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Host Factors that Contribute to Recurrent Staphylococcal Skin Infection

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Abstract

Purpose of review—*Staphylococcus aureus* is the most common cause of skin and soft tissue infections (SSTI) in the United States and elsewhere. Recurrent infections occur frequently in patients with *S. aureus* SSTI, underscoring the need to better understand the nature of protective immunity against these infections. Here, we review recent findings concerning the host factors that predispose to *S. aureus* SSTI.

Recent findings—Recurrent infections occur in nearly half of all patients with *S. aureus* SSTI. Epidemiologic and environmental factors, such as exposure to health care, age, household contacts with *S. aureus* SSTI, and contaminated household fomites are associated with recurrence. The majority of the population has evidence of antistaphylococcal antibodies, but whether these are protective remains enigmatic. In contrast, recent clinical and experimental findings clearly highlight the critical roles of innate and T cell-mediated immunity in defense against these infections. *S. aureus* interferes with innate and adaptive immunity by a number of recently elucidated mechanisms.

Summary—Recurrent *S. aureus* SSTIs are common, suggesting incomplete or absent protective immunity among these patients. Our understanding of protective immunity against recurrent infections is incomplete, and further basic and translational investigation is urgently needed to design strategies to prevent and treat these infections.

Keywords

MRSA; skin infection; recurrence; antibody-mediated immunity; innate immunity; T cell-mediated immunity

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Conflicts of interest.

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INTRODUCTION

S. aureus is a commensal bacterium and a pathogen that causes a range of infections in health care settings and in the community, including sepsis, pneumonia, osteomyelitis, septic arthritis, bloodstream infection, and skin and soft tissue infection (SSTI) [1]. *S. aureus* is by far the most common cause of SSTI in the United States, and these infections represent an enormous burden, both in terms of financial and health-care related resources [2]. Recurrent SSTIs are common and the emergence of multi-drug resistant *S. aureus* isolates limits available antimicrobial therapies. A recent report documented that, among adults and children with a *S. aureus* SSTI in Chicago and Los Angeles, a recurrent SSTI was reported in 39% of patients within 3 months, and more than 50% within 6 months [3]. The extremely high rate of recurrence in this study is concordant with other reports [4] and underscores the need to better understand the host factors that predispose to recurrent infection.

TEXT OF REVIEW

Epidemiology of recurrent *S. aureus* SSTI – populations at risk

Although many risk factors for recurrent *S. aureus* SSTI have been identified, it is important to recognize that the vast majority of recurrent infections occur in individuals without identified risk factors. Individuals with persistent exposure to health care settings have a high rate of recurrent infections, which is likely due to a combination of health care exposure and the presence of comorbid conditions that predispose to *S. aureus* infections, such as diabetes mellitus, chronic renal failure requiring hemodialysis, and any condition necessitating surgical correction or palliation [5].

An important risk factor for recurrent infection is age: children may be particularly susceptible to recurrence. Of 95 children who were treated for a purulent SSTI at the Johns Hopkins ED in 2006–7, 22% had another SSTI within 3 months. It is possible that the genetic background of the infecting isolate or the antibiogram may have had an impact on the risk of recurrence because those with an initial MRSA infection were more likely than those with an MSSA infection to have a recurrence (28% vs. 5%) [6]. In one retrospective study, at least 5% of children with community-associated *S. aureus* infections had at least one recurrence; remarkably, more than 70% of these children had no known risk factors for recurrent infection, and fewer than 5% of the infections were not an SSTI [7]. In another study, recurrent infection (primarily SSTI) occurred in 50% of children with *S. aureus* SSTI within 12 months, compared with 22% of children with invasive *S. aureus* infection [4].

Although recurrent *S. aureus* SSTIs occur frequently in children, they are also common among adults. For example, recurrence rates among adults with a community-onset SSTI have been reported to be 21 – 50% [3,8]. Populations with increased frequency of recurrent *S. aureus* infection include incarcerated individuals [9], military personnel [10], men who have sex with men [11], and travellers to certain regions [12]. Environmental factors may also be important in recurrence; for example, recurrent infections in patients with a *S. aureus* SSTI were associated with contaminated household fomites and SSTI in household contacts [3].

