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SKIN, SOFT TISSUE, BONE AND JOINT INFECTIOUS DISEASE (N SAFDAR AND A POP-VICAS, SECTION EDITORS)

Prevention Strategies for Recurrent Community-Associated *Staphylococcus aureus* Skin and Soft Tissue Infections

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Abstract

Purpose of Review *Staphylococcus aureus* skin and soft tissue infections (SSTI) are a major source of morbidity. More than half of patients experiencing SSTI will have at least one recurrent infection. These infections frequently cluster in households. Given the burden these infections pose to patients and healthcare, prevention strategies are of major clinical importance and represent an active area of research. Bacterial colonization is frequently an early and critical step in the pathogenesis of infection. As such, strategies to prevent reinfection have aimed to decrease staphylococcal colonization of the skin and mucus membranes, a process referred to as decolonization.

Recent Findings Treatment of acute SSTI with incision and drainage and systemic antibiotics is the mainstay of therapy for healing of the acute infection. Systemic antibiotics also provide benefit through reduced incidence of recurrent SSTI. Education for patients and families regarding optimization of personal and household hygiene measures, and avoidance of sharing personal hygiene items, is an essential component in prevention efforts. For patients experiencing recurrent SSTI, or in households in which multiple members have experienced SSTI, decolonization should be recommended for all household members. A recommended decolonization regimen includes application of intranasal mupirocin and antiseptic body washes with chlorhexidine or dilute bleach water baths. For patients who continue to experience recurrent SSTI, periodic decolonization should be considered.

Summary Personal decolonization with topical antimicrobials and antiseptics reduces the incidence of recurrent *S. aureus* SSTI. Future avenues for investigation include strategies for household environmental decontamination as well as manipulation of the host microbiota.

Keywords *Staphylococcus aureus* · Methicillin-resistant *Staphylococcus aureus* · Skin and soft tissue infection · Prevention · Decolonization

Introduction

Skin and soft tissue infections (SSTI) are common events in both adults and children, occurring with an annual incidence of approximately 48 per 1000 persons in the USA [1]. SSTI is a generic term which can be applied to a wide variety of skin infections including impetigo, folliculitis, cellulitis, and cutaneous abscesses. While abscesses and cellulitis comprise the bulk of infections in most reports [1, 2], and will be the focus of this review, it is likely that more minor infections go unreported. Although SSTIs may be caused by a number of organisms, the etiologic agent for the vast majority is *Staphylococcus aureus*, accounting for > 70% of cases in some studies [3••]. The emergence of community-associated methicillin-resistant *S. aureus* (CA-MRSA) in the late 1990s and early 2000s necessitated a shift in empiric antimicrobial decisions for SSTI in many institutions. Notably, by the mid-2000s, some centers were reporting that up to 75% of CA-*S. aureus* infections were MRSA [4, 5]. In the USA, the increase in CA-MRSA was largely attributable to the increased prevalence of the USA300 clone [5, 6]. These changes in

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microbiology and epidemiology were also associated with an increase in severe invasive disease attributable to CA-MRSA including necrotizing pneumonia, severe sepsis, and osteoarticular infections [4, 7].

Microbial colonization is defined as the survival of a microorganism on the surface of or within a host without causing clinical disease. *S. aureus* colonizes the anterior nares, pharynx, rectum, and skin (particularly in the axillae, inguinal folds, and perineum) [8, 9•, 10]. Colonization is an established risk factor for subsequent infection [2, 11, 12•]. Specifically, colonization with *S. aureus* (in particular MRSA) is associated with an 8–12-fold increased risk of subsequent infection [8, 12•, 13]. Moreover, Von Eiff reported that among adults with *S. aureus* bacteremia, 82% were colonized in the nares with an identical strain [14]. Importantly, the epidemiology of, and risk factors for, both *S. aureus* (and MRSA) infection and colonization are quite similar. Notably, *S. aureus* colonization may be intermittent or persistent [8, 15]. *S. aureus* colonization may be influenced by patient age as well as race/ethnicity, socioeconomic strata, and comorbidities. Specifically, school age children (6–11 years old) have been reported to have a higher incidence of *S. aureus* colonization compared to adolescents, adults, or even younger children [16]. Likewise, children are disproportionately affected by *S. aureus*/MRSA SSTI compared to adults [17, 18]. In addition, MRSA colonization and SSTI are more common among those with certain immunocompromising conditions (e.g., HIV, end-stage renal disease, diabetes mellitus) or with compromised skin integrity (e.g., injection drug users and those with chronic dermatologic conditions), athletes who participate in contact sports, and those who live in close confines (e.g., military recruits and prisoners) [2, 12•, 18–22].

Epidemiology of Recurrent *S. aureus* SSTI

Among those patients with a primary (i.e., first occurrence of) SSTI, the likelihood of developing a recurrent SSTI has varied in the literature ranging from 20 to 70% [23, 24, 25•, 26, 27, 28, 29•]; MRSA infections are particularly likely to recur. The risk factors for recurrent SSTI are similar to those associated with the development of a primary SSTI. In patients with underlying conditions which predispose to SSTI, poor control of the chronic disease (such as poorly controlled eczema or a high viral load in the setting of HIV infection) is likely associated with recurrent infection [30, 31]. As stated above, persons with chronic dermatologic conditions (e.g., atopic dermatitis) are particularly susceptible to frequent skin infections. In addition, recurrent skin infections themselves may also be a warning sign of an immunocompromising condition, particularly those involving granulocytes and/or T or NK cells (such as Hyper IgE Syndrome). With these caveats being stated, however, the vast majority of persons with recurrent *S. aureus* SSTI are immunocompetent [32].

