Prevention of Recurrent Staphylococcal Skin Infections

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Synopsis

Staphylococcus aureus infections pose a significant health burden. The emergence of community-associated methicillin-resistant *S. aureus* has resulted in an epidemic of skin and soft tissue infections (SSTI), and many patients experience recurrent SSTI. As *S. aureus* colonization is associated with subsequent infection, decolonization is recommended for patients with recurrent SSTI or in settings of ongoing transmission. *S. aureus* infections often cluster within households and asymptomatic carriers serve as reservoirs for transmission; therefore, a household approach to decolonization is more effective than measures performed by individuals alone. Other factors, such as environmental surface contamination, may also be considered. Novel strategies for the prevention of recurrent SSTI are needed.

Keywords

Staphylococcus aureus; MRSA; skin infection; prevention; decolonization; staphylococcal vaccine; pediatrics

INTRODUCTION

"Once the organisms gain a foothold, they may be very difficult to eradicate; sometimes boil after boil appears and these lesions may continue to develop in crops for months. The scalp, face, and shoulders are favorite sites but any part of the body may be involved; in some instances, the entire body is covered with furuncles." These prescient words, found in the

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chapter on skin infections from the 11th Edition (1940) of Holt's Diseases of Infancy and Childhood [1], are as true today of *Staphylococcus aureus* skin and soft tissue infections (SSTI) as they were in the pre-antibiotic era. SSTI are among the most common reasons for healthcare visits in the United States, accounting for over 14 million outpatient and emergency department visits annually [2]. Moreover, these infections frequently recur, leading to substantial morbidity in the pediatric population and provoking frustration for both patients and clinicians. In this review, we will describe the epidemiology of *S. aureus* SSTI, with a focus on recurrent SSTI; delineate the current paradigm of SSTI pathogenesis; and provide evidence-based recommendations for treatment and prevention of these infections.

THE EMERGENCE OF COMMUNITY-ASSOCIATED METHICILLIN-RESISTANT *S. AUREUS*

Staphylococcus aureus is a Gram-positive commensal bacterium that colonizes the anterior nares, as well as other anatomic sites, of approximately one third of the human population [3–7]. Upon leaving the site of colonization, *S. aureus* can infect virtually any body site, making it the most prevalent pathogen isolated from SSTIs, a leading cause of food-borne illness, the second leading cause of infectious endocarditis [8], and an important cause (~2%) of all hospital admissions [9]. With an estimated incidence of 32 infections per 100,000 persons, *S. aureus* has surpassed *Streptococcus pneumoniae* and *Haemophilus influenzae* to become the most common invasive bacterial pathogen in the United States [10].

A major challenge posed by *S. aureus* is antimicrobial resistance. Soon after the β-lactam antibiotics penicillin and methicillin were introduced into clinical practice, strains of antibiotic-resistant *S. aureus* were identified [11]. Over the next several decades, methicillin-resistant *S. aureus* (MRSA) became an important healthcare-associated pathogen, complicating the care of post-surgical and dialysis patients and the chronically ill [12–15]. Treatment was challenging, owing to resistance to multiple antibiotics, and by the turn of the century, MRSA accounted for nearly 60% of all *S. aureus* isolates recovered from hospital intensive care units [16]. At present, it is projected that MRSA infections account for >100,000 hospitalizations each year in the U.S. [17].

In the late 1990s, a shift in MRSA epidemiology occurred. After the alarming deaths of four previously healthy Midwestern children following infection with MRSA [18], it was realized that MRSA infections were no longer restricted to those with chronic illnesses or frequent hospitalizations; rather MRSA had emerged as a community pathogen, capable of infecting healthy hosts, and thus was termed community-associated (CA) MRSA. Initially thought to represent a feral strain of healthcare-associated (HA) MRSA that had "escaped" into the community, it was soon determined that CA-MRSA strains were fundamentally different from traditional HA-MRSA strains. Compared to HA-MRSA strains, CA-MRSA strains exhibit a faster bacterial doubling time *in vitro* [19], possess a smaller gene cluster (Staphylococcal Cassette Chromosome *mec*) conferring resistance mainly to β-lactam antibiotics (although resistance to other antimicrobials has recently emerged) [20–36], and exhibit altered regulation of exotoxins and other virulence factors [37–41], characteristics

which are thought to correlate with the aggressive clinical behavior and transmissibility of CA-MRSA. CA-MRSA causes a broad spectrum of disease entities, ranging from asymptomatic colonization to SSTI (particularly purulent abscesses) to invasive infections (e.g., fulminant necrotizing pneumonia, musculoskeletal infections, fatal bacteremia) [37, 42–47]. The host and bacterial determinants driving this spectrum are not well understood. Recently, highly virulent strains of methicillin-susceptible *S. aureus* (MSSA) belonging to the same genetic lineage as the current CA-MRSA epidemic strains (USA300) have been described [48, 49]. These strains share phenotypic similarities with MRSA USA300 strains, leading to SSTI, recurrent abscesses, and invasive, necrotizing infections.

EPIDEMIOLOGY OF PEDIATRIC *S. aureus* SSTI

The most common manifestation of CA-MRSA infection is SSTI. Although many SSTIs are superficial, they carry significant morbidity, including pain and subsequent scarring caused by drainage procedures and time lost from school and work by patients and their families. While many patients with CA-MRSA SSTIs are treated as outpatients, patients with moderate to severe SSTI often require hospitalization. SSTI now ranks among the top 10 reasons for pediatric hospital admission [50].

The epidemiology of staphylococcal SSTI changes rapidly and in the past 15 years, the landscape has been dominated by CA-MRSA. In 2005, Purcell *et al.* demonstrated a substantial rise in MRSA infection incidence, increasing from <10 cases annually in the 1990s to nearly 500 cases annually by 2003 [51]. By 2005, several centers across the U.S. reported that CA-MRSA accounted for nearly 75% of all staphylococcal infections [43]. These high rates of CA-MRSA necessitated changes in empiric antibiotic therapy when MRSA was suspected [52], particularly for SSTI in which well over 50% of infections in most centers were due to CA-MRSA [43, 44, 51, 53, 54]. More recently, Gerber *et al.* performed a retrospective, observational study using the Pediatric Health Information System (PHIS), a database of clinical and financial data from >40 tertiary care children's hospitals in the U.S. Over the 6-year study period, the investigators identified nearly 60,000 children with *S. aureus* infections, 51% of whom had infection with MRSA; SSTI comprised 61% of these infections [55].