Innate and adaptive immunity against *S. aureus* SSTI – Overview

Many interactions of *S. aureus* with host immunity have been well characterized. As is the case with many pathogens, innate immunity is the first line of defense against *S. aureus*. Innate defenses against cutaneous *S. aureus* infection include the barrier function of skin, antimicrobial peptides, complement, neutrophils, macrophages, and other innate immune cells, such as $\gamma\delta$ T cells [13]. It is less well understood how (and if) the adaptive immune system reacts to *S. aureus* infection or colonization in order to shape memory responses that protect against recurrent infections. Adaptive immunity is traditionally classified into cell-mediated (T lymphocyte) and humoral (B lymphocyte/antibody) immunity. Vaccines against *S. aureus* infections have targeted humoral immunity, but the failure of several candidates despite high levels of vaccine-specific antibody among vaccinated individuals [14] demonstrates a need to better understand both the mechanisms of protective immunity and those employed by *S. aureus* to evade immune surveillance and defense.

Neutrophils as the first line of innate defense against primary *S. aureus* SSTI

Neutrophils have long been established as critical for defense against *S. aureus* SSTI. For example, chronic granulomatous disease or congenital neutropenia result in a high risk of recurrent infection [15]. Congruent with human disease, neutrophils are required for defense in a mouse model of *S. aureus* SSTI [16]. However, demonstrating a role for neutrophils is highly dependent on assay conditions, particularly in the presence of opsonizing antibody [17]. Moreover, the timing of the neutrophil response may be critical. For example, abrogation of integrin-mediated neutrophil crawling prior to infection worsened lesion severity in a mouse model of *S. aureus* SSTI, but abrogation shortly after infection improved outcomes [18]. This suggests that, although neutrophils are clearly critical to control *S. aureus* SSTI, a sustained neutrophil response may prevent resolution of infection.

Innate defenses against *S. aureus* SSTI – other considerations

Other recent mechanistic insights into important immune pathways include the identification of the proinflammatory interleukin (IL) -1 β , acting via the IL-1R and the NALP3 inflammasome, as critical for defense against *S. aureus* SSTI [13]. The innate $\gamma\delta$ T cells are a key source of IL-17 after *S. aureus* infection, and have been identified as critical in a mouse model of SSTI [13,19]. This role may be distinct from the role of IL-17 in adaptive immunity against *S. aureus* SSTI (discussed below). IL-33 increases the antibacterial capacity of dermal macrophages, and thereby promotes defense against *S. aureus* SSTI, by activation of inducible nitric oxide synthase [20]. At the same time, the IL-20 cytokine family, implicated in inflammatory skin diseases such as atopic dermatitis, suppresses IL-17 and IL-1 β responses to promote *S. aureus* SSTI in mice [19].

The importance of innate immunity is highlighted by several recent reports documenting novel mechanisms by which *S. aureus* subverts innate defenses. For example, α -hemolysin (Hla) binds the cellular receptor ADAM10, thereby disrupting epithelial integrity in the skin, lung, and vascular endothelium [21]. Interestingly, the Hla-ADAM10 interaction in myeloid-lineage cells protects against *S. aureus* SSTI, but exacerbates *S. aureus* pneumonia [22], suggesting that the role of specific immune effector mechanisms may be highly dependent on the site and type of infection. Therefore, what is relevant in one model or

infectious syndrome may not be in another. Hla also lyses perivascular macrophages, leading to decreased neutrophil transmigration and more severe skin lesions [23]. Other recently elucidated innate evasion mechanisms include *S. aureus* promoting neutrophil killing by binding to the chemokine receptors CXCR1 and CXCR2 via the leukotoxins LukED and HlgAB [24,25]. *S. aureus* toxins also bind the chemokine receptors CCR2 (HlgAB) and CCR5 (Panton Valentine leukocidin – PVL) [25,26]. PVL and HlgBC also interfere with complement-mediated innate immunity by binding to the complement receptors C5aR and C5L2 [25,27].