It is well established that clusters of *S. aureus*/MRSA SSTIs may occur within households [2, 9, 33, 34]. Given the intermittent nature of *S. aureus* colonization and the intimate proximity of persons within household units, it is conceivable that family members may "pass" *S. aureus* to one another following a period of eradication after treatment. In this way, colonized household members may serve as a reservoir for recurrent *S. aureus* infections [35, 36].

Decline in CA-MRSA Incidence While the incidence of CA-MRSA SSTI dramatically rose in the early 2000s, recent studies among both adult and pediatric populations in the USA have reported substantial changes in the proportion of *S. aureus* isolates that are methicillin-resistant [37, 38]. Sutter reported data from the Military Health System which illustrated that, following a peak in 2007 (at 46.4%), the proportion of all *S. aureus* that were MRSA declined to 31.6% by 2014 [39•]. Similarly, a study by Acree et al., investigating the antimicrobial susceptibility and incidence of *S. aureus* skin infections in Chicago from 2006 to 2014 [38], revealed a decrease in MRSA SSTI incidence in both adults and children, with a concomitant increase in methicillin-susceptible *S. aureus* (MSSA, by + 1.9%/year) during the study period. Interestingly, a large proportion of these recently recovered MSSA strains possess the USA300 genetic background present in the predominant CA-MRSA clone circulating during the previous decade [37, 40, 41]. While these shifts in antimicrobial susceptibility are important for choosing an appropriate empiric therapy, the principles of management for recurrent skin infections are likely the same in MRSA and MSSA SSTI.

The Role of the Environment and Pets in Recurrent SSTI

S. aureus can survive on environmental surfaces for prolonged periods of time [42]. Recent household investigations of patients with CA-MRSA infections have revealed a high burden of *S. aureus* environmental surface contamination (ranging from 24 to 64% of surfaces sampled), particularly with a strain concordant with the index patient's infecting isolate [43–46]. Surfaces most frequently contaminated are those which come into direct contact with the infected patient (e.g., bed linens) and those handled by multiple household members, some of which are not likely to be cleaned frequently, such as the television remote control, telephone, toys, and computer keyboard/mouse. This environmental *S. aureus* contamination persists over time, serving as a reservoir for transmission between household members [47]. Moreover, household environmental contamination also poses risk for recurrent

infection [44, 47]. A study by Knox et al. revealed that index patients with CA-MRSA infections living in a household in which environmental contamination with a strain concordant with the index patient's infecting strain was detected, had a 2-fold higher rate of recurrent infection than those living in a household without environmental contamination. However, environmental contamination may impart a lower risk of infection for other family members lacking a history of SSTI, as the incidence of interval infections did not differ between non-index household members living in households with or without environmental contamination [43]. Thus, environmental contamination is but one factor in the complex pathogenesis and transmission of staphylococcal SSTI, and an important avenue for future research (e.g., environmental household surface decontamination to prevent subsequent infections) [48].

The role of pets in SSTI recurrence in humans, and the directionality of transmission between humans and pets, is unclear. In households of patients with persistent *S. aureus* colonization or infection, *S. aureus* carriage has been detected in pets. Transmission has also been noted between companion animals and veterinary personnel [49–55]. It has been proposed that pets are passive carriers of *S. aureus*, rather than natural hosts, and while they may serve as reservoirs for transmission, their carriage often resolves spontaneously [56–58]. The World Association for Veterinary Dermatology has provided strategies to potentially reduce transmission between humans and their pets, including hand hygiene before and after contact with pets, temporarily isolating the pet from a patient with active infection until antibiotic treatment has been initiated and clinical response begins, and washing the pet bedding and disinfecting kennels or crates during decolonization of the household members (see below) [57, 59].

The Impact of Acute Management of SSTI on Incidence of Recurrent SSTI

The Infectious Diseases Society of America (IDSA) published Clinical Practice Guidelines for the Treatment of MRSA Infections in 2011 [60] which state that incision and drainage is the mainstay of treatment for purulent SSTI, while the role of systemic antibiotics in the treatment of uncomplicated skin abscesses is unclear. Since the publication of these guidelines, several large, multicenter trials have been published demonstrating definitive benefit of systemic antibiotic therapy in SSTI management, in conjunction with incision and drainage, regardless of abscess size [3, 61••, 62]. In a five-center clinical trial conducted by Daum et al., 786 patients with limited skin abscesses (≤ 5 cm) were randomized to receive clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), or placebo for 10 days, in conjunction with abscess incision and drainage. At the test of cure visit, occurring 7–10 days after completion of the study medication, patients receiving clindamycin (83.1%) or TMP-SMX (81.7%) were significantly more likely to achieve clinical cure compared to patients in the placebo group (68.9%); no significant difference was noted between the clindamycin and TMP-SMX groups [3]. Additionally, a multicenter randomized clinical trial enrolling 1247 patients with uncomplicated skin abscess conducted by Talan et al., demonstrated that, in conjunction with incision and drainage, patients receiving TMP-SMX for 7 days were significantly more likely to achieve clinical cure (80.5%) than patients randomized to placebo (73.6%) [61••]. Importantly, in addition to improving cure rates for the acute infection, both of these trials demonstrated a significantly reduced incidence of recurrent SSTI in patients receiving systemic antibiotics [3, 61••]. A retrospective study by Hogan et al. investigated the mechanism driving the reduced incidence of recurrent SSTI in patients receiving systemic antibiotics [63]. This study demonstrated that, in pediatric patients with *S. aureus* SSTI and concurrent *S. aureus* colonization, those who received IDSA guideline-recommended systemic antibiotics [60] were significantly less likely to remain colonized at follow-up sampling 1 month after antibiotic administration (48%) compared to those who did not receive systemic antibiotics (77%, $p = 0.004$). Further, those subjects who remained colonized with *S. aureus*, in either group, were more likely to develop recurrent SSTI over 1 year (57%) compared to those from whom *S. aureus* had been eradicated (30%, $p < 0.001$). Ultimately, incision and drainage of purulent collections remains a critical aspect of SSTI management, which in combination with systemic antimicrobials, yields optimal clinical outcomes.