MRSA colonizes the anterior nares, throat, rectum, and skin (axilla, inguinal area, and perineum) [4–7, 56–59]. MRSA carriage is a risk factor for the development of subsequent infections [3, 6, 60–64]. Colonized individuals also are important sources for transmission [65]. Up to 10% of healthy individuals in the U.S. are colonized with MRSA [45, 46]. The prevalence of MRSA colonization has significantly increased over the past decade [46, 47], accompanied by a rise in MRSA infection incidence. Two studies, utilizing data from the National Ambulatory Medical Care Survey and a large integrated health plan in Northern California, have identified children and African-Americans as being disproportionally affected by the current CA-MRSA epidemic [2, 66, 67]. In addition to race and age, there are specific populations who have experienced a substantial increase in SSTI due to CA-MRSA (Box 1). These include military personnel, in whom MRSA colonization significantly increases the risk of developing SSTI (compared to MSSA colonization) [63]; prisoners [68–70]; and athletes, in whom colonization can be detected frequently within

sports teams, though outbreaks are sporadic [71–74]. In each of these high-risk groups, risk factors for infection include close contact, compromised skin integrity, and increased prevalence of colonization; in addition, outbreaks are often linked to periods of increased colonization or exposure to specific strains of *S. aureus*, e.g., USA300 CA-MRSA.

Box 1

Risk Factors for *S. aureus* SSTI

- *S. aureus* colonization

- Injection drug use

- Diabetes mellitus

- Chronic dermatologic conditions (e.g., eczema)

- Recent use of antimicrobial agents

- African-American race

- Previous SSTI

- Close contact with an SSTI patient

- Participation in contact sports

- Military personnel

- Prisoners

PATHOGENESIS OF *S. AUREUS* SSTI

In the development of SSTI in an otherwise healthy individual, the site of symptomatic infection is first colonized with a relatively low number of bacteria. Staphylococci easily accomplish this, since over 80% of humans are intermittently colonized at some point with *S. aureus*, including 10–15% of humans who are persistently colonized [3, 75, 76]. Since colonization alone is insufficient to initiate disease, *S. aureus* must then reach the deeper portions of the epidermis and dermis through microabrasions of the skin, traumatic injury, or skin disruption due to inflammatory lesions (e.g., eczema). *S. aureus* possess a number of virulence determinants responsible for initiation and maintenance of infection [77–90], representatives of which are listed in Table 1. Upon invasion, the host inflammatory response leads to microvascular leak, production of inflammatory cytokines/chemokines, and recruitment of leukocytes (in particular, neutrophils).

SSTI CHARACTERISTICS AND INITIAL MANAGEMENT

SSTI are best characterized by depth of infection and associated skin structures as described in Box 2. The Infectious Diseases Society of America (IDSA) asserts that incision and drainage (I/D) represents primary treatment for purulent staphylococcal skin abscesses [91]. The procedural approach to abscess drainage has been recently reviewed [92]. It is important to note that sufficient drainage, with disruption of loculations and facilitation of ongoing

drainage, is challenging in the pediatric population, often requiring sedation and post-procedural pain management. What is gained by this approach, however, is nearly immediate pain relief from large abscesses, faster wound healing and access to material for bacterial culture.

Box 2

Manifestations of skin infections

Erysipelas

Superficial skin infection characterized by well-demarcated, intensely erythematous lesions. Nearly universally due to S. pyogenes.

Cellulitis

Painful infection of the dermis and subcutaneous tissues, often occurring near breaks in the skin.

Impetigo

Relatively superficial infection leading to bullous or non-bullous lesions.

Folliculitis

Superficial or deep inflammation of the hair follicle leading to papulopustular lesions.

Furuncle

Extension of suppurative infection from the hair follicle, leading to infection of the deeper skin structures (typical abscess)

Carbuncle

An aggregate of infected follicles leading to a deep, painful mass

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Traditionally, drainage has been the mainstay of therapy for the majority of staphylococcal abscesses [93]; this has held true in the contemporary era of CA-MRSA in several studies. In a prospective cohort study by Lee *et al.* of children presenting to a large emergency department with SSTI, >75% of children experienced clinical cure following I/D, even if prescribed an antibiotic that was ineffective (based on eventual susceptibility results) [94]. Similarly, Chen *et al.* determined that among children with SSTI who experienced spontaneous drainage or had I/D performed, despite MRSA being the causative agent in 69%, no differences were evident in clinical cure between those receiving cephalexin vs. clindamycin [95]. Two randomized trials, one in adults [96] and one in children [97], have compared trimethoprim-sulfamethoxazole (TMP/SMX) to placebo after I/D of suspected staphylococcal abscesses. While both trials showed that the clinical cure rate did not differ between treatment groups, receipt of antimicrobial therapy resulted in a lower incidence of early recurrent disease. While current data are reassuring that antimicrobial agents are not required in all children, definitive data are not yet available in this population. An NIH-sponsored clinical trial [98] is expected to answer this question more completely, comparing the effectiveness of clindamycin, TMP/SMX, or placebo, in conjunction with I/D, in the treatment of limited abscesses in adults and children.

