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Progress in the Development of Effective Vaccines to Prevent Selected Gram Positive Bacterial Infections

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Abstract

Infections due to virulent gram positive bacteria, such as *Staphylococcus aureus*, group B streptococci and group A streptococci remain significant causes of morbidity and mortality despite progress in antimicrobial therapy. Despite significant advances in the understanding of the pathogenesis of infection due to these organisms, there are only limited strategies to prevent infection. In this paper, we review efforts to develop safe and effective vaccines that would prevent infections due to these 3 pathogens.

Keywords

vaccine; gram positive bacteria; Streptococcus; Staphylococcus

Staphylococcus aureus

Staphylococcus aureus (*S.aureus*) is an important human pathogen and is a leading cause of community and hospital-acquired soft tissue, blood-borne and device related infections in adults and children. Increasing rates of methicillin-resistant community- and nosocomially acquired strains complicate treatment and prevention of these infections. Risk factors for infection include disruption of mucosal or cutaneous surfaces, introduction of a foreign body or medical device, surgery, hemodialysis or host immunosuppression. Innate immunity to infection requires intact mucosal and skin surfaces, polymorphonuclear leukocytes and intact cellular and humoral immune responses. Because data suggest that immunity to *S. aureus* infection does not exist and that recovery from infection does not necessarily confer resistance, there is a critical need for an effective vaccine.¹ Strategies to prevent infection are largely based on surgical antisepsis, wound prophylaxis and use of topical antibiotics to eliminate carriage in high-risk populations. Immunologic attempts using either immune serum/toxoids or vaccines to prevent infection have targeted virulence factors that promote bacterial attachment, invasion or evasion of host immunity [Table 1].^{2–7} To date, no vaccine has been consistently successful, although some have prevented infection in laboratory animals, veterinary populations and humans.³ Most vaccine constructs elicit humoral responses; however, the role of opsonic antibodies in human staphylococcal infection is uncertain because the titer of antistaphylococcal antibodies does not necessarily correlate with protection.⁶

S. aureus strains have been tested as whole cell or lysate vaccines.^{8–11} Data from whole cell vaccines demonstrate mixed results. Whole cell vaccines failed to evoke protective immune responses in a rabbit model of catheter-associated infection¹⁰ but protected lactating ewes and cows in an animal model of mastitis¹² and protected mice from challenge infections.¹³ A polyvalent whole cell lysate vaccine containing 5 strains of *S. aureus* designed to reduce dairy cattle mastitis has been commercially available for veterinary use for years [Lysigin®]. However, this vaccine is not universally protective and data are mixed concerning efficacy. Whole cells combined with α -hemolysin failed to protect peritoneal dialysis patients from nasal colonization or infection,⁸ however, auto-vaccination with a formalin-inactivated Methicillin-resistant *S. Aureus* (MRSA) strain isolated from a patient with mediastinitis improved antimicrobial efficacy in the resolution of the infection.¹⁴ Additionally, auto-vaccination has had limited success in improving antibiotic therapy for mastitis in dairy cattle.

Several surface-associated molecules have been studied as potential vaccine constructs. Sero-epidemiologic studies reveal that human sera contain antibodies against a number of staphylococcal antigens, including capsular polysaccharide (CP).¹³ Several polysaccharide serotypes have been studied. The majority of clinical isolates belong to serotypes 5 and 8. Protection from infection has been demonstrated in several models when animals have been passively immunized with anti-CP antibodies.^{15, 16} However, CP is weakly immunogenic, and protective efficacy usually requires conjugation to a carrier molecule. In fact, *S. aureus* CP5 conjugated to *Pseudomonas aeruginosa* exotoxin A protected mice against challenge infection with the homologous serotype.¹⁷ Antibodies evoked by a bivalent CP5 and CP8 conjugated to exotoxin A vaccine transferred to rats were protective in a catheter-related infection model.¹⁵

The CP5 and CP8 exotoxin A conjugate vaccines have been tested in humans. Both evoked type-specific, opsonophagocytic antibodies in healthy humans without significant reactogenicity.¹⁸ Subsequently, the bivalent CP5/CP8 construct (StaphVax®) was evaluated in clinical trials in patients with end stage renal disease receiving hemodialysis.^{19, 20} The vaccine evoked lower levels of antibodies than anticipated but still partially reduced the risk of *S. aureus* bacteremia at certain time intervals within the study.^{20–22} Unfortunately, serum antibody concentration fell over time. In a second, larger study, the investigators identified a booster effect when patients were revaccinated 2–3 years later, but these patients were not protected against bacteremia.^{4, 19–21} A multi-component vaccine containing protein conjugates of CP5, CP8, teichoic acid, α -toxin and Panton-Valentine leukocidin (Penta Staph) is being evaluated.⁴ Polyclonal immune globulin against the CP5/CP8 exotoxin A conjugate evoked in healthy humans (AltaStaph®) when administered to very low birth weight infants in a phase I–II safety trial was well tolerated but did not statistically reduce *S. aureus* bacteremia.^{23, 24} In a later study, administration of AltaStaph® as adjunctive to antimicrobial therapy failed to improve survival in patients with *S. aureus* bacteremia.²⁵

Several surface adhesins have been studied as potential vaccine or toxoid candidates. Pagibaximab®, a mouse chimeric monoclonal antibody against lipoteichoic acid (LTA) is being evaluated for clinical use. Early evidence suggests that it may reduce the frequency of *S. aureus* bacteremia in low birth weight infants.²⁴ Poly-N-acetyl glucosamine (PNAG) is an intercellular adhesin whose deacylated form when conjugated to diphtheria toxin evokes opsonophagocytic antibodies that protect mice from challenge infections.²⁶ Multiple microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) have also been studied.²⁶ These molