Vaccines for *Staphylococcus aureus* Infections

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INTRODUCTION

Nearly three quarters of a century after the introduction of the potent anti-staphylococcal drug penicillin, *Staphylococcus aureus* remains a significant bacterial cause of morbidity and mortality in the human population. This gram-positive organism exists as a commensal in the human, residing in the nares or on the skin of approximately one-third of individuals at any time (1,2). The epithelial layer of the skin and mucous membranes proves to be a potent host defense mechanism against staphylococcal infection. A breach of this barrier, however, predisposes the host to a myriad of disease manifestations resulting from *S. aureus* invasion of the tissues. The remarkable pathogenic potential of this organism has been demonstrated over the past decade, with the rapid spread of highly virulent *S. aureus* strains worldwide (3–6). A collection of features distinguishes these strains from those previously associated with disease. Most isolates carry the SCC*mec* IV genetic element that confers resistance to β-lactam antimicrobials, rendering this entire class of antimicrobials obsolete (7). In addition, they demonstrate a novel epidemiologic pattern, frequently being transmitted outside the hospital environment, among otherwise healthy individuals; thus they have been designated community-associated methicillin-resistant *S. aureus* (CA-MRSA) (8–10). Finally, a growing number of studies have defined unique virulence traits expressed by these strains. The factor that has garnered the majority of attention by virtue of its high degree of epidemiologic association with invasive *S. aureus* disease is Panton-Valentine leukocidin (PVL), a pore-forming cytotoxin with specificity for leukocytes (11–15). The genes encoding PVL are present on a bacteriophage, a mobile genetic element that contributes to genomic plasticity through horizontal gene transfer (16). Additional phage-encoded proteins that have been demonstrated to contribute to the virulence phenotype include the plasminogen activator staphylokinase (Sak) (17–19), the immunomodulatory proteins CHIPS (chemotaxis inhibiting protein) and SCIN (staphylococcal complement inhibitor) (20–22). Most recently, Wang et al., have defined a novel class of secreted staphylococcal peptides termed ''phenol-soluble modulins'' (PSMs) that are highly expressed in current CA-MRSA isolates, and contribute to the destruction of human neutrophils (23). While it is unlikely that a single factor in CA-MRSA strains is solely responsible for the high virulence phenotype, it is readily appreciated that a constellation of pathogenic traits may render these strains more capable of causing significant infection in healthy hosts.

The emergence of these strains, coupled with current antimicrobial resistance patterns, has raised concern of the potential of this pathogen to reach epidemic proportions (24,25). The cumulative burden of *S. aureus* infection heightens the demand for vaccines that are capable of inducing protection against a wide array of disease manifestations within a broad population of individuals. This approach clearly necessitates the targeting of bacterial virulence factors that are essential to the pathogenesis of the organism, irrespective of the specific type of infection. Further, the current spectrum of disease observed in the pre-vaccine era requires novel strategies to facilitate early identification of the pathogen and the development of disease-specific immunotherapy to be used independently or in concert with antimicrobial drugs.

PATHOGENESIS OF *STAPHYLOCOCCUS AUREUS* INFECTION

S. aureus achieves success as a pathogen through a combination of factors. First, its close relationship with the human host as a commensal positions the organism in immediate proximity to the tissues in which it is suited to cause disease. Indeed, colonization with *S. aureus* is a significant risk factor for the development of invasive disease (26–28). Second, the dynamic spread of the organism is facilitated primarily through person-to-person contact. The human population thereby serves as a ready conduit for transmission. Lastly, a number of virulence factors intrinsic to the organism work together in a concerted fashion to permit host tissue invasion, bacterial proliferation, and evasion of the host defense, culminating in the spread of the pathogen.

Clinical Manifestations of Disease

Essentially, every organ system and tissue of the human is susceptible to infection with *S. aureus*. The most common site of infection is the skin and soft tissues, however this pathogen also results in frequent infection of the deep tissues, causing pneumonia upon replication in the lungs, osteomyelitis of the skeletal system, and endocarditis when affecting the lining of the heart (29). Bloodstream infection, or septicemia, is often related to seeding of these deeper organs, and in and of itself accounts for approximately 75,000 cases of disease per year in the United States alone (30). The direct consequence of *S. aureus* infection of specific tissues is further confounded by a number