Application of *Staphylococcus aureus* Vaccines

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Staphylococcus aureus, a prevalent human pathogen and a leading cause of hospital-acquired infections, is increasingly evolving antibiotic-resistant strains, increasing mortality and morbidity rates. Anti-staphylococcal vaccine research for prevention and treatment has become a priority. Antibodies against specific *S. aureus* components, toxins, and polysaccharides have demonstrated encouraging results in animal studies regarding protection against colonization or infection. However, human immunization trials have yielded less optimistic outcomes, with no anti-staphylococcal having passed clinical trials up to now. Although multiple formulation attempts triggered strong antibody responses, the vaccines could not effectively prevent *S. aureus* infections.

Keywords: *Staphylococcus aureus* ; vaccines

1. Introduction

The rise in *Staphylococcus aureus* antibiotic resistance poses a significant healthcare challenge of the twenty-first century [1]. Although new antibacterial medications are constantly being developed, there are still isolates identified that are resistant to even the most cutting-edge antibiotics, such as linezolid [1].

Gram-positive *S. aureus* is well known for the number and severity of infections it causes in hospitalized patients [2]. The illnesses include localized skin infections, bacteremia, and septic shock [2]. *S. aureus* frequently colonizes human skin and mucosa, especially the upper airways, although some strains appear to prefer the gastrointestinal tract [3].

In addition to being a significant cause of severe toxin-mediated diseases, such as toxic shock syndrome, epidermolysis syndromes, and gastroenteritis, *Staphylococcus aureus*—despite being a commensal of human skin and the nares—frequently causes bacteremia, skin and soft tissue infections, pneumonia, osteomyelitis, and septic arthritis [4][5].

S. aureus colonizes a wide variety of tissues, which can either result in less-severe manifestations such as folliculitis, or in potentially fatal infections like pneumonia, endocarditis, osteomyelitis, and sepsis [6][7]. The pathogen is known to cause recurring diseases, indicating that humans do not naturally develop a strong, long-lasting immune response against it [6]. In recent decades, the need for a vaccine to prevent the spread of *S. aureus*-related invasive disease has significantly grown [4]. It is vital to develop an effective vaccine to lower the frequency of fatal diseases [6]. Numerous antigens found on the surfaces of *S. aureus* strains have been researched for their vaccination potential, either curative or preventive [6]. Understanding the immune response to a particular organism is frequently necessary for the development of a vaccine so that it may be improved upon through thoughtful vaccine design [5]. Natural anti-*S. aureus* immunity has been extensively studied, but further research is needed to bridge the gap to vaccines [2].

2. Application of *Staphylococcus aureus* Vaccines

Staphylococcus aureus has the ability to permanently colonize humans; as a result, the bacteria and the host immune system constantly interact [8]. The finding that all people already have antibodies against *S. aureus* antigens supports this [8]. *S. aureus* colonization increases the risk of infection following surgery or trauma, despite the fact that it generally does not trigger infection in healthy persons [9]. Vaccines are promising substitutes for harmful antibiotics [9].

In a trial aimed at reducing *S. aureus* colonization, antibody concentrations dramatically increased following conjugate-vaccine immunization, regardless of age, occupation, or colonization status [10]. Despite this increase in humoral antibody concentrations, five additional patients became colonized, and 74% of those with persistent colonization maintained their status [10].

Active immunization can considerably lower lung bacterial loads one day after *S. aureus* pneumonia infection [11]. Although the bacterial loads in the control group decreased with time, they remained significantly higher than those in the

$IsdB_{151-277}ClfA_{33-213}$ group [11]. While pneumonia severity was controlled in the $IsdB_{151-277}ClfA_{33-213}$ group, it grew worse over time in the control group [11]. Another respiratory disease that would benefit from a *S. aureus* vaccine is bronchiectasis [12][13]. Genetic and environmental factors contribute to the development of bronchiectasis, though its exact etiopathology is still unknown [12][13]. It is an irreversible lung disease characterized by chronic inflammation of the of the proximal and medium-sized bronchi (>2 mm in diameter), and recurrent bacterial infections [12]. Although this pathology is common, it represents a significant cause of respiratory morbidity [12]. This compromises mucociliary clearance, rendering airways more susceptible to pathogen colonization [12].

