin alone, intranasal mupirocin with daily CHG bathing, or intranasal mupirocin plus daily bathing with dilute bleach (a quarter cup of 6% sodium hypochlorite per tub of water). At 1 month, *S. aureus* eradication occurred in only 38% of the control group versus 56% with mupirocin alone ($P = 0.03$), 55% in the mupirocin and CHG group ($P = 0.05$), and 63% in the mupirocin and bleach group ($P < 0.01$) (125). The most recent IDSA guideline on MRSA recommends that children and adults who have recurrent MRSA skin and soft tissue infections should use intranasal mupirocin and bathe with bleach made with one-fourth cup of bleach in a one-quarter tub (approximately 13 gallons), which represents 2.5 μl/ml. These baths should last for 15 min and be performed twice weekly over the course of 3 months (126).

Oral Care

To date, the only large, well-controlled clinical trials of oral care interventions in at-risk patients involve the use of chlorhexidine. Oral care with CHG is now standard practice for the prevention of VAP; however, recent systematic literature reviews and meta-analyses indicate limitations of the current evidence. Studies involving cardiac surgery patients reveal the most compelling data, where reductions in VAP rates, mortality, and length of stay have been realized through the use of chlorhexidine (127, 128). Reports vary on the potential impact of chlorhexidine use in other patient populations. When tested in intensive care populations outside cardiac surgery, chlorhexidine did not achieve the same positive outcomes in in regard to mortality and decreased length of stay (129, 130), although evidence around possible decreases in VAP rates among severely ill patients intubated for more than 1 day is growing (131, 132). Finally Klompas et al. published an article on the reappraisal of routine oral care with CHG (133). They pointed out that previous meta-analyses may be misleading because they fail to distinguish cardiac surgery and noncardiac surgery. They found that cardiac surgery patients who were randomized to receive CHG experienced fewer respiratory tract infections (RR = 0.56; 95% CI, 0.41 to 0.77), yet there was not a significant difference in risk of VAP among RCTs of non-cardiac surgery patients (RR = 0.88; 95% CI, 0.25 to 2.14). They concluded that routine oral care with CHG prevents health care-associated pneumonia only among cardiac surgery patients and not in non-cardiac surgery patients. They admitted that their findings are not conclusive and that large, adequately powered randomized trials are necessary, especially with non-cardiac surgery patients.

ORAL AGENTS

Systemic antibiotics are usually unable to attain adequate concentrations in secretions to eradicate nasal *S. aureus*. Therefore, decolonization regimens may use a combination of oral antibiotics with topical therapies. Oral therapy may be particularly useful for patients colonized at multiples sites or extranasal sites.

A double-blinded RCT of 94 patients over 7 days evaluated whether rifampin (300 mg twice daily) and novobiocin (500 mg twice daily) combined or rifampin (300 mg twice daily) and trimethoprim (160 mg)-sulfamethoxazole (800 mg twice daily) combined decreased whole-body *S. aureus* colonization (134). It found that 67% (30 of 45 patients) of the rifampin and novobiocin group and 53% (26 of 49 patients) of the rifampin and trimethoprim-sulfamethoxazole group were decolonized. Risk factors for unsuccessful decolonization were found to be older age, MRSA-positive wound culture, and greater than one colonized site. An open-label RCT of hospitalized patients assessed a 7-day regimen of 2% CHG bathing once daily, 2% intranasal mupirocin used three times daily, 300 mg of oral rifampin twice daily, and 100 mg of doxycycline given twice daily compared with no treatment for MRSA decolonization at all body sites (135). Of the 146 patients who were randomized, 112 patients were evaluated at 3 months. At 3 months, 74% (64 of 87 patients) of the treatment group and 32% (8 of 25 patients) of the control group had negative MRSA cultures (RR = 1.55; 95% CI, 1.17 to 2.04; $P < 0.01$). However, adverse events occurred in a quarter of the patients, including nausea, vomiting, and diarrhea. Cluzet et al. recently published a study to evaluate both colonization duration and predictors of clearance of MRSA colonization. They found that treatment of skin and soft tissue infection with clindamycin was associated with earlier clearance of MRSA colonization (136). Although the use of oral agents in decolonization of patients with *S. aureus* has been evaluated in several studies, the optimal dose and duration of therapy are still unclear, as well as whether combination therapy is preferred over monotherapy. Rifampin, quinolones, trimethoprim-sulfamethoxazole, novobiocin, clindamycin, doxycycline, and minocycline have all been evaluated as oral decolonizing agents, but current data have not demonstrated a preferred agent (134, 137). In addition, it is unclear whether oral agents are more efficacious than topical decolonizing agents. The risk of resistance and side effects must be taken into consideration when evaluating these therapies. Current guidelines recommend against routine use of oral agents for decolonization (126).