Adaptive immunity against *S. aureus* SSTIs – limitations of animal models

A key unanswered question is whether or not *S. aureus* SSTIs (or any *S. aureus* infections) elicit immunity that protects against recurrent infection. Because of the uncertainty resulting from clinical studies, there is an urgent need to better understand protective immunity in experimental models of *S. aureus* SSTI. Several mouse models of primary *S. aureus* SSTI in naïve animals have been reported. For example, subcutaneous or epicutaneous inoculation results in dermonecrotic lesions with underlying abscess formation that resemble infections in humans [28,29]. These models have proven invaluable for understanding the microbial determinants of virulence and innate immune responses. However, these models employ infection in mice that are immunologically naïve to *S. aureus*, a major limitation given the nearly ubiquitous presence of antistaphylococcal antibodies in the human population.

There are other important limitations to the mouse models. First, mice are probably not a natural reservoir of *S. aureus*, and are believed to be resistant to the effects of superantigens, limiting our ability to understand the contributions of these important virulence factors to the pathogenesis of these infections [30]. Second, the structure of mouse skin is different from human skin [31]. Third, there are important differences between human and mouse innate and adaptive immune responses, particularly when considering the role of innate immune cells such as $\gamma\delta$ T cells [32]. However, the relatively low cost, availability, and the ability to interrogate host immune mechanisms through the use of genetically modified mice are significant advantages that must be considered.

Cell-mediated immunity

T lymphocytes are clearly important in adaptive immunity against *S. aureus* SSTI. For example, patients with the Hyper-IgE syndrome, characterized by defects in Th17/IL-17 immunity, are at high risk for recurrent skin and pulmonary infections [33]. These observations have led many to believe that targeting the Th17/IL-17 pathway will be essential to vaccine design. Along these lines, at least one candidate vaccine in preclinical evaluation, NDV-3, protects against *S. aureus* SSTI via IL-17A and the related T cell cytokine, IL-22 [34]. However, the mechanisms underlying recurrent staphylococcal disease in Hyper-IgE syndrome remain incompletely understood and are likely more complex than simply IL-17 deficiency; the immunodeficiency is actually comprised of a heterogeneous collection of phenotypes caused by multiple genetic mutations [35].

In further support of a role for T cells in defense against *S. aureus* SSTI, patients with poorly controlled HIV (as assessed by low CD4⁺ T cell counts and high viral loads) frequently

have recurrent SSTI [36], although there are conflicting data on the importance of CD4+ counts as a predictor of SSTI risk [37]. Patients with atopic dermatitis are also susceptible to *S. aureus* SSTI, which may be partly due to increased levels of Th2 cytokines and subsequent STAT6 expression, that may increase susceptibility to Hla-induced keratinocyte death [38].

A recently reported mouse model has provided experimental support for a role for T cells in protection against recurrent *S. aureus* SSTI. In this model, primary and secondary SSTI were separated by 8 weeks [39]. Interestingly, primary SSTI protected BALB/c, but not C57BL/6 mice against recurrent experimental SSTI, resulting in smaller skin lesions, a decrease in the number of bacteria recovered from the skin lesions, and attenuated local inflammation. Effector T cell mechanisms were critical, because protection occurred even in the absence of B cells and antibody, and adoptive transfer of T cells from *S. aureus*-infected BALB/c mice protected naïve mice. Primary SSTI elicited differential T cell polarization, with a Th17/IL-17A-biased response in BALB/c mice, compared with a Th1/IFN γ -biased response in C57BL/6 mice, suggesting opposing roles for Th17 and Th1 responses in protection. Indeed, neutralization of IL-17A abrogated protection, and neutralization of IFN γ enhanced protection.

In further support of a role for T cell-mediated immunity, Murphy et al reported that intraperitoneal infection of mice with *S. aureus* elicits $\gamma\delta$ T cell-mediated protection against secondary infection [40]. Although $\gamma\delta$ T cell-mediated protection against primary infection required IL-1 signaling, consistent with other reports documenting the importance of this cytokine in innate immune defense against *S. aureus* SSTI [13], IL-1 was dispensable for expansion of the memory $\gamma\delta$ T cell population. These findings highlight the potential distinction between innate and adaptive mechanisms, and underscore the importance of investigating immune defenses in the setting of animals that have previously been exposed to *S. aureus*.