Patients for whom antibiotics are currently recommended include patients at the extremes of age and those with severe or extensive disease, rapidly progressing cellulitis, abscess in an anatomic location that precludes adequate drainage, systemic illness or hemodynamic instability, associated septic phlebitis, or failure to improve after incision and drainage alone [91]. As antimicrobial resistance has increased, choices of orally effective antimicrobials have diminished. Agents with *in vitro* activity against MRSA are provided in Table 2. Although antibiotic selection should be directed by one's regional antibiogram, for many communities, clindamycin and TMP/SMX remain good first line therapeutic agents for suspected CA-MRSA SSTI. However, in a large retrospective study of Tennessee children, Williams *et al.* found that TMP/SMX was less effective than clindamycin in both treating an initial abscess and preventing recurrences of disease [99]. Among 6407 children who underwent drainage, 9% experienced treatment failures within 14 days, and 23% had recurrence within one year; both of these outcomes were more likely in children receiving TMP/SMX, compared with clindamycin. Among 41,000 children who did not undergo a drainage procedure, TMP/SMX remained significantly less effective than clindamycin for the initial treatment of SSTI. Despite these observed differences, however, the overall success of TMP/SMX was high and, given its availability, tolerability, and low cost, TMP/SMX remains a first-line SSTI agent targeting MSSA and MRSA alike.

EPIDEMIOLOGY OF RECURRENT SSTI

As many as 70% of patients with CA-MRSA SSTI will experience recurrent SSTI over one year (Table 3), even after successful initial treatment [59, 97, 99–105]. These recurrent infections may necessitate repeated courses of antibiotic therapy, further driving development of antibiotic resistance [106, 107]. The risk factors governing these recurrent infections are not yet clear, though there are certainly pathogen-level, host-level, and environmental-level variables that contribute to CA-MRSA transmission and risk of recurrence [108–110]. As described above, the prescription of systemic antibiotics for SSTI treatment [96, 97], as well as the choice of antibiotic prescribed [99], may influence the incidence of recurrent infection. This may be due to reduction of the staphylococcal colonization burden, thereby eliminating the endogenous source for infection. Indeed, several prospective studies have demonstrated eradication of MRSA carriage following treatment of SSTI with clindamycin [111, 112].

Clustering of *S. aureus* infections occurs in households [113–124]. Additionally, a high proportion of household members of patients with MRSA infection are colonized with MRSA, frequently with strains identical to those recovered from index patients [119, 125]. Although these colonized contacts are often asymptomatic, they serve as important sources for ongoing transmission within households [5, 65, 106, 125–129], leading to reacquisition and recurrent infection. Households with young children may have greater risk of transmission through close personal contact [111, 119, 130].

PREVENTION STRATEGIES: DECOLONIZATION

S. aureus carriage is a risk factor for the development of subsequent infection [3, 6, 60–64], and recurrent *S. aureus* SSTI are frequently caused by the same strain type [104, 131, 132].

Thus, decolonization (i.e., "the use of antimicrobial or antiseptic agents to suppress or eliminate *S. aureus* carriage" [91]) is often prescribed in an attempt to prevent recurrent infections. Such therapies have traditionally been implemented in healthcare settings to prevent nosocomial *S. aureus* and MRSA infections [133–144]. During the ongoing CA-MRSA epidemic, these measures have been extrapolated to patients in community settings [91, 145, 146]. While application of these therapies for a discrete period is effective for MRSA eradication, their effectiveness in infection prevention varies by study, and maintenance of eradication often diminishes over time [101, 103, 133–136, 141–144, 147–149]. Thus, the optimal preventive strategy for recurrent *S. aureus* SSTI remains elusive, and a wide variety of treatment and decolonization practices exist [91, 145, 150].

Who should undergo decolonization?

Prior history of SSTI is a risk factor for recurrent SSTI [64, 151]. This association, coupled with the pursuit of judicious use of topical antimicrobials, suggests that decolonization is likely not necessary for patients experiencing a first SSTI. Indeed, the IDSA MRSA Clinical Practice Guidelines state that decolonization may be considered, upon optimizing wound care and hygiene (see below), for patients experiencing recurrent SSTI and for households in which there is ongoing transmission [91].

S. aureus transmission frequently leads to infections in multiple household members; thus, when decolonization is prescribed, it should be performed by all household members. A randomized trial of 183 households conducted by Fritz *et al.* compared the effectiveness of decolonization of the index patient alone ("index group") to decolonization of all household members ("household group"). The 5-day decolonization regimen included hygiene education, twice daily application of 2% intranasal mupirocin, and daily body washes with 4% chlorhexidine. Three months following randomization, the incidence of SSTI was significantly lower in index patients assigned to the household decolonization group compared to those in the index group (28% vs. 47%, respectively, p=0.02). This benefit was also demonstrated for household contacts (at 3 months: 4% incidence in household group vs. 10% in index group, p=0.01) [103].

Hygiene strategies

Before staphylococcal eradication measures are prescribed, attention to basic wound care and personal hygiene should be addressed. Education should be provided to patients and their families regarding the transmissibility of *S. aureus*, particularly through contact with open wounds and contaminated surfaces. Patients should be encouraged to adopt enhanced hygiene practices, including regular bathing and frequent hand washing with soap and water or alcohol-based hand sanitizers. Patients and their contacts should avoid sharing personal hygiene items (e.g., towels, deodorant, cosmetics, brushes, razors, toothbrushes, or other items that come into contact with the skin). Additional measures that may reduce transmission and infection risk include using pump or pour lotions (rather than those in jars), keeping fingernails clean and trimmed short, avoiding loofas in the bath or shower, and changing underwear, sleepwear, towels, and washcloths daily [59, 91, 101, 103, 119, 146, 152].

Environmental surfaces serve as reservoirs for MRSA transmission and MRSA strains can persist in the environment for prolonged intervals, posing risk for the development of recurrent infections [34, 106, 109, 121–123, 128, 151, 153–156]. Thus, a barrier should be used between bare skin and surfaces touched by multiple people (e.g., exercise equipment). Additionally, patients with recurrent SSTI may consider performing environmental hygiene measures, focusing on frequently touched surfaces and using commercially available disinfectants [91, 152]. Routine laundry procedures, following the label directions on the detergent and the clothing or linens to be washed, are usually sufficient to disinfect items; use of hot water or bleach for all household laundry is not necessary [152].