SELECTIVE DIGESTIVE OR 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. CHG is sometimes used in the approach (see above). Reported effects on patient outcomes have been conflicting.

D'Amico and colleagues (138) performed a meta-analysis of RCTs from 1984 to 1996. They evaluated two categories of trials. The first consisted of those that assessed topical and systemic antibiotics against a control group with no treatment. The second category of trials assessed topical antibiotics with or without systemic antibiotics against either systemic antibiotics or a placebo. They concluded that the combination antibiotic prophylaxis with both topical and systemic antibiotics was associated with a decrease in respiratory tract infections and mortality among critically ill patients. A 2007 meta-analysis evaluated the association between oral decontamination and the incidence of VAP (139). 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 = 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 (140). Each ICU was randomized to implementation of 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 = 0.86; 95% CI, 0.740 to 0.99; and SDD: OR = 0.83; 95% CI, 0.72 to 0.97). For patients receiving SDD or SOD, ICU bloodstream infections were statistically significantly lower for *S. aureus* and nonfermenting Gram-negative organisms, especially *Pseudomonas aeruginosa* and *Enterobacteriaceae*, than with standard care. There was also a reduction in the number of rectal swabs positive for Gram-negative bacteria among patients who received SDD and in the number of oropharyngeal swabs in both the SDD and SOD groups (140). In a follow-up study (11), the investigators looked at the ecological effects of SDD and SOD. During SDD, the average proportion of patients who were intestinally colonized with Gram-negative bacteria resistant to ceftazidime was 5%, that for tobramycin was 7%, and that for ciprofloxacin was 7%, and this increased significantly to 15%, 13%, and 13%, respectively, postintervention ($P < 0.05$). For organisms resistant to ceftazidime, 39.9% were *Enterobacter cloacae* and 26.2% were *Escherichia coli*. For organisms resistant to ciprofloxacin and tobramycin, most were *E. coli*: 50% for ciprofloxacin and 48.2% for tobramycin. When SDD and SOD were implemented, the proportion of respiratory tract isolates that were resistant to all three antibiotics was less than 7%. However, that proportion of isolates that were resistant gradually increased during the intervention to 10% or more for ceftazidime, tobramycin, and ciprofloxacin in the postintervention period. For organisms resistant to ceftazidime, 38.2% consisted of *Enterobacter cloacae* and 33.6% of *Pseudomonas aeruginosa*. For organisms resistant to ciprofloxacin and tobramycin, most were *P. aeruginosa*: 49.6% for ciprofloxacin and 43.5% for tobramycin (11).

In another follow-up study (141), 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. 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 (142), the authors compared SDD to SOD in regard to antibiotic resistance and patient outcomes. 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 = 0.42; 95% CI, 0.29 to 0.60), including aminoglycoside-resistant Gram-negative pathogens (OR = 0.54; 95% CI, 0.31 to 0.97).

Price et al. (143) 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. 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 actually associated with higher mortality (OR = 1.25; 95% CI, 1.05 to 1.5). About half of patients in this analysis were ventilated ICU patients from the Netherlands. There remains concern that SDD or SOD may result in selection of resistant organisms. Daneman et al. (144) published a systematic review and meta-analysis on the effect of select decontamination on antimicrobial resistance. 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.

