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Immunoglobulins' Response During Staphylococcal Infections: A Review

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Abstract

Staphylococcus aureus infects the human nasal cavity and integument, and also result in bloodstream and soft tissue infections. Antibiotic resistance strains appeared in the last decades. These infections are corelated with weak antibacterial treatment and high death rates. Methicillin-resistant Staphylococcus aureus (MRSA) is a common causative agent of dangerous blood infection; anyhow, immunological treatments may target surface molecules in Staphylococcus. However, S. aureus release coagulase (Coa), that trigger host clotting mechanisms. Traditionally, new immunological strategies against bacterial pathogens have focused on antibodies that target cell surface-exposed virulence factors or bacterial toxins. In this study, a monoclonal antibody was developed against IsaA, a proposed soluble lytic transglycosylase in Staphylococcus aureus, and its therapeutic potential was evaluated in two mouse infection models. Previous studies examining the relationship between antibody responses and clinical outcomes in S. aureus bacteremia have produced inconsistent findings, and vaccination protocols have not succeeded in clinical trials. Elevated antibody levels against peptidoglycan generally correlated with increased IgG antibodies to teichoic acid, although no cross-reactivity between peptidoglycan and teichoic acid was detected. The recent emergence of community-acquired methicillin-resistant S. aureus (MRSA) has raised concerns regarding more severe and persistent disease following invasive infections. Overall, staphylococcal peptidoglycan is immunogenic in humans, and measuring IgG antibodies to peptidoglycan could serve as a valuable tool for diagnosing and monitoring serious staphylococcal infections.

Keywords: Immunoglobulins, IgG, IgM, Staphylococcus aureus, MRSA

Introduction

Staphylococcal infection continues to pose a formidable threat in community and hospital environment (Chen, Bubeck Wardenburg, & Otto, 2023; François et al., 2017), not only because of the pathogenic versatility exhibited by staphylococci species (including Staphylococcus aureus and coagulase-negative staphylococci) but also their ability to evade immunity and relapse. The recent worldwide evolution of staphylococcal resistance to antibiotics, especially methicillin-resistant S. aureus (MRSA), has brought back attention to immunoglobulin-based or antibody- based approaches as complementary or alternative strategies for conventional antimicrobials (François et al., 2017; Ke et al., 2024).

In the present review, we survey the landscape of immunoglobulin (Ig) responses during staphylococcal infections, mapping how different antibody classes contribute to defense, how *Staphylococcus* species undermine those defenses, and where gaps remain to guide future research and translational application. In staphylococcal infection, the humoral (adaptive) immune response encounters two basic hurdles: first, to produce immunoglobulin carrying sufficiently high affinity for antigen; and second, to neutralize or bypass microbial offensive tactics. The human antibody response to S. aureus is highly heterogeneous: in a population-based cohort of almost 1000 individuals, IgG and IgA responses to 79 staphylococcal antigens varied by several orders of magnitude, and none of the recorded host-specific factors (e.g., colonization status, sex, age, BMI) could capture more than a fraction of the variance (Meyer et al., 2021). Systemic (IgG) responses are considered to be of major importance for invasive disease, while mucosal responses (IgA) contribute to barrier or colonization defense (Meyer et al., 2021).

However, a large proportion of people carry S. aureus asymptomatically, and it is not known whether the common anti-staphylococcal antibody responses are indeed protective or simply ephemeral correlates of exposure. In fact, chronic exposure to S. aureus through colonization presumably accounts for a basal humoral “memory” that could possibly impact the response to an infective challenge or a vaccination (Karauzum et al., 2017). However, some immunodeficiency states show reduced selective antibody response to S. aureus antigens associated with susceptibility: as an example, patients suffering from STAT3-hyper IgE syndrome were reported to present significantly lower amounts of S. aureus–specific IgG despite recurring infections, while replacement therapy by immunoglobulins improved their specific IgG levels and their disease course (Stentzel et al., 2017). These studies emphasize that it is not just the amount, but specificity and function of antibodies are also important in staphylococcal immunity.