Wound Care and Hygiene Education

Basic wound care is essential for patients with SSTI to prevent spread of infection to others and/or the development of new lesions in the affected patient [60]. Importantly, patients and their families should be educated about the transmission of *S. aureus*, namely that it occurs through direct contact with infected tissues and/or colonized skin/mucus membranes. Given that patients are commonly colonized in the nose and/or pharynx, touching the nose, mouth, or face may serve to promote spread of *S. aureus*. Patients should be encouraged to engage in frequent hand hygiene with soap and water, or alcohol-based sanitizers, as well as regular daily bathing. The value of such simple hygiene practices was underscored in a recent study which revealed that bathing/showering at least once daily and the use of antibacterial soaps were each independently associated with reduced prevalence of MRSA colonization [64•]. In addition, many experts recommend avoidance of the sharing of personal hygiene items such as razors, towels, deodorant, or other items that come in direct contact with skin [60]. Additional interventions which may be helpful include the use of liquid soaps (rather than bars of

soap), trimming fingernails, and washing towels/washcloths, underwear, and sleepwear/pajamas after each use [24, 25•, 29••, 60].

Decolonization with Topical Antimicrobials/Biocides

As described above, *S. aureus* (and specifically, MRSA) is a common colonizer of the skin, nasopharynx, and rectum, and colonization frequently precedes infection. Moreover, it is established that individuals who experience persistent/intermittent staphylococcal colonization are frequently colonized by the same strain type over time. Similarly, patients with recurrent infection are often reinfected with the same strain of *S. aureus* [36, 65, 66]. Thus, it is conceivable that eliminating, or at least decreasing the burden of staphylococcal colonization, may interrupt the cycle of recurrent infection. Much research and clinical practice has been devoted to the application of intranasal or topical antimicrobials to achieve this goal, often referred to as decolonization. Although the majority of literature and efforts in this regard have focused on the prevention of healthcare-associated infections (HAIs), many have attempted to extrapolate these practices to the community setting for the prevention of recurrent SSTI. Studies addressing these questions, however, have been quite variable in design, treatment regimens, and outcomes (colonization vs. SSTI, duration of follow-up, etc.) making formulation of specific management recommendations challenging.

The Questions of Decolonization: "Who? Where? When? How many? How often?"

When considering decolonization for SSTI prevention, the first clinical question to address is "Who should undergo decolonization?" While reinfection/recurrent infection is common after a primary SSTI, many patients are cured after incision and drainage and/or antimicrobial therapy. The IDSA clinical practice guidelines for the management of MRSA infections suggest that decolonization may be considered for patients with recurrent MRSA SSTI and/or households with suspected ongoing transmission following optimization of wound care and hygienic measures [60]. Given the rise in MSSA SSTI incidence over the past decade, one may generalize these recommendations to cases of recurrent MSSA SSTI as well.

Additionally, the administration of the decolonization protocol to all household members should be considered. A randomized trial of 183 households of children with CA-*S. aureus* SSTI compared the effectiveness of decolonization of the index patient alone to decolonization of the entire household for *S. aureus* eradication and preventing subsequent SSTI. In this study, the decolonization regimen consisted of twice daily intranasal mupirocin and daily 4% chlorhexidine gluconate body washes, both administered for 5 days (both of these agents will be discussed in more detail below). The household decolonization group experienced a lower incidence of SSTI in both the index patient and household members compared to those randomized to index decolonization only over 12 month follow-up [29••]. Such data adds credence to the hypothesis of household members serving as reservoirs of *S. aureus* and contributing to reinfection. Despite the potential effectiveness of such measures, one obvious challenge with such an approach is the burden placed on all household members by aggressive hygiene/decolonization interventions and concerns regarding compliance. In one multicenter study, 223 households of adult and pediatric patients with acute SSTI were randomized into one of the three arms: (1) hygiene education, (2) hygiene education plus decolonization, and (3) hygiene education plus decolonization with daily telephone reminders regarding the study [67]. The decolonization regimen consisted of twice daily mupirocin for 7 days and chlorhexidine body wash on days 1 and 7. Overall, there was a very low incidence of infections during the study; no statistically significant benefit was observed with household decolonization compared to household hygiene education in terms of prevalence of colonization at follow-up samplings (a secondary outcome in this study). Notably, however, only 26% of households reported 100% compliance with the study protocol and only 56% had ≥ 50% compliance, suggesting the practical challenges of the "whole family" approach. Additional unanswered or incompletely answered questions regarding this subject include (1) whether administration of the decolonization protocol to all household members is necessary or if it should only be administered to contacts who are themselves colonized or who have had recent infections (a topic of a currently ongoing study [68]); (2) when, or how often, the protocol should be implemented (i.e., single applications, weekly application, monthly application, etc.); and (3) whether the household decolonization approach is more effective in households with children compared to those comprised solely of adults.