When challenged with *S. aureus*, mice immunized with recombinant ClfA showed fewer instances of severe arthritis than mice immunized with a control antigen [14]. The protection provided by active immunization is antibody mediated, as evidenced by the fact that mice passively immunized with rat and rabbit anti-ClfA antibodies were protected against *S. aureus* arthritis and sepsis-induced death [14]. When considered collectively, these data strongly imply that ClfA is a key virulence factor for septic arthritis and a fantastic target for the development of immune therapies against *S. aureus* [14].

The direct binding of platelets by bacteria is a critical factor in the development of infective endocarditis (IE) [15]. For pathogenetic events that take place after the initial colonization of the valve surface—vegetation development and septic embolization—staphylococcus–platelet binding appears to be essential [15].

Inducing coagulation may promote the formation of new platelet and fibrin deposits on top of the infection nidus, protecting vegetation-adherent bacteria from further mechanical detachment and/or cellular host defense systems [16].

The likelihood of valvular infection depends on both the level of post-challenge bacteremia and the ligand-receptor interactions between the surface components of damaged valves and bacteria [16].

Although the proportion of staphylococci and streptococci has varied over time and by region, these two organisms have together accounted for about 80% of IE cases [17]. While the percentage of IE caused by viridans-group streptococci has decreased, the prevalence of *S. aureus* and coagulase-negative staphylococci has increased in tandem with the rise in healthcare-associated IE [17]. The third most common cause of IE is enterococci, which are becoming increasingly associated with medical interactions [17]. When infections with Gram-negative and fungal pathogens do arise in IE, they are mainly linked to health care [17].

Because of the severity of *S. aureus* infection, individuals in high-risk groups who are exposed to situations that enhance their chances of contracting *S. aureus* bacteremia should consider receiving suitable prophylaxis [18]. Patients are frequently prescribed prophylactic antibiotics; however, a lot of *S. aureus* strains, particularly those with nosocomial origins, are multiresistant. Additionally, certain antibiotic classes may cause allergies in certain patients [18]. Up to now, a number of studies have been carried out with the goal of creating a preventive vaccine, but they have been unsuccessful in creating a safe and reliable *S. aureus* IE vaccine [18].

For patients in critical care units or undergoing planned surgery, a vaccine that triggers an immediate protective response against *S. aureus* infection would be ideal [19]. The 4C-Staph vaccine, when appropriately adjuvanted, may help to accomplish this [19]. In a study, a novel small molecule targeting TLR7 adsorbed to alum was added to 4C-Staph to create 4C-Staph/T7–alum [19]. This vaccine formulation was tested as a single dose in mice models of *S. aureus* kidney abscess and peritonitis [19].

The 4C-Staph/T7–alum vaccine outperformed the 4C-Staph–alum formulation by more than 100 times, lowering the bacterial load in the kidneys of mice infected intraperitoneally and protecting around 80% of vaccinated animals from the catastrophic results associated with an intraperitoneal infection (i.p.) challenge [19]. Surprisingly, compared to 54% of 4C-Staph–alum vaccinated mice, 91% of mice that survived the i.p. had no detectable staphylococci in their kidneys [19]. These observations demonstrated that 4C-Staph/T7–alum facilitated more-effective control of bacteria than 4C-Staph–alum. Nonetheless, they revealed that using survival rates alone to estimate *S. aureus* vaccination efficiency might lead to overestimation of outcomes [19].

Several factors complicate the clinical evaluation of an investigational *S. aureus* vaccine at each stage of its development, one of which is the high likelihood that the final target population for any vaccine will be larger than can be investigated in efficacy trials [20]. When one takes into account the diversity of human populations at risk for *S. aureus* infection as well as the various comorbidities within those populations, one can appreciate the complexity of any potential clinical development plan [20].

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