Topical antimicrobial agents

While multiple agents and technologies have been proposed or evaluated for *S. aureus* decolonization [157], this review will focus on those most readily prescribed and available to patients. An important consideration of any decolonization regimen, regardless of efficacy, is the time and financial burden encumbered by patients, which heavily influences adherence and thus, the effectiveness of these measures.

Mupirocin (pseudomonic acid A) is produced naturally by *Pseudomonas fluorescens* [158–160]. Mupirocin targets the bacterial isoleucyl-tRNA synthetase, resulting in protein synthesis inhibition [161]. Mupirocin has antimicrobial activity against staphylococcal and streptococcal species and is prescribed for topical treatment of skin infections as well as eradication of *S. aureus* (both MSSA and MRSA) nasal carriage.

Retapamulin (Altabax, GlaxoSmithKline, Research Triangle Park, NC) is a semisynthetic antimicrobial derived from the natural compound pleuromutilin, produced by the edible mushroom *Pleurotus mutilus* [162, 163]. Retapamulin inhibits *S. aureus* protein synthesis by binding to the 50S ribosomal subunit [164, 165]. At present, retapamulin is approved for treatment of impetigo due to MSSA or *Streptococcus pyogenes*. Retapamulin has demonstrated activity against *S. aureus* strains exhibiting resistance to methicillin and mupirocin as well as several other systemic antibiotics [162, 163, 166]. A Phase I/IIa randomized, double-blind, placebo-controlled trial evaluated 3- and 5-day regimens of retapamulin (1%) ointment applied to the anterior nares twice daily in patients persistently colonized with *S. aureus*. Both retapamulin regimens demonstrated efficacy in *S. aureus* eradication 28 days following application, compared to placebo [167]. An ongoing randomized trial aims to determine the effectiveness of retapamulin in eradication of mupirocin-resistant MRSA from adult carriers [168].

Chlorhexidine gluconate is a broad-spectrum biguanide cationic bactericidal agent [169, 170]. At low concentrations, chlorhexidine disrupts cytoplasmic membrane integrity; at high concentrations, it causes microbial cytoplasmic contents to congeal [169]. Multiple preparations of chlorhexidine exist, including a liquid topical antiseptic available without a prescription (Hibiclens, Mölnlycke Health Care, Norcross, GA), an oral rinse, and impregnated cloths [171]. Attractive for the purposes of decolonization, chlorhexidine provides residual antibacterial activity on the skin [148, 172]. Of note, as chlorhexidine may result in ocular and ototoxicity, patients should be instructed to avoid the eyes and ears when using this agent.

Bleach, or sodium hypochlorite, has antimicrobial activity against *S. aureus* both *in vivo* and *in vitro*. Dilute bleach water baths have traditionally been recommended by dermatologists to treat eczema, presumably by suppressing *S. aureus* growth, which is correlated with disease severity [173–177]. The recommended dilution of bleach varies [91, 101, 146, 173, 176]. An *in vitro* assay determined that the hypochlorite concentration necessary for maximal *S. aureus* killing was 2.5 μL of 6% hypochlorite per mL of water (equal to approximately ½ cup bleach in ¼ bathtub full of water), with an exposure time of 15 minutes yielding a >4-log decrease in *S. aureus* [175]. In clinical practice, to minimize skin irritation, a dilution of ¼ cup household bleach in ¼ bathtub (~13 gal) of water is recommended; for non-standard bathtubs, 1 teaspoon of bleach should be added per gallon of water. Individuals should soak in the dilute bleach water for 15 minutes. As household bleach is readily available and inexpensive, bleach baths are attractive for the purpose of decolonization. Additionally, soaking body areas that are frequently colonized with *S. aureus* (e.g. the groin and axillae) likely provides optimal antimicrobial effect. However, in large families, this strategy may be cumbersome and impractical. A recent feasibility study evaluated a body wash gel preparation of sodium hypochlorite (CLn BodyWash, Top MD Skin Care, Inc., Dallas, TX) in atopic dermatitis patients whose eczematous lesions yielded *S. aureus* [177]. Over 12 weeks, patients experienced significant improvement in severity of their atopic dermatitis; parents reported that the body wash was easier to administer than dilute bleach water baths.

Oral antibiotics for decolonization

Trials evaluating the effectiveness of systemic antibiotics in eradicating *S. aureus* or MRSA carriage have produced disparate results. Many of these trials have demonstrated emergence of resistant organisms with the use of oral antibiotics. Additionally, systemic antimicrobials traditionally used for decolonization, in particular rifampin, have been associated with toxicities. Thus, oral antibiotics should be reserved for patients with acute infections and are generally not recommended for staphylococcal decolonization alone [91, 143, 178].

Effectiveness of decolonization in preventing SSTI

Several trials have evaluated decolonization measures among healthy individuals in community settings (Table 4). *S. aureus* colonizes the anterior nares and the skin at multiple anatomic sites [4–7, 56–58, 179], and a greater number of colonized sites confers increased risk of infection [59]. Additionally, the buttocks and lower extremities are frequent sites for *S. aureus* SSTI [49, 104, 145, 180]. Thus, a decolonization approach targeting intranasal and skin carriage has the greatest potential for success. Among recent trials, studies prescribing both intranasal mupirocin and antimicrobial body washes demonstrated significantly reduced incidence of SSTI [101, 103, 181], while studies employing only intranasal mupirocin [147] or only antimicrobial body washes [59, 110, 180] showed no significant effect on SSTI incidence.

Many trials to date have prescribed a brief decolonization regimen (e.g., 5 days) [101, 103]; although reduced SSTI incidence was demonstrated in the months immediately following decolonization, many participants experienced recurrent infection over longer intervals. These findings likely reflect ongoing exposure to colonized individuals and environmental

reservoirs, and suggest that, especially for patients experiencing multiple infection recurrences, a periodic approach to decolonization may provide more effective, sustained protection [182]. A randomized trial of pediatric patients with SSTI by Kaplan *et al.* evaluated daily hygienic measures alone compared with hygienic measures accompanied by twice-weekly dilute bleach water baths performed for 3 months. Over the 12-month study period, the incidence of medically attended recurrent SSTI did not differ significantly between the group performing bleach baths compared to the hygiene-only group (17% vs. 21%, respectively, p=0.15) [59]. Of note, as not all patients with recurrent SSTI seek medical attention [7], the effectiveness of this intervention may have been underestimated.