Decolonization: "With What?"

The next major clinical questions in this line of thinking regard the choice of agents to be used for decolonization. Most research in this area, as well as most clinical practice, utilizes a combination of an intranasal antimicrobial as well as a topical biocide agent along with optimization of hygiene practices. A

number of agents which may be considered for decolonization are discussed in detail below (Table 1).

Intranasal Mupirocin

Mupirocin is a topical antimicrobial agent with activity against a number of Gram-positive organisms. Mupirocin inhibits bacterial protein synthesis through a unique mechanism involving inhibition of the isoleucyl-tRNA synthetase. Mupirocin is approved for the management of minor *S. aureus* soft tissue infections and is widely used intranasally for MRSA/*S. aureus* decolonization. Intranasal mupirocin is commonly used in the hospital setting to prevent infection (especially surgical site infections [SSI] and central line associated bloodstream infections) among those with *S. aureus*/MRSA colonization. Most studies regarding intranasal mupirocin have evaluated the benefits of this agent as part of an infection prevention bundle in hospitalized patients along with hygienic interventions and antimicrobial body washes [69–71]. In one small trial, the use of mupirocin ointment intranasally alone for 5 days each month was compared with placebo for decolonization and SSTI prevention in the community setting. Mupirocin use was associated with a reduction in both *S. aureus* colonization and skin infections compared to placebo ointment over 1 year [72]. A number of other trials for SSTI prevention and/or decolonization have illustrated benefits of mupirocin use concomitantly with other measures to reduce SSTI incidence, albeit the benefits are likely impacted by the specific population under study [24, 29••, 73, 74]. Based in part on these data, the IDSA guidelines suggest that a 5–10-day course of twice daily nasal mupirocin with or without antimicrobial body washes (see below) may be considered in patients with recurrent MRSA SSTIs following optimization of wound care and hygiene [60].

Intranasal Retapamulin

Retapamulin is a topical semisynthetic pleuromutilin derivative approved for the treatment of minor skin and soft tissue infections secondary to MSSA or group A *Streptococcus*. Retapamulin has a distinct mechanism of action from that of mupirocin, acting on the 50s ribosomal subunit, and thus offers a theoretical advantage in the cases of mupirocin resistance or failure. Moreover, given their distinct mechanisms of action, co-resistance to both retapamulin and mupirocin is relatively uncommon in *S. aureus*. In a study conducted in a population with a high baseline prevalence of mupirocin-resistant *S. aureus*, only 2% of 400 isolates exhibited in vitro resistance to both mupirocin and retapamulin [75•]. In principle, retapamulin may be effective when used for nasal decolonization. A phase 1/2A placebo-controlled clinical trial assessed the impact of either a 3- or 5-day course of intranasal retapamulin on *S. aureus* colonization; both regimens were superior to placebo for decolonization at the 28-day endpoint [76]. Another clinical trial attempted to assess the efficacy of nasal retapamulin compared to placebo for the eradication of colonization with MRSA strains resistant to mupirocin in adults [77]. Unfortunately due to poor enrollment ($n = 53$), largely the result of the strict requirement for mupirocin-resistant MRSA colonization, the study was closed prior to achieving targeted enrollment, though the investigators reported no adverse events with intranasal retapamulin. There are no published studies which evaluate the efficacy of intranasal retapamulin for prevention of SSTIs. Thus, further research is needed to understand the role of retapamulin in the management of recurrent SSTIs and/or MRSA decolonization.

Intranasal Iodophor

The use of povidone-iodine (PI) has been a long-standing approach for skin disinfection prior to invasive procedures. Given its broad spectrum of antimicrobial activity, interest exists in the application of intranasal PI for decolonization. The majority of literature surrounding this subject has examined the perioperative application of intranasal PI to diminish colonization, with an ultimate goal of reducing SSI. There are no published studies utilizing this agent to reduce SSTI in the community setting. The employment of infection prevention bundles which include intranasal PI has been associated with a reduced incidence of SSI in orthopedic patients [78]. In one open-label trial [79], patients were randomized to either 5 days of twice daily nasal mupirocin or two applications of 5% nasal PI 2 hours prior to surgery; patients in both groups also underwent chlorhexidine bathing. Colonization cultures were obtained preoperatively and 1–2 days postoperatively. Notably, the incidence of SSI was substantially reduced in the PI group; however, this group was also more likely to have persistent *S. aureus* colonization postoperatively. Given the substantial differences in how these agents were applied (twice daily for 5 days vs. 2 doses preoperatively), interpretation of these results is challenging. Peng et al. evaluated the efficacy of intranasal PI for *S. aureus* nasal decolonization in adults undergoing elective orthopedic surgery [80]. Patients identified as *S. aureus* carriers were given intranasal PI twice daily for 5 days prior to surgery and were rescreened on the day of surgery. These investigators noted that *S. aureus* was successfully eradicated from 95% of patients using this regimen; however, no long-term follow-up data were reported, nor was a comparator group used. Further study is necessary before recommendations can be made regarding the role of intranasal PI for decolonization in the community setting.