Several recent studies have examined the role of SDD in reducing colonization, infections, and outbreaks caused by multidrug-resistant Gram-negative bacteria. Huttner et al. (145) 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*. 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. (146) 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 gastrointes-

TABLE 3 Pooled relative risks evaluating the protective effect of decolonization among studies that evaluated cardiac operations and total joint arthroplasties[a]

SSI type	Pooled relative risk (95% CI)		
	All studies	Cardiac studies	Total joint arthroplasty or orthopedic studies
Gram positive	0.41 (0.30–0.55)	0.46 (0.32–0.67)	0.32 (0.22–0.47)
S. aureus	0.39 (0.31–0.50)	0.45 (0.34–0.58)	0.32 (0.21–0.47)
MRSA	0.30 (0.15–0.62)	0.69 (0.36–1.31)	0.16 (0.09–0.28)
MSSA	0.50 (0.37–0.69)	0.46 (0.29–0.72)	0.56 (0.31–1.01)

[a] Adapted from reference 38 by permission from BMJ Publishing Group Limited.

tinal carriage. 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 (147), nonabsorbable oral antibiotics were administered for up to 60 days or until decolonization was documented in patients colonized with CRE. 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 (147).

In summary, despite a large number of favorable studies in this area, clinicians are still unclear on the appropriate use of SDD and SOD. Based on studies performed in ICUs that had low levels of antibiotic resistance, SDD or SOD most likely does not result in increased resistance in Gram-negative bacteria. However, the use of SDD where resistant Gram-negative bacteria may be endemic has resulted in conflicting results. Therefore, in settings where resistant Gram-negative bacteria are endemic, SDD should be used only with careful microbiological monitoring for development of resistance. Larger studies that include longitudinal investigation of selection for drug resistance and other poor outcomes are needed to determine the optimal use of SDD or SOD, especially in health care settings where antimicrobial resistance is endemic.

Other interesting investigational decolonizing agents that need more study include bacteriophages, fecal microbiota transplant, and probiotics (76, 148). Clinical trials should be performed to investigate these agents.

DECOLONIZATION PRIOR TO SURGERY

The strongest evidence supporting decolonization is among surgical patients. More studies have evaluated decolonization among surgical patients than among any other patient population (38, 42, 44). Studies have shown that decolonization can decrease the incidence of Gram-positive SSIs after some types of surgery (38, 149). 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 (determined via PFGE) of *S. aureus* colonizing and infecting isolates are identical in 75% to 85% of surgical patients (56, 149).

There is strong evidence that nasal and skin decolonization prior to cardiac and orthopedic surgery is effective at preventing SSIs caused by Gram-positive organisms that are susceptible to mupirocin and CHG. A meta-analysis of 17 RCTs or quasi-experimental studies that included cardiac and orthopedic surgery patients evaluated the effectiveness of preoperative decolonization (38). All but one of the studies included in the meta-analysis used mupirocin ointment for nasal decolonization, but one study used nasal CHG (150). The meta-analysis found that decolonization was significantly protective against Gram-positive SSIs, specifically *S. aureus* SSIs (Table 3).

Decolonization was protective against SSIs when the site of decolonization was the nares alone and when both the nares and the skin were decolonized. Additionally, decolonization was found to be effective against both MRSA and MSSA SSIs. One of the larger RCTs included in that meta-analysis was performed in the Netherlands, which experiences very little MRSA (149). That study used PCR to rapidly identify *S. aureus* carriers and randomized 918 carriers to either placebo or nasal mupirocin and CHG soap. It 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 ($P = 0.005$) (151).

Studies that found a protective effect against SSIs used nasal mupirocin twice daily for 3 to 5 days prior to surgery and CHG bathing once daily for 2 to 5 days prior to surgery (56, 152, 153). If a patient was unable to complete the decolonization regimen before surgery, the studies also recommended continuing nasal decolonization during the postoperative period but discontinuing the CHG postoperatively (152, 153).

A 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 (152).

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. 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). This significant decline was also seen when the study was limited to only patients undergoing hip and knee arthroplasty (rate ratio = 0.48; 95% CI, 0.29 to 0.80), but it was not statistically significant when the study was limited to only patients undergoing cardiac surgery (rate ratio = 0.86; 95% CI, 0.47 to 1.57). However, the number of cardiac surgery patients was much smaller than the number of orthopedic surgery patients, so the cardiac analysis may have been underpowered.