Based on existing evidence, guidance from the CDC and IDSA, and our clinical experience, we propose a preventive approach to recurrent staphylococcal SSTI which optimizes hygiene measures, targets nasal and skin colonization, and includes all household members (Figure 1).

A POTENTIAL UNDESIRABLE REPERCUSSION OF DECOLONIZATION: ANTIMICROBIAL RESISTANCE

An important consideration for *S. aureus* decolonization is the emergence of staphylococcal strains resistant to topical antimicrobials, which has been demonstrated *in vitro* and *in vivo* (Table 5) [158–160, 170, 183–186]. This resistance in turn predicts failure of *S. aureus* decolonization efforts and has led to hospital outbreaks with resistant strains [159, 183, 187–195]. An additional concern is that the genes conferring resistance to mupirocin (most commonly *mupA*) and chlorhexidine (most commonly *qac A/B* or *smr*) are carried on plasmids that can also harbor genes conferring resistance to other systemic antibiotics [159, 169, 183, 188, 196–199]. A challenge to U.S. clinicians is the paucity of commercially available resistance testing for mupirocin and chlorhexidine; at present there are no interpretive breakpoints established by the Food and Drug Administration [159].

FUTURE DIRECTIONS

Despite the effectiveness of topical antimicrobials in eradicating *S. aureus* carriage, patients continue to suffer a high burden of subsequent SSTI over time [101, 103, 110, 147]. Thus, novel strategies are needed for the prevention of recurrent staphylococcal infections.

Vaccine

Vaccine development for *S. aureus* has been stymied by multiple factors, including lack of understanding of human immunity to staphylococci, redundancy of virulence determinants within the staphylococcal genome, and failure of previous vaccine candidates. The first of these failures involved a capsular polysaccharide vaccine (StaphVAX, Nabi Pharmaceuticals) given to hemodialysis patients at high risk for *S. aureus* disease [200]. In this study, the vaccine adequately elicited anti-capsular antibodies but failed to protect recipients from clinical disease. This vaccine has been modified significantly to include other targets and is currently in clinical development (PentaStaph, GSK). The second clinical failure occurred with a monovalent IsdB-based vaccine (V710, Merck) [201] in which vaccine recipients, who were undergoing cardiothoracic surgery, experienced greater

mortality than placebo recipients. Despite these failures, staphylococcal vaccine development, as well as strategies for passive immunization [202], continues. Once available, a suitable vaccine will be targeted to individuals at high risk for SSTI and those with recurrent infections.

Bacterial Interference and Probiotics

The endogenous microbiota (i.e., normal flora) exist in a delicate balance, vying for nutrients and adhesion sites. In this competition, commensal bacteria may interfere with the adherence and pathogenesis of potential pathogens, thereby protecting the host [203, 204]. Additionally, the endogenous microbiota may activate or augment host defenses against bacterial invaders. The concept of bacterial interference, or the use of a non-pathogenic organism to interfere with colonization and infection of a potentially pathogenic organism, is not novel. Indeed, the practice was implemented in the 1960s in an effort to abate *S. aureus* outbreaks among newborns due to epidemic strain type 80/81. The concept emerged from an observation that infants colonized with a non-epidemic strain type with apparent low pathogenicity, known as 502A, were at decreased risk for colonization and infection with strain type 80/81. Newborns intentionally inoculated with 502A in the nares and/or umbilicus were less likely to acquire strain type 80/81 and had a reduced incidence of infection with this epidemic strain [129, 205–210]. It is important to note, however, that following dissemination of this practice, reports emerged of infants developing pustulosis, conjunctivitis, and other infections, including one infant who died of meningitis and septicemia, all due to the 502A strain [211–213].

The balance of organisms within the host microbiota may play an important role in *S. aureus* colonization and development of symptomatic infection. In this contemporary CA-MRSA era, a U.S. military study comparing microbial communities within the anterior nares between soldiers with and without SSTI revealed a significantly higher abundance of *Proteobacteria* in the anterior nares of the non-SSTI group compared to soldiers with active SSTI [214]. Thus, perhaps manipulation of heterologous components of host microbiota may provide resilience against *S. aureus* colonization and infection. Uehara *et al.* conducted a trial in Japan in which persistent *S. aureus* nasal carriers were inoculated with a strain of *Corynebacterium* sp. (Co304) vs. sequential inoculation with saline and *S. epidermidis*. Of the 17 participants receiving *Corynebacterium* inoculation, *S. aureus* was completely eradicated in 71%. In contrast, eradication of *S. aureus* carriage was not demonstrated when NaCl and *S. epidermidis* were applied to the nares [215]. A trial conducted in Switzerland showed that consumption of a probiotic (a fermented milk drink containing *Lactobacillus* GG, *L. acidophilus*, *Streptococcus thermophilus*, and *Bifidobacterium* sp.) reduced nasal carriage of potentially pathogenic bacteria (*S. aureus*, *Streptococcus pyogenes*, β-hemolytic streptococci, and *H. influenzae*) compared with eating standard yogurt [216].

SUMMARY

Ultimately, the optimal regimen for long-term *S. aureus* eradication and prevention of recurrent infections remains unclear. Until a more definitive prevention strategy is available, disruption of colonization, targeting multiple anatomic sites with topical antimicrobials, and effective hygiene are the cornerstones of SSTI prevention. At present, the low rate of

staphylococcal resistance to commonly prescribed topical agents makes these agents highly effective in temporarily decolonizing the anterior nares and skin. Given the transmission dynamics of *S. aureus* within households, decolonization of all household members optimizes this approach.

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Key Points

xThe majority of children with a *Staphylococcus aureus* skin and soft tissue infection will experience a recurrent infection within one year.