Table 1 Summary of antimicrobial and antiseptic agents studied for decolonization

Agent	Class of antimicrobial	Mechanism of action	Published uses	Recommended administration for decolonization /prevention of SSTI
Mupirocin	Unique, derived from *Pseudomonas fluorescens*	Bacteriostatic	Topical administration for minor SSTI	Administered intranasally twice daily for 5–10 days, may be repeated monthly in patients with recurrent SSTI
		Inhibition of isoleucyl-tRNA synthetase	Intranasal administration for decolonization and prevention of HAI and SSTI	
Retapamulin	Pleuromutilin	Bacteriostatic	Topical administration for minor SSTI due to MSSA and group A *Streptococcus*	Consider use for intranasal decolonization in patients failing mupirocin-based decolonization regimens
		Protein synthesis inhibition, inhibition of 50s ribosomal subunit	Single study suggesting efficacy for staphylococcal decolonization vs. placebo	
Povidone-iodine (PI)	Iodophor	Bactericidal	Extensive experience for topical disinfection prior to invasive procedures	Data insufficient to recommend intranasal iodophor preparations for prevention of SSTI at this time
		Forms complexes with microbial proteins, DNA, cell membranes	One clinical trial suggesting possible efficacy of intranasal PI for prevention of SSI	
			Quasi-experimental studies suggesting benefits at reducing intranasal colonization in surgery patients	
Ethanol-containing preparations	Alcohol-based cleanser	Bactericidal	Extensive experience for topical disinfection prior to venipuncture	Data insufficient to recommend intranasal ethanol preparations for prevention of SSTI at this time
		Disruption of cell membrane, protein denaturation	Extensive data supporting benefits of alcohol-based hand hygiene	
			Single trial suggesting that intranasal alcohol may be beneficial for nasal decolonization	
Chlorhexidine gluconate (CHG)	Biguanide antiseptic	Bactericidal	Extensive experience for topical disinfection prior to invasive procedures, supported by national guidelines	Apply to body directly starting below the jaw, rinse with tap water and then bath as per routine for prevention of SSTI
		Disruption of cell wall, cell membrane, membrane potential	Numerous studies (clinical trials, quasi-experimental, observational) support use of CHG as part of bundle to prevent HAI, guidelines endorse	Can be repeated twice a week if SSTIs recur
			Observational and clinical trials support use for *S. aureus* decolonization in community setting	Avoid use of CHG and bleach together
			Clinical trials utilizing CHG along with hygiene intervention +/− mupirocin have been conflicting with regard to efficacy at SSTI prevention	
Sodium hypochlorite (bleach)	Chlorine-based disinfectant	Bactericidal	Extensive experience with sodium hypochlorite for surface disinfection in hospital and community settings	Bleach baths can be considered along with intranasal antimicrobials in efforts to reduce *S. aureus* colonization and/or prevent SSTI
		Protein denaturation, membrane disruption	Observational studies as well as clinical trials suggest that sodium hypochlorite may be beneficial at mitigating flares/bacterial colonization in patients with eczema	The following regimen is recommended: 1 teaspoon (5 ml) of bleach per gallon of bath water (or ¼ cup per ¼ tub of water). The patient should soak in the bath for 15 min twice weekly
			Clinical trials suggest bleach baths may be helpful at decreasing *S. aureus* colonization	
			Large clinical trial of bleach baths failed to demonstrate a benefit for prevention of medically attended SSTI	

SSTI skin and soft tissue infection, *HAI* healthcare-associated infections, *MSSA* methicillin-sensitive *Staphylococcus aureus*

Intranasal Alcohol

Hand hygiene is the cornerstone of any infection prevention initiative; most studies suggest that alcohol-based hand antisepsis is superior to traditional soap-and-water washing in reducing bacterial burden on hands [81]. Moreover, alcohol-based hand rub dispensers have become prevalent in many institutions and have eliminated many barriers to good hand hygiene (such as limited access to sinks and perceived reduction in efficiency) [82, 83]. It is also conceivable that such alcohol-based preparations may have a role in decreasing staphylococcal colonization and subsequent SSTI, though data are limited. One randomized double-blind controlled trial conducted at a South Carolina hospital attempted to address the role of such agents in nasal decolonization [84]. Healthcare workers with *S. aureus* nasal colonization were randomized to apply either an alcohol-soaked nasal swab or a placebo-soaked swab at the time of starting their daily shift, at + 4 hours (h). and + 8 h. Subjects were screened for nasal colonization with quantitative cultures prior to the start of their shift and 10 h later (after the end of their shift). The alcohol preparation included 70% ethanol along with emollients and benzalkonium chloride (which is notably a quaternary ammonium compound antiseptic); the placebo consisted of sterile phosphate-buffered saline along with 0.017% peppermint oil to mask the smell. The group applying the alcohol nasal preparation experienced substantial reductions in *S. aureus*, as well as overall bacterial colony counts, compared to the placebo group. Further study is needed to better understand the role of nasal alcohol preparations in infection prevention efforts.