A study performed in Ireland evaluated whether cardiac surgery should be delayed until MRSA-colonized patients were fully decolonized (154). In this study, elective surgery patients were screened for MRSA colonization in the preoperative clinic, and if they were positive, the surgery was delayed until a decolonization regimen was completed. Urgent surgery patients were screened for MRSA when they were admitted to the hospital, but their surgery was not delayed. Rather, the decolonization regimen was implemented for MRSA-colonized patients postoperatively. This study found that the decolonization regimen was associated with fewer MRSA infections among patients who received preoperative decolonization. The authors recommended that when clinical urgency permits, surgery should be delayed in order to implement the decolonization regimen, particularly prior to operations that include implantation of prosthetic material (e.g., valve replacement) or among diabetic patients. However, they also concluded that they do not support risking cardiac death by delaying urgent surgery.

A meta-analysis by Kallen et al. aimed to determine whether intranasal mupirocin decolonization could prevent SSIs caused by any pathogen (42). 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. The recent Society for Healthcare Epidemiology of America compendium of strategies to prevent SSIs stated that screening for *S. aureus* and decolonization with agents such as mupirocin could be done as a special approach when basic approaches are not enough, especially among patients undergoing some orthopedic and cardiothoracic procedures (155).

ECONOMIC VIABILITY

Currently, evaluations of the cost-effectiveness of horizontal and vertical decolonization interventions have been limited. A series of economic computer models found that screening and nasal decolonization are cost-effective in some patient populations but not others. Murthy et al. (156) evaluated a bundled intervention that included PCR screening for MRSA prior to surgery, decolonization of patients positive for MRSA with mupirocin and CHG, and contact isolation for MRSA-positive patients. They found that this was not strongly cost-effective, meaning that the costs avoided through reducing MRSA infections did not offset the costs of screening. However, this model was based on data from a hospital in Geneva, which may have lower rates of MRSA colonization than U.S. hospitals. Conversely, using data inputs from the United States, multiple studies found that MRSA screening and decolonization prior to cardiac, vascular, or orthopedic surgery or heart-lung transplant was cost-effective from the third-party payer perspective and the hospital perspective (50, 157–161). However, Lee et al., found that screening and decolonization of pregnant women prior to cesarean delivery were not cost-effective (162).

Additionally, other economic models have found MRSA screening and decolonization to be cost-effective among hemodialysis patients, ICU patients, and all hospitalized patients (163–167). Two different studies performed cost analyses of universal decolonization in the ICU setting and found it to be cost-effective (167, 168). One economic model compared seven different strategies to prevent MRSA transmission and infection in ICUs and found that the strategies that included decolonization were less expensive and more effective than other strategies (165).

UNIVERSAL DECOLONIZATION VERSUS TARGETED DECOLONIZATION

Currently, there is debate as to whether decolonization regimens should be performed only among patients who are colonized with pathogens that are sensitive to the decolonizing agents (e.g., *S. aureus*) or whether all high-risk patients should receive decolonizing agents without being screened for colonization. Universal decolonization, i.e., decolonizing all high-risk patients regardless of colonization status, requires health care workers only to provide the decolonizing agents to the patients without the labor of screening. Targeted decolonization requires the collection of a screening swab and laboratory testing before decolonization. This usually entails nasal screening for *S. aureus* colonization. Targeted decolonization is considered by some to be the preferred standard because antimicrobial agents would be used only in patients who need them, which may prevent antimicrobial resistance. However, this strategy would not identify patients who are *S. aureus* colonized at extranasal body sites, would not decolonize patients with false-negative results, and would not decolonize patients who are colonized with other pathogens such as Gram-negative organisms, yeasts, and the skin commensal organism CNS.

Depending on the patient populations, different laboratory tests may be appropriate for screening. If fast results are needed, real-time PCR can be used to test nasal swabs for both MRSA and MSSA within 1 h (169). However, PCR is more costly than both chromogenic agar (test time is at least 1 to 2 days) (170) and standard culture (test time is approximately 2 to 3 days) (171). Fast results may be needed in the preoperative clinic so that patients can be sent home with mupirocin and CHG as needed and these decolonizing agents can be used prior to surgery. Slower methods could be used for other patient populations who have frequent contact with the health care system and longer periods of time at risk and thus could obtain their decolonizing agents at their next health care visit (e.g., dialysis patients). However, any

type of screening is likely to be more expensive and certainly utilizes more health care worker time than universal decolonization (160, 161, 165).