S. aureus infections cluster within households, likely due to colonization of family members and household environmental surfaces.

A combined approach of nasal and skin decolonization is often effective in temporarily eradicating staphylococcal colonization and reducing subsequent SSTI.

A household approach to decolonization is more effective in reducing SSTI occurrence than decolonization efforts aimed at the individual patient alone.
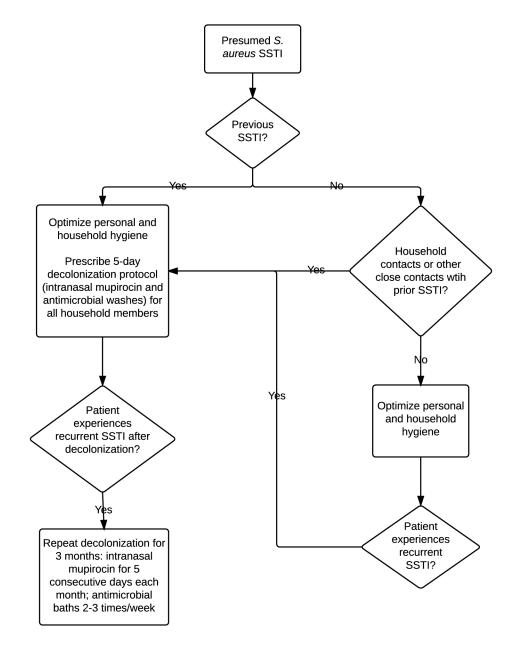
Figure 1. Recommended approach to prevention of recurrent staphylococcal SSTI
For all patients with *S. aureus* SSTI, we recommend optimizing hygiene measures. For those experiencing recurrent SSTI, or for households in which multiple members have experienced *S. aureus* infection, we recommend decolonization with a regimen that includes the application of an intranasal antibiotic (twice daily for 5 days) and daily antimicrobial body washes (performed daily for 5 days; for individuals with sensitive skin, these washes may be performed every other day for 7–10 days). These measures should be performed by all household members and may be considered for other close contacts on a case-by-case basis. Patients and their household contacts should change their bedding at the onset and again at the completion of the decolonization regimen and towels should be changed daily during the 5-day protocol. For individuals experiencing recurrent SSTI after the optimization of personal and household hygiene measures and the performance of

decolonization by all household members, clinicians may consider prescribing a three-month regimen of periodic decolonization, in which an intranasal antibiotic is applied to the anterior nares twice daily for five consecutive days each month and antimicrobial body washes are performed two to three times each week.

Table 1

Staphylococcus aureus virulence determinants involved in SSTI pathogenesis

Activity	Mechanism	Virulence Determinant
Adherence to host tissue		MSCRAMMs [77]
Tissue Destruction		Alpha toxin [78]
Nutrient Acquisition	Essential Metal Acquisition	Isd system [79]
Disruption of Host Defense	Impaired Chemotaxis	ChIPS, Eap [80, 81]
	Phagocyte Destruction	Leukocidins (LukAB, LukDE, PVL), PSM [82–84]
	Impaired Opsonization	Protein A, Polysaccharide capsule [85]
	Impaired Intracellular Killing	Staphyloxanthin, Catalase, Superoxide dismutase [86–90]

Table 2

Systemic antimicrobial agents for the treatment of *Staphylococcus aureus* SSTI

Antimicrobial Agent	Recommended Pediatric Dose Range (Oral)	Comments
Clindamycin	30–40 mg/kg/day divided q6–8h	• Excellent bioavailability • Noxious smell and taste of oral suspension • Often effective to instruct families to open capsules and sprinkle onto pudding/ice cream • Inducible and constitutive resistance is highly variable between geographic regions (>20% in some areas)
Trimethoprim-Sulfamethoxazole	10–20 mg/kg/day divided q12h	• Very low resistance rates • Clinical data confirm effectiveness • May have reduced activity against *S. pyogenes*, though data are not clear
Doxycycline	2.2 mg/kg/day divided q12h	• Very low resistance rates • Inappropriate for children <8 years of age • Photosensitivity
Linezolid	30 mg/kg/day divided q8h	• High susceptibility rates • Excellent bioavailability • Expensive, compared to other agents
Fluoroquinolones	(varies by individual quinolone)	• Excellent bioavailability • Overly broad-spectrum • Resistance can occur quickly while on therapy due to mutations in DNA gyrase
Rifampin	10 mg/kg/day	• Excellent bioavailability and tissue penetration • Can never be given as single agent as resistance quickly emerges

Table 3

Incidence and Risk Factors Associated with Recurrent Skin and Soft Tissue Infection

Study Reference	Population; Year(s) Study Performed	Study Design	Treatment or Intervention	Longitudinal Timeframe	Proportion of Patients with Recurrent SSTI	Factors Associated with Recurrent SSTI
Bocchini et al, 2013 [104]	12,836 children presenting to Texas Children's Hospital (TCH; Houston, TX) with community-associated S. aureus infection; 2001–2009	Retrospective cohort study	N/A	76 months	5% presented to TCH with documented recurrent S. aureus infection (694 with recurrent S. aureus infection of any etiology; 637 with recurrent S. aureus SSTI)	• Age 36 months
Williams et al, 2011 [99]	47,501 children with incident SSTI enrolled in Tennessee Medicaid; 2004–2007	Retrospective cohort study	Treatment with clindamycin, trimethoprim-sulfamethoxazole (TMP/SMX), or a β-lactam antibiotic	365 days	14% overall had a documented recurrent SSTI (23% in patients undergoing drainage; 18% of those without drainage)	• In patients undergoing drainage, recurrent SSTI was higher among patients prescribed TMP/SMX or a β-lactam antibiotic • In patients without drainage, prescription of TMP/SMX was associated with recurrent SSTI
Chen et al, 2009 [100]	95 children with purulent SSTI in Baltimore, MD; 2006–2007	Subgroup analysis of a double-blind, randomized, controlled trial comparing cephalexin to clindamycin	Treatment with cephalexin or clindamycin (assignment not specified)	3 months	22% reported recurrent SSTI	• Baseline MRSA SSTI (compared to baseline MSSA SSTI)
Fritz et al, 2012 [103] [and Fritz unpublished data]	183 children with acute CA-S. aureus SSTI and concurrent S. aureus colonization in St. Louis, MO; 2008–2009	Randomized, controlled trial comparing individual vs. household decolonization	All patients were assigned a 5-day decolonization regimen of enhanced personal and household hygiene, intranasal 2% mupirocin ointment application twice daily, and daily 4% chlorhexidine body washes	12 months	63% reported recurrent SSTI (72% in index decolonization group; 52% in household decolonization group)	• Multiple sites of S. aureus colonization at baseline • History of SSTI in year prior to study enrollment • Younger age • Baseline MSSA SSTI (compared to baseline MRSA SSTI) • Participants prescribed clindamycin for their baseline SSTI were less