Chlorhexidine Gluconate Body Washes

Chlorhexidine gluconate (CHG) is a biguanide antiseptic that non-specifically disrupts the bacterial cell wall and interferes with cellular membrane potential [85]. CHG body washes, oral rinses, skin antisepsis, and central line care decrease the colonization burden with bacterial pathogens, as well as minimize the likelihood of exogenous pathogens coming into contact with patients. In turn, these practices decrease rates of HAIs in adults as well as specifically rates of bacteremia and surgical site infections in children [86–91]. Notably numerous different CHG-containing products/preparations exist including body washes available over the counter, oral rinses, and impregnated washcloths. Given the success with the use of this agent in bundle approaches at HAI reduction, as well as CHG's in vitro activity against *S. aureus*, many have used this agent for decolonization of the skin and prevention of SSTI. While a number of studies have illustrated the effectiveness of CHG for decolonization in the community setting, results regarding the efficacy for the prevention of SSTIs have been conflicting (in part likely related to heterogeneity in study design). Ellis et al. [92••] conducted a large, three-arm randomized controlled trial of > 30,000 subjects, comparing hygiene education vs. enhanced hygiene interventions vs. hygiene interventions with weekly CHG bathes among military recruits (a particularly high-risk population). While the investigators found no statistically significant reduction in MRSA SSTI or overall SSTI incidence between intervention groups, the incidence of purulent SSTI of any etiology was significantly reduced in the group receiving CHG. Concerns were raised by the investigators, however, regarding adherence to assigned treatment regimens which may have resulted in potential bias. By contrast, a quasi-experimental study among military recruits noted a significant reduction in SSTI and specifically MRSA SSTI incidence following implementation of a bathing protocol including CHG [93]. In a randomized trial of community-dwelling adults and children, the use of 4% CHG body washes daily in addition to nasal mupirocin for 5 days was associated with a reduction in SSTI incidence at 1 month compared to controls, though this effect was not sustained at 4 months [24]. The most common adverse event related to CHG use is a mild dermatitis that typically resolves following cessation of CHG use. Based in part on these data, the IDSA guidelines state that the application of CHG skin antiseptic solutions for 5–14 days along with intranasal mupirocin twice daily for 5–10 days can be used in patients to prevent recurrent SSTI once wound care and hygiene interventions have been maximized [60].

Dilute Bleach Baths

Bleach (sodium hypochlorite) has antimicrobial activity against a wide range of pathogens, including *S. aureus*. Pathogen colonization and infection (particularly with *S. aureus*) are associated with eczema exacerbations [94]. For years, many dermatologists have recommended dilute bleach baths to their patients with eczema, as bleach is believed to reduce the burden of microorganisms (including *S. aureus*) on the skin, thereby decreasing the frequency of eczema flares. In one study, the use of bleach baths along with intranasal mupirocin was associated with a significant reduction in eczema severity scores [95]. The minimum concentration of hypochlorite necessary to achieve a therapeutic effect is unclear. In one in vitro study evaluating the time-kill properties of bleach against *S. aureus*, the use of 2.5 μl of 6% commercial bleach per ml of water (roughly equivalent to ½ cup of standard household bleach in ¼ bathtub of water, assuming a standard-sized bathtub) was associated with a > 4-log decrease in *S. aureus* colony-forming units (CFUs) following a 15-min exposure [96]. By contrast, a 1.2-μl/ml dilution resulted in a 2-log decrease in CFU. To minimize potential skin/eye irritation, the IDSA guidelines suggest that dilute bleach baths using 1 teaspoon (5 ml) of bleach per gallon of bath water (or ¼ cup per ¼ tub [~ 13 gal] of water) for 15 min twice weekly can be used along with intranasal mupirocin for 5–10 days to decrease SSTI recurrence [60]; this concentration is roughly equivalent to that