Meta-analyses of decolonization studies among surgical and nonsurgical populations found that universal and targeted decolonization strategies resulted in similar protection against *S. aureus* infections (38, 44). The only multicenter study that compared universal and targeted decolonization head-to-head found that in the ICU, universal decolonization was more successful than targeted decolonization at reducing the number of BSIs caused by any pathogen, including Gram-positive skin commensal organisms, Gram-positive noncommensal organisms, Gram-negative organisms, and *Candida* species. There was not a significant difference in the reduction of MRSA BSIs between the universal and targeted decolonization groups; however, there was a trend toward a larger reduction among the universal decolonization group (40). Similarly, a study that evaluated universal CHG bathing in ICUs found that universal decolonization led to a decline in both VRE and MRSA acquisition and BSIs caused by any pathogen (e.g., staphylococci, enterococci, Gram-negative bacilli, and fungi) (26). Thus, universal decolonization is effective at reducing the total number of positive cultures, including those that may be due to contamination.

Universal decolonization can dilute the effects of the decolonization regimen. One RCT screened patients preoperatively for *S. aureus* nasal carriage but then nasally treated all patients with mupirocin or placebo before the nasal culture results were known. That study did not show a significant decline in overall infections after surgery but did show a significant decline in infections among those who were *S. aureus* colonized (56).

The patient population must also be factored into the decision of targeted versus universal decolonization. Universal decolonization may be preferred in ICU settings, in which there is concern over both endogenous infection and exogenous patient-to-patient transmission. In the ICU setting, missed colonization sites or false-negative tests could result in the spread of pathogens from one patient to another. Conversely, targeted decolonization may be preferred for preoperative and dialysis settings, where endogenous infections are the main concern. There are even differences in the preoperative setting. Targeted decolonization may be feasible for elective procedures but not for urgent procedures such as emergency coronary artery bypass graft. A compromise between the two types of decolonization prior to surgery would be to attempt targeted decolonization with the knowledge that some patients will be missed (e.g., those undergoing urgent or emergent procedures). Then, if a patient presented to surgery with unknown results, an informed decision could be made based on colonization rates in the community or in that surgical population to determine whether that patient could be treated as colonized. Those patients could receive a dose of mupirocin and a CHG bath prior to surgery and finish the 3 to 5 days of mupirocin after surgery (153).

The primary concern regarding universal decolonization is the emergence of resistance to the decolonizing agents. Most studies of short-term use have not seen significant emergence of mupirocin or CHG resistance (172). However, increased use of decolonizing agents could lead to selection for resistant strains. One study found that patients with persistent *S. aureus* carriage after decolonization were statistically more likely to be *S. aureus* colonized with isolates with combined LL-MR and chlorhexidine resistance before decolonization than patients who were successfully decolonized (173). Another study showed that decolonization with chlorhexidine in the ICU led to selection of a nonepidemic MRSA strain (ST239) that had reduced susceptibilities to chlorhexidine (174).

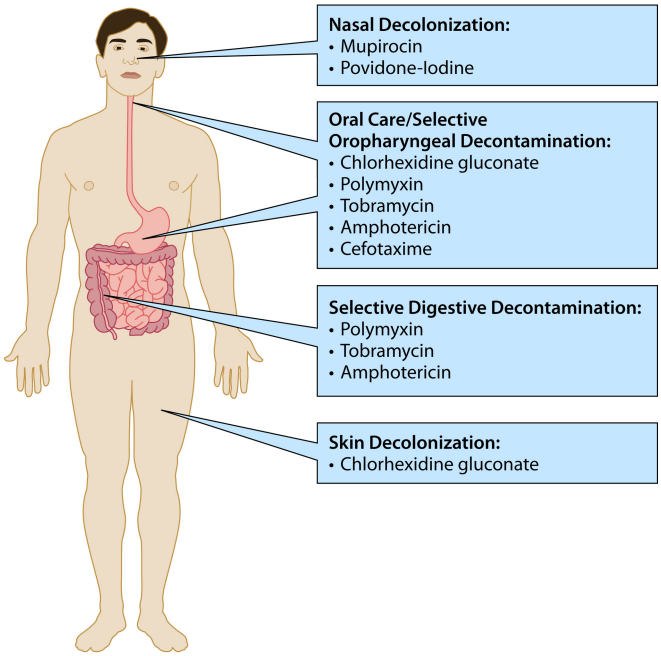

FIG 1 Recognized decolonization strategies to prevent health care-associated infections.