Antibody-mediated immunity

Whereas T cell-mediated immunity is clearly important in adaptive immunity against *S. aureus*, a role for antibody-mediated immunity has not been definitively established. Patients with defects in antibody-mediated immunity, such as X-linked hypogammaglobulinemia, may have increased risk of recurrent *S. aureus* SSTI, but this association is not entirely clear [41]. Natural antibodies against *S. aureus* in humans are detectable shortly after birth, but have not been demonstrated to be protective [42]. Furthermore, a substantial body of evidence suggests that infection elicits antibody responses in patients, but whether these are protective is not clear. Children with *S. aureus* SSTIs developed transient humoral responses that were not associated with protection against recurrent SSTI; however, invasive *S. aureus* infection elicited higher antibody levels against Hla, and these children had a lower risk of recurrent infection, suggesting a protective role for these antibodies [4]. Compared with healthy controls, children with invasive *S. aureus* infection, but not *S. aureus* SSTI, had higher levels of antibody against bicomponent leukotoxins, but it is not known if these are associated with protection against subsequent infection [43]. Therefore, it is clear that anti-staphylococcal antibodies are

common in the population, regardless of known infection history, and that these antibody repertoires are not entirely protective.

In the mouse model of recurrent SSTI discussed above, adoptive transfer of serum and purified antibody from previously infected BALB/c mice protected naïve BALB/c and C57BL/6 mice against *S. aureus* SSTI, demonstrating a clear role for antibody-mediated immunity in this model [39]. Importantly, serum from infected C57BL/6 mice did not protect mice of either genetic background, suggesting that comparison of protective BALB/c and nonprotective C57BL/6 serum might identify antigen-specific protective antibody repertoires, an important direction for future research.

Another model of reinfection has recently been reported, in which primary SSTI with 1×10^7 CFU in C57BL/6 mice was followed 21 days later by secondary SSTI with $3\text{--}4 \times 10^7$ CFU [44]. Mice that were primarily infected with *S. aureus* had larger lesions after a second SSTI, compared with mice that were primarily infected with an isogenic *S. aureus* isolate in which Hla was deleted. There were no significant differences in the number of bacteria recovered from skin lesions 1 or 3 days after the second SSTI. Therapeutic delivery of a recombinant inactive Hla mutant or an ADAM10 inhibitor decreased the severity of secondary SSTI. These results support the hypothesis that Hla suppresses local inflammatory responses and the subsequent development of Th1 and Th17 responses [45].

Interfering with protective antibody?

The findings that some antibody responses may protect against *S. aureus* SSTI are difficult to reconcile with the notion that the nearly ubiquitous anti-staphylococcal antibody repertoire have not been demonstrated to be protective. One possible explanation is that only a limited antigen-specific repertoire is protective, and the majority of anti-staphylococcal antibodies are not protective. It appears that *S. aureus* is capable of patterning the host antibody response in order to favor nonprotective responses. For example, in a small study of patients with *S. aureus* infection (primarily SSTI), Pauli et al demonstrated that activation of B cells was limited, with a predominant bias toward those having specificity toward staphylococcal protein A (SpA), suggesting that this response limits development of antibody against other *S. aureus* antigens [46]. Therefore, it is plausible that this immunodominant response prevents the development of an otherwise protective antibody repertoire.

CONCLUSION

Recurrent *S. aureus* SSTI are extremely common, occurring in up to half of infected patients. Environmental and epidemiologic factors are clearly associated with recurrence, as are comorbid conditions. Clinical investigations have identified innate and T cell-mediated immunity as important mechanisms of protection against recurrent infection, but the role of antistaphylococcal antibodies, which are present in nearly all sampled individuals, is less clear. It is likely that *S. aureus* inhibits protective antibody responses, at least partly via protein A, with a resulting antibody response that is skewed toward a nonprotective repertoire. Several recently described animal models of recurrent infection show promise, and point to multiple mechanisms of defense against recurrent SSTI requiring both

antibody- and T cell-mediated immunity. Additional investigation is necessary to define the nature of protective immunity elicited by *S. aureus* infections.

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KEY POINTS

- Recurrent *S. aureus* SSTI is very common.
- Most recurrent *S. aureus* SSTIs occur in patients without identified risk factors.
- Innate immunity is the first line of defense against *S. aureus* SSTI.
- T cell-mediated immunity is clearly important in adaptive defense against recurrent *S. aureus* SSTI.
- The role of antibody-mediated immunity against recurrent *S. aureus* SSTI remains incompletely defined.