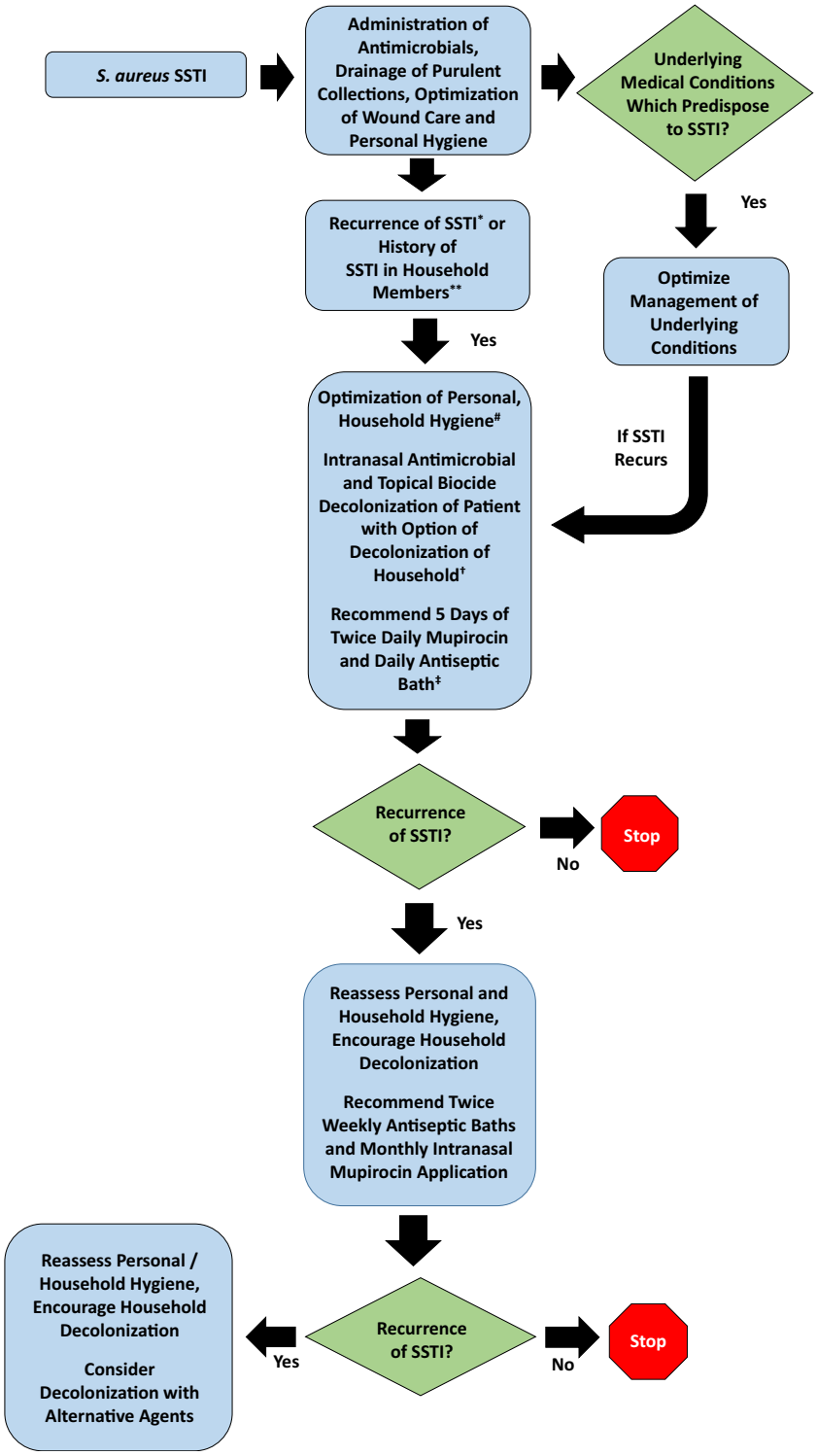
which achieved a lower effect (2-log decrease) in the previously quoted in vitro study. Importantly, however, data are lacking that dilute bleach baths reduce the incidence of recurrent *S. aureus* SSTI. In a large ($n = 947$) single-center randomized trial of dilute bleach baths (employing the 5-ml household bleach per 1 gal tap water concentration) along with hygiene education in children with SSTI vs. hygiene education alone, there was no difference in the incidence of medically attended SSTI at 1 year [25•]. It is possible that the outcome of medically attended SSTI, rather than all SSTI, and/or the concentration of bleach used in this study, may have underestimated the potential impact of this intervention. Importantly, no adverse events were noted in this study other than very mild skin and eye irritation that were attributed to other causes. Notably, in another trial, the use of bleach baths along with intranasal mupirocin did reduce the incidence of *S. aureus* colonization at 4 months compared to those receiving hygiene education alone [24]. Additionally, it is worth noting that bleach baths may be a more economical decolonization regimen than the use of CHG washes. In families with young children, it is important to acknowledge the potential safety concerns of bleach; it is recommended that parents/guardians store the undiluted bleach in a safe location out of the reach of small children to minimize the risk of accidental ingestion or contact with eyes.

Interest also exists in the use of sodium hypochlorite in other forms. In a pilot study, the use of a body wash containing 0.006% sodium hypochlorite in children with moderate-severe eczema who were also colonized with *S. aureus* resulted in improved eczema severity scores at 12 weeks; additionally, the investigators noted a reduction in bacterial colonization determined by quantitative cultures at 1 month [97]. Further studies are underway to determine the effectiveness of such hypochlorite preparations in the management of eczema [98]. While it is conceivable that the use of sodium hypochlorite body washes may be beneficial to patients with recurrent SSTI, data are currently not sufficient to recommend their use.

Areas of Investigation: Microbial Interference and Probiotics

Manipulation of the skin and nasal microbial communities through "bacterial interference" (i.e., the employment of non-pathogenic organisms to impede or outcompete colonization by potential pathogens) as an infection prevention or treatment approach is an exciting avenue for investigation [99••, 100]. Indeed, an inverse relationship has been observed between the presence of *S. aureus* and a variety of other flora, including coagulase-negative staphylococci, *Corynebacterium* spp., *Dolosigranulum* spp., *Streptococcus* spp., *Propionibacterium* spp., and *Bacillus* spp. [101–109]. This relationship is purported to be facilitated through eliciting host immune responses, competition for nutrients and niche, and production of antimicrobial peptides, bacteriocins, and lipopeptides [99••, 109–116]. A recent investigation of bacterial interference among patients with atopic dermatitis colonized with *S. aureus* was conducted in the USA [115]. Selected strains, specific to each patient, of *S. hominis* or *S. epidermidis* were formulated in a cream vehicle base and applied to the forearm of each subject; vehicle alone was applied to the contralateral arm (i.e., participants served as their own controls). *S. aureus* was measured on both forearms before and 24 h after application; *S. aureus* colonization was significantly reduced from the treatment arm compared to the control arm. Additionally, a recent phase II randomized clinical trial recruited patients with documented *S. aureus* colonization from a Veterans Affairs medical center [117]. Subjects were randomized to ingest *Lactobacillus rhamnosus HN001* capsules vs. placebo once daily for 4 weeks. At the end of the intervention period, gastrointestinal tract *S. aureus* colonization was significantly eradicated from the group randomized to receive *L. rhamnosus HN001* compared to those receiving placebo, though colonization at other body sites (e.g., nares, axilla) was not affected. Further study is needed to better understand the potential future role of bacterial interference in mitigating *S. aureus* colonization and preventing infection.