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						likely to have a recurrent infection likely to have a recurrent infection
Miller et al, 2015 [105]	330 adults and children treated for *S. aureus* SSTI in Los Angeles, CA and Chicago, IL; 2008–2010	Prospective cohort study	N/A	6 months	51% reported recurrent SSTI	• Hospitalization in the prior 3 months • Household fomite contamination with MRSA • Lack of participation in contact sports
Kaplan et al, 2014 [59]	987 children with suspected *S. aureus* SSTI or invasive infection in Houston, TX; 2009–2012	Randomized, controlled trial comparing hygienic measures alone vs. hygienic measures plus bleach baths	Participants in the intervention arm bathed in dilute bleach water twice weekly for 3 months	12 months	19% reported medically-attended recurrent SSTI (21% hygiene group; 17% bleach bath group)	• Multiple sites of *S. aureus* colonization at baseline • Age 1.86 years • White race (compared to African-American and Hispanic) • Incidence of recurrence did not differ between children with MRSA vs. MSSA baseline infections

Table 4

Staphylococcus aureus Decolonization Trials Conducted in Healthy Populations

Study Reference	Population; Year(s) Study Performed	Study Design	Intervention	Length of Follow-Up Period Following Randomization	Outcomes
Raz et al, 1996 [182]	34 children and adults with a history of 3 staphylococcal SSTI in the prior year who were also colonized with *S. aureus* in Israel	Randomized double-blind placebo controlled trial	Baseline decolonization performed by all participants: mupirocin 2% ointment applied to the anterior nares twice daily for 5 days. Participants were then randomized to two groups: 1 Nasal mupirocin application twice daily for 5 days each month for 1 year 2 Application of placebo in the same fashion	12 months	• *S. aureus* eradication was significantly higher in the mupirocin group vs. the placebo group • SSTI incidence was significantly lower in the mupirocin group vs. the placebo group
Ellis et al, 2007 [147]	134 U.S. Army personnel enrolled in the Health Care Specialist Course colonized with CA-MRSA, Fort Sam Houston, TX; 2005	Cluster randomized, double-blind placebo controlled trial	Participants were randomized at the class level to perform: 1 Mupirocin 2% ointment applied to the anterior nares twice daily for 5 days 2 Application of placebo in the same fashion	8–10 weeks	• CA-MRSA eradication was significantly higher in the mupirocin group vs. the placebo group • SSTI incidence was not significantly reduced in the mupirocin group • Colonization acquisition and SSTI incidence were not reduced in the contacts of individuals performing mupirocin decolonization
Whitman et al, 2010 [110]	1562 U.S. Marine recruits attending Officer Candidate School, Quantico, VA; 2007	Cluster randomized, double-blind controlled trial	Participants were randomized at the platoon level to perform: 1 Application of 2% chlorhexidine-impregnated cloths (Sage, Cary, IL) applied over the entire body 3 times a week for 6 weeks 2 Application of control cloths (Comfort Bath; Sage) in a similar fashion	6 weeks	• *S. aureus* colonization incidence was significantly lower in the chlorhexidine group than the control group • SSTI incidence did not significantly differ between intervention groups
Fritz et al, 2011 [101]	300 children and adults with acute CA-SSTI with *S. aureus* colonization in St. Louis, MO; 2007–2009	Randomized, open-label four-arm controlled trial	Participants were randomized equally to perform 1 of 4 5-day decolonization protocols: 1 Enhanced personal and household hygiene alone (controls)	4–6 months	• Compared to controls, at 1 month, all interventions had a significantly higher rate of eradication. At 4 months, only the group performing hygiene, mupirocin, and bleach baths (Group 4) had a significantly

Study Reference	Population; Year(s) Study Performed	Study Design	Intervention	Length of Follow-Up Period Following Randomization	Outcomes
			2 Enhanced hygiene with intranasal 2% mupirocin ointment application twice daily **3** Enhanced hygiene, twice daily intranasal 2% mupirocin, and daily 4% chlorhexidine body washes **4** Enhanced hygiene, twice daily intranasal 2% mupirocin, and daily dilute bleach-water baths		• higher rate of eradication compared to controls • At 1 month, the group performing hygiene, mupirocin, and chlorhexidine (Group 3) had a significantly lower SSTI incidence compared to controls. At 4 and 6 months, none of the interventions resulted in a decreased SSTI incidence compared to controls
Fritz et al, 2012 [103]	183 children with acute CA-S. aureus SSTI and concurrent S. aureus colonization and their household contacts (844 total participants) in St. Louis, MO; 2008–2009	Randomized, open-label two-arm controlled trial	A 5-day decolonization regimen (including enhanced personal and household hygiene, intranasal 2% mupirocin ointment application twice daily, and daily 4% chlorhexidine body washes) was prescribed to two randomization groups: **1** Decolonization was performed by the index patient with acute SSTI alone **2** Decolonization was performed by all household members	12 months	• Index patient S. aureus eradication did not differ between groups • Index patient SSTI incidence was significantly lower in the household decolonization group vs. the index decolonization group • Household contact SSTI incidence was significantly lower in the household decolonization group vs. the index decolonization group
Kaplan et al, 2014 [59]	987 children with suspected S. aureus SSTI or invasive infection in Houston, TX; 2009–2012	Randomized, single-blinded controlled trial	Participants were randomized equally to perform: **1** Hygienic measures (controls) **2** Hygienic measures plus bleach baths twice a week for 3 months	12 months	• Incidence of medically-attended SSTI did not differ significantly between groups
Ellis et al, 2014 [180]	30,209 U.S. Army personnel enrolled in Infantry One Station Unit Training, Fort Benning, GA; 2010–2012	Cluster randomized trial	Platoons were randomized to: **1** Standard hygiene: Preventive medicine briefing, standardized SSTI treatment, and cleaning of high-touch common surfaces with standard disinfectants **2** Enhanced standard hygiene: Standard Hygiene (as above), an extra 10-minute shower with soap and a washcloth once a week, provision of a first aid kit, and supplemental SSTI	14 weeks	• Incidence of purulent SSTI (of any etiology) was significantly lower in the chlorhexidine group • Incidence of MRSA SSTI did not differ significantly between intervention groups