Staphylococci are highly skilled in both circumventing and sabotaging host humoral defense mechanisms. One of the most characteristic evasive mechanisms is an evasion mediated by protein A (SpA) which specifically binds Fc portion of IgG and prevents efficient opsonization and phagocytosis209. (Thammavongsa, Kim, Missiakas, & Schneewind, 2015; Mukherjee & Foster, 2016). S.aureus also expresses a variety of virulence factors inducing superantigens, immune modulator proteins, and proteases that inactivate or degrade antibodies, or prevent complement activation (Chen et al., 2023; François et al., 2017). Its immune-evading proteins arm it to escape almost every immunological weapon of the host (Loomba & Wardenburg, 2019). Some are even proteases that negate antibody production or B cell differentiation, thereby further crippling host defense (Chen et al., 2023).

Furthermore, S. aureus can switch to biofilm lifestyles and intracellular forms or remain as small-colony variants (SCVs) to evade immunity by immunoglobulin surveillance or antigen expression reduction (Ke et al., 2024; Lapeyre et al., 2025). Such strategies may limit antibody access to targets, attenuate immune activation, or promote relapse of disease after treatment. In view of these challenges, antibody therapy against staphylococci has come a long way from just toxin-neutralzing immunoglobulins. Human monoclonal antibodies (mAbs) to important virulence antigens, including alpha-toxin, ClfA (clumping factor A), and other surface proteins have all progressed into preclinical and early clinical stages of development (François et al., 2017; Ke et al., 2024). For instance, commercial IVIGs harbor antibodies to neutralize S. aureus cytotoxins such as LukAB at functional potency equivalent to convalescent sera (Wood et al., 2016).

Immunoglobulin G in Staphylococcal infections

Staphylococcus aureus is an opportunistically living bacterium that results a range of dangerous infections elated with high death rates, by strains that resist to antimicrobials. Previous studies have focused on infection-related immune reactions, clints have been subjected to sample collection from three different infection locations; Prosthetic joint infection, skin and soft tissue infection (SSTI). Activity of serum IgG has been investigated with a series of recombinant polypeptides, comprising more than 2,652 in vitro–translated open reading frames (ORFs) derived from a community-acquired methicillin-resistant S. aureus USA300 strain. Increased reactivity level has been investigated for many types of polypeptides with serum immunoglobulins in all types of infections. Collectively, elevated IgG responses were primarily targeted toward a specific group of secreted proteins. (Radke et al., 2018). It was observed

that clients submitted with decreased count of Staphylococcus aureus, so that specific serum IgG were used to detect recurrent S. aureus infections. Immunoglobulin replacement therapy enhanced *S. aureus*-specific IgG levels in STAT3-HIES patients and mitigated disease severity, indicating that humoral immunity contributes to *S. aureus* clearance (Stentzel et al., 2017).

Staphylococcus aureus results in a wide range of dangerous bacterial infections resulting in high death and health deterioration globally. It was found that neutralizing antibody (NAb) and immunoglobulin G (IgG) levels in pediatric patients (less than year) were extensively less than those in other communities. Regarding adult and geriatric individuals and young pediatric patients (between two to ten years) had similar IgG levels but extensively lower anti-AT NAb concentrations. So that, the formation of anti-AT NAbs seems to happen after of AT-specific IgG, which suggests the magnification of the immune reaction to AT. However, Anti-AT IgG concentrations were just above that in subjects infected with *S. aureus* than in those with no colonization. The susceptibility status of methicillin by colonizing *S. aureus* had no impact on anti-AT antibody concentrations in subjects eith long term infection with *S. aureus*. The greatest NAb and anti-AT IgG concentrations were reported in patients under dialysis infected abruptly with *S. aureus*. The Nab and Anti-AT IgG concentrations were well associated in subjects more that ten years, without regarding to of bacterial-host status. These findings exhibit that AT trigger a burst IgG activity in pediatric patients which then be stable before adolescence, upgrade into greater concentrations of NAbs in uninfected adolescents, and are increased at chronic *S. aureus* infection. (Wu et al., 2018).