Fig. 1 Recommended strategies for treatment and prevention of *Staphylococcus aureus* skin and soft tissue infections (SSTI). For patients presenting with acute SSTI, incision and drainage, in conjunction with systemic antimicrobials, is the mainstay of therapy. All patients/families should receive education regarding *S. aureus* transmission, wound care, and personal and household hygiene measures. Patients with underlying medical conditions, such as eczema or diabetes, should be evaluated and management of these conditions optimized. * indicates that patients with recurrent SSTI should be queried for warning signs of immunodeficiency such as other frequent infections, chronic diarrhea, weight loss, failure to thrive, and/or fever of unknown origin, and evaluated accordingly if these findings exist. ** indicates that history should be obtained regarding the presence of other household members with history of *S. aureus* infections. # indicates that personal/household hygiene interventions to consider include, but are not limited to, regular bathing; use of liquid soaps (as opposed to bars of soap), regular laundering of bedding; washing towels/washcloths, sleepwear, and underwear after each use; trimming fingernails; and avoiding sharing of personal hygiene items such as razors, deodorant, or cosmetics. † indicates that decolonization of all household members may be more important in households with young children or those with multiple family members experiencing *S. aureus* infections. ‡ indicates that mupirocin should be administered twice daily intranasally for 5–10 days. Topical biocides which may be considered for decolonization include chlorhexidine gluconate (CHG) or dilute bleach baths. CHG solutions may be applied directly to the body below the jawline and then rinsed off with tap water; patients may then bathe per their regular routine. CHG washes are recommended to be used for 5–14 days. For patients using bleach baths, the recommended regimen is as follows: 1 teaspoon (5 ml) of bleach per gallon of bath water (or ¼ cup per ¼ tub of water). The patient should soak in the dilute bleach bath for 15 min for 5–14 days



Recommended Approach

Given that *S. aureus* may colonize multiple body sites, reinfection may occur through a variety of sources. Based on the recommendations of the U.S. Centers for Disease Control and Prevention and the IDSA, the research data presented above, and our clinical experience, we recommend a multifaceted approach to decolonization and SSTI prevention (Fig. 1). Patients and their families should be provided thorough education regarding *S. aureus* transmission and management of staphylococcal SSTI. For patients experiencing a recurrent SSTI, strict attention should be paid to adequate drainage of the purulent infection and systemic antibiotic treatment, local wound care, and hygiene measures (e.g., frequent handwashing, regular bathing, not sharing personal

hygiene items). In addition to the patient with recurrent SSTI, the option of decolonizing all household members should be discussed with the family, taking into consideration history of SSTI in other household members, the presence of children in the household (as transmission may be higher in households with children), and the potential benefits and challenges of this approach. The recommended regimen should include intranasal mupirocin twice daily for 5–10 days along with antiseptic bathing (either with dilute bleach or CHG) for 5–14 days. Factors influencing decisions regarding the topical antiseptic agent chosen, as well as decolonization of the entire household, include costs, patient lifestyle, and willingness of the household to participate. Regardless, it is important to discuss the potential limitations of decolonization and provide realistic expectations as recurrent infections still occur in 20–52% [25•, 29••] of patients even when managed aggressively. For patients experiencing recurrence after an initial decolonization attempt, in conjunction with optimization of personal/household hygiene and management of underlying conditions, we recommend performing antiseptic bathing two times each week as well as monthly intranasal mupirocin application (twice daily for 5 consecutive days each month) and/or changing decolonization agents. Finally, it is important to impart knowledge regarding hygiene interventions and the transmission of *S. aureus* in a nonjudgmental fashion to minimize any potential feelings of stigmatization by the patient/family [118], focusing on the ubiquity of *S. aureus* in the environment.

Potential Unintended Consequences of Decolonization: Reduced Antimicrobial Susceptibility

While there is clear potential benefit from topical antimicrobials, any attempt to pharmacologically modify the natural flora has the capacity to promote reduced susceptibility over time. A number of investigators have reported in *S. aureus* isolates the emergence of reduced susceptibility to mupirocin and/or antiseptics (primarily CHG) following widespread use of these agents, including in pediatric populations [119–123]. The clinical significance of these organisms is controversial; the mupirocin/CHG MICs in these organisms, while many-fold higher than that seen in the "wild-type," are typically much lower than the concentrations contained in many clinically used preparations. However, in reports from inpatient settings and the community, colonization with these resistant organisms has been associated with the failure of mupirocin-CHG-based decolonization regimens and the emergence of breakthrough infections [75•, 124–127]. Additionally, the organisms exhibiting resistance or tolerance to topical antimicrobials are often resistant to other systemic antimicrobials [75•]. The observed co-resistance to systemic antimicrobials and antiseptics is related to both the action of the encoded resistance gene (as in the case of cross-resistance to CHG and ciprofloxacin [128]) and the shared location of topical and systemic antimicrobial resistance genes on the same mobile genetic elements (such is the case with genes conferring mupirocin and clindamycin resistance [129]). Thus, these organisms are of clinical import and further study and surveillance is needed.

Conclusions

Recurrent *S. aureus* SSTIs contribute to substantial morbidity and place significant strains on the healthcare system. While the optimal strategy to interrupt the cycle of reinfection is unclear, the utilization of a multimodal approach including adequate drainage and treatment of the primary infection, education, hygiene interventions, and intranasal mupirocin and topical antiseptic agents, with inclusion of the entire household when possible, appears to result in the best outcomes. Further study is needed to better understand the social and behavioral determinants, the immunologic mechanisms, and the impact of microbial communities driving these infections, to ultimately inform the development of more definitive therapies.

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Compliance with Ethical Standards

Conflict of Interest Stephanie A. Fritz declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- •• Of major importance

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