There is also the concern that providing mupirocin and CHG to patients who are not colonized with *S. aureus* could lead to selection for other pathogens with resistance genes against those agents. Although there have been only a few isolated examples in which the use of these antimicrobials has promoted the spread of extremely drug-resistant organisms (e.g., extremely drug-resistant strains of *Klebsiella pneumoniae* classified as ST258), this is still cause for concern (175). Additionally, the resistance genes in other pathogens (e.g., CNS) could horizontally transfer from those pathogens to *S. aureus* at a later time, leading to resistance in *S. aureus* (176).

CONCLUSIONS

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 (28). The majority of these health care-associated infections may be preventable by evidence-based interventions. Based on the evidence described here, decolonization is one such intervention that can reduce rates of health care-associated infections.

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 products (Fig. 1). Mupirocin still remains the gold standard agent for nasal decolonization of *S. aureus*, but there is concern about mupirocin resistance, and alternative agents are needed. The most promising new agents for nasal decolonization are retapamulin, povidone-iodine, and alcohol-based nasal antiseptics.

Chlorhexidine gluconate (CHG) is the skin decolonization agent that has the strongest evidence base. CHG skin decolonization is an effective horizontal strategy to reduce both the biobur-

den on the skin and subsequent infection. However, with widespread use, we need to monitor for the incidence of chlorhexidine resistance. There is evidence that oral chlorhexidine is effective at reducing respiratory infections among cardiac surgery patients, but larger trials need to be done in noncardiac patients to determine the usefulness of this strategy.

Orally administered systemic decolonizing agents, such as oral rifampin, may be acceptable for extranasal decolonization of *S. aureus*, but it is currently unknown whether systemic oral decolonization is more efficacious than topical decolonization for removing *S. aureus*. There is also evidence to support decolonization with SDD and SOD, but more studies are needed to assess the collateral damage from this strategy, particularly the selection for drug resistance in Gram-negative organisms.

The strongest evidence for decolonization is among surgical patients in order to prevent SSIs. The populations that may benefit the most are patients undergoing cardiac and orthopedic surgery. According to recent recommendations, decolonization prior to surgery is considered to be a special approach to prevent SSIs (155). Thus, it should be strongly considered based on the local epidemiology of each institution. Acute short-term use of decolonizing agents, such as prior to surgery, is recommended in order to avoid adverse outcomes such as recolonization and resistance. Resistance to both mupirocin and chlorhexidine has been seen when they are used over a long time period.

There have been only a few multicenter, randomized trials evaluating decolonization. Of the few that exist, even fewer have compared decolonizing agents head-to-head to determine the superiority of an agent or a decolonizing protocol. Most studies use simple before-after quasi-experimental study designs that rely on historical control groups. That study design may lead to biased results due to regression to the mean, secular trends, or seasonal effects. Future research in this field should include large trials evaluating decolonizing agents in other patient populations such as patients in ICUs and long-term-care facilities, using standardized methods to measure both colonization and decolonization. Large randomized trials should also compare newer decolonizing agents head-to-head against currently used agents.

ACKNOWLEDGMENTS

E.J.S. is currently conducting a trial in which participating hospitals are receiving products contributed by Mölnlycke Health Care and Sage Products; however, the manufacturers had no part in the design or implementation of the trials.

M.L.S. received support under CDA 11-211 from the VA.

The opinions expressed in this document are those of the authors and do not reflect the official position of the U.S. Department of Veterans Affairs.

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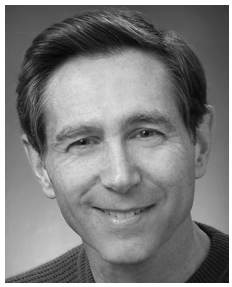

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