Staphylococcus aureus is an opportunistic bacterium responsible for various severe infections that contribute to considerable morbidity, with many strains showing growing resistance to antibiotics. Despite multiple attempts, all vaccine candidates developed thus far have failed to generate effective protective immunity in humans. Hence more clearly defined antigenic targets in human infection are warranted. For investigating immune responses associated with infection, patients were sampled at onset and convalescence of three clinical types of infection: skin and soft tissue infection (SSTI), prosthetic joint infection (PJI), pediatric hematogenous osteomyelitis (PHO). Earlier research has identified a hierarchy among the numerous proteins within the *S. aureus* "immunome," providing valuable insight for the development of future protective immunotherapies (Radke et al., 2018). Opsonization of *Staphylococcus aureus* (Oxford strain) and the levels of specific IgG subclass antibodies against formalin-treated staphylococci were analyzed in plasma samples from 30 patients suffering from notable *S. aureus* infections, along with 40 healthy adults and 20 children. No statistically significant differences were observed in IgG2 and IgG4 concentrations between the groups, and IgG3 was undetectable. However, the median plasma IgG1 concentration was markedly elevated in individuals with staphylococcal infection (Monteil et al., 1990).

Staphylococcal protein A (SpA) is a highly conserved and multifunctional virulence factor produced by *Staphylococcus aureus*. It binds to the Fc region of all human IgG subclasses except IgG3, thereby disrupting antibody and complement attachment to the bacterial surface and hindering effective phagocytic clearance. Due to its anti-opsonic function, SpA has generally not been considered a suitable surface antigen for promoting bacterial phagocytosis. In this study, human sera were analyzed for the presence of antibodies capable of opsonizing SpA. The results showed that sera containing IgG3 specific to SpA successfully opsonized the bacteria and facilitated Fcγ receptor-dependent interactions and phagocytosis. Moreover, IgG3 Fc demonstrated a markedly greater ability to promote phagocytosis of SpA-expressing *S. aureus* than IgG1 Fc under near-physiological conditions. The findings also revealed that the phagocytic activity of anti-SpA antibodies is determined by the specific epitopes targeted by IgG molecules on the SpA protein (Boero et al., 2022).

Immunoglobulin M in Staphylococcal infections

Among patients with *Staphylococcus aureus* infections, elevated IgM antibody levels against staphylococcal antigens—detected via radioimmunoassay—were found in 15 of 20 individuals with endocarditis, 10 of 25 with complicated bacteremia, 2 of 22 with uncomplicated bacteremia, and 3 of 24 with nonbacteremic infections. In the control groups, increased IgM antibody levels were observed in 6 of 28 individuals with gram-positive infections, 3 of 18 with gram-negative infections, 2 of 22 with rheumatoid arthritis, and 3 of 55 uninfected participants. Simultaneous elevation of both IgG and IgM

antibodies occurred in 22 of 45 patients with endocarditis or complicated bacteremia, compared to 3 of 45 patients with other staphylococcal infections and 4 of 120 control subjects. Early in the disease course, only IgM antibodies were detected in 7 of 15 patients with staphylococcal endocarditis or complicated bacteremia. IgG or IgM antibody levels remained high for at least four weeks following the start of therapy (Wheat et al., 1981).

Staphylococcus aureus is one of the main human pathogenic bacteria. The infection caused by it is well-controlled by the immunological mechanisms that fight against bacterial infections. elevated levels of opsonic IgG immunoglobulins, gotten in laboratory animal vaccination studies, have steadily not succeeded to give protective effect in mans and animals. Antibody responses were investigated to the wall teichoic acid (WTA) of surface glycan for S. aureus and the occurrence of IgG antibodies and WTA-specific IgM in the serum of healthy populations were also diagnosed and detected. Practically, Wall teichoic acid (WTA)–specific IgM antibodies demonstrate superior efficiency compared to IgG in promoting opsonophagocytic killing of *Staphylococcus aureus* and can confer protection against systemic *S. aureus* bacteremia when used for passive immunization. Clinically, individuals suffering from *S. aureus* bloodstream infections exhibit markedly reduced levels of WTA-specific IgM, while their IgG concentrations remain comparable to those of healthy individuals. Of note, low WTA-IgM concentrations are closely related to both high mortality and a decreased abilty of bacteria opsonization, confirming the importance of IgM as defense against invasive S. aureus challenging (Hendriks et al., 2024).