Study Reference	Population; Year(s) Study Performed	Study Design	Intervention	Length of Follow-Up Period Following Randomization	Outcomes
			education for trainees and drill sergeants education for trainees and drill sergeants 3 Chlorhexidine: Standard and Enhanced Hygiene components (as above) plus 4% chlorhexidine body wash (after using their personal soap) for the extra shower once a week		

Table 5

Staphylococcus aureus Mupirocin and Chlorhexidine Resistance Among Selected Populations

Study Reference	Population; Year(s) Study Performed	Study Design/ Intervention	Mupirocin resistance	Chlorhexidine resistance	Other findings/Notes
McNeil et al. 2011 [197]	68 children presenting with recurrent community-onset SSTI (136 *S. aureus* isolates) in Houston, TX; 2001–2009	Retrospective study	14.7% of *S. aureus* infecting isolates were positive for mupirocin resistance	N/A	• Mupirocin resistance occurred more commonly among *S. aureus* isolates recovered from recurrent SSTI cultures than initial SSTI cultures • Mupirocin resistance was more common in MSSA than MRSA isolates • Mupirocin resistance was associated with clindamycin resistance
Fritz et al, 2013 [190]	1089 adults and children presenting with community-onset SSTI (2425 *S. aureus* isolates) in St. Louis, MO; 483 patients were enrolled in decolonization trials, of which 408 were assigned intranasal mupirocin and/or chlorhexidine body washes; 2007–2009	Cross sectional study followed by a randomized controlled trial	2.1% of patients were colonized or infected with a mupirocin-resistant *S. aureus* strain at baseline	0.9% of patients were colonized or infected with a *S. aureus* strain harboring *qacA/B* at baseline	• Colonization with a mupirocin-resistant *S. aureus* strain precluded decolonization efforts • A higher proportion of colonizing isolates recovered at longitudinal samplings (following decolonization) were mupirocin-resistant and/or chlorhexidine-resistant compared to those obtained at baseline
Al-Zubeidi et al, 2013 [131]	105 children presenting to the emergency department with community-onset MRSA SSTI (248 isolates) in St. Louis, MO; 2005–2011	Retrospective study	6.7% of patients were infected with a mupirocin-resistant MRSA isolate	N/A	
Johnson et al, 2013 [184]	281 MRSA isolates obtained from pediatric emergency department and hospitalized patients in Nashville, TN; 2004–2009	Retrospective study	N/A	18.5% of MRSA infecting isolates harbored *qac A/B* or *smr* (13.9% harbored *smr* only, 4.3% harbored *qac A/B* only and 1 isolate contained both *smr* and *qacA/B*)	• USA300 MRSA isolates were less likely to harbor *qac A/B* or *smr* compared to non-USA 300 isolates
McNeil et al, 2013 [185]	179 patients with underlying malignancy with *S. aureus* infection (most commonly bacteremia, yielding 156 *S. aureus* isolates for analysis) in Houston, TX; 2001–2011	Retrospective study	N/A	7.6% of infecting *S. aureus* isolates harbored *qacA/B*	• The prevalence of *qacA/B*-positive *S. aureus* isolates rose significantly over the study period (4.5% in 2007 to 22.2% in 2011), coinciding with increased chlorhexidine use

Study Reference	Population; Year(s) Study Performed	Study Design/ Intervention	Mupirocin resistance	Chlorhexidine resistance	Other findings/Notes
					• Ciprofloxacin-resistance was associated with the presence of *qacA/B*
McNeil et al, 2013 [186]	216 congenital heart disease patients with *S. aureus* infection (most commonly SSTI, surgical site infection, and bacteremia/infective endocarditis, yielding 183 *S. aureus* isolates for analysis) in Houston, TX; 2001–2011	Retrospective study	N/A	16.9% of infecting *S. aureus* isolates harbored *qacA/B*	• The prevalence of *qacA/B*-positive *S. aureus* isolates rose significantly over the study period (5% in 2006 to 45.5% in 2011) • The presence of *qacA/B* in *S. aureus* isolates was associated with the presence of central lines, nosocomial acquisition, bacteremia, and prolonged hospitalization
McNeil et al, 2014 [183]	400 children presenting with community-onset *S. aureus* SSTI in Houston, TX (200 isolates from patients with a first-time *S. aureus* SSTI episodes and 200 isolates from patients with 3 *S. aureus* SSTI episodes); 2010–2012	Retrospective study	9.8% of patients were infected with a mupirocin-resistant *S. aureus* isolate	14% of patients were infected with a *S. aureus* isolate harboring *smr*	• 9.5% of patients were infected with a retapamulin-resistant *S. aureus* isolate • Previous mupirocin use was associated with increased mupirocin resistance • Mupirocin resistance was more prevalent in patients with a higher number of recurrent SSTIs • Chlorhexidine resistance was more prevalent in isolates recovered from recurrent SSTI (vs. first-time SSTI)