Immunoglobulin A in Staphylococcal infections

Infection by Staphylococcus aureus may cause dangerous diseases such as antibiotic-resistant endocarditis, pneumonia and toxic shock with septicemia because the nasal colonization in healthy individuals is a key factor for the biomedical effect of Staphylococcus aureus. In the invasive infections and nasal carriage it rapidly approaches the host defenses where a plethora of mediators that subversion of host defense are generated. SSL7, a staphylococcal superantigen-like protein, has been shown to tightly interact with IgA and with the complement component C5.506–508 This allows SSL7 inhibition of immune mechanisms relying on these important mediators. Here we solved the 3D structure of the SSL7–IgA1 Fc complex at 3.5 Å resolution. The structural data showed that two molecules of SSL7 bind to the Fc moiety (one per heavy chain) largely at the interface of the Cα2-Cα3 domains. Each IgA chain provides an extensive binding surface, with SSL7 covering much of the lateral face of the Cα3 region. Despite this, the orientation of SSL7 permits potential association with secretory IgA. Importantly, the same IgA residues that engage SSL7 are also recognized by the leukocyte IgA receptor FcαRI (CD89). This overlap clarifies why SSL7 effectively blocks FcαRI-mediated IgA effector activities, including phagocytosis, degranulation, and respiratory burst. Consequently, the ability of Staphylococcus aureus to interfere with IgA-driven immune defense likely supports its persistence in mucosal sites, such as the nasal cavity, and may enhance its capacity to cause systemic infections (Ramsland et al., 2007)

The relationship between of infection caused by MRSA and glomerulonephritis (GN) was efficiently reported in many countries in the east and west. Nowadays, During a 10-month period at a single medical center, seven renal biopsies demonstrating IgA-dominant or co-dominant glomerulonephritis (GN) were obtained from seven patients who had underlying staphylococcal infections but no evidence of endocarditis. All renal samples were processed using standard histopathological techniques, and seven cases of primary IgA nephropathy served as controls. Among the infected patients, four had methicillin-resistant Staphylococcus aureus (MRSA), one had methicillin-resistant S. epidermidis (MRSE), and two had methicillin-sensitive S. aureus infections. Three patients developed infections following surgical procedures, while two were diabetics with infected lower-limb ulcers. All patients were in acute renal failure with active urine sediment and heavy proteinuria. Histologically, the majority (n = 14) of biopsies demonstrated mild glomerular hypercellularity, two cases demonstrated marked mesangial and intracapillary hypercellularity—one (the MRSE associated case) with large glomerular hyaline thrombi but negative cryoglobulin test. Some hyaline thrombi were also observed in two other samples. IgA was predominantly or co-dominantly demonstrated on immunofluorescence of all biopsies. On electron microscopy all cases had mesangial deposits of electron-dense material, and occasional deposits on glomerular capillary wall were also seen in four biopsies. In GN associated with MRSE, subendothelial electron-dense deposits were more

pronounced. These findings indicate that staphylococcal infection–associated GN, especially stemming from MRSA, is a problem in the United States and may be on the rise. The differentiation of staphylococcal infection–associated GN from primary IgA nephropathy is critical to avoid inappropriate immunosuppressive therapy (Satoskar et al., 2006).

Conclusion

Immunoglobulins are important in host defense against *Staphylococcus aureus* infection. But they are often ineffective against microbial biofilms. Because there are still plenty of knowledge gaps about the interplay of Ig responses and biofilm production, elucidating these areas is a fundamental step to develop new therapeutic strategies. Future are also suggested to identify alternative approaches to increase the effect of immunoglobulins, and elucidating molecular mechanisms underlying biofilm-induced resistance that can be used as target for new treatment strategy in order to enhance clinical success in staphylococcus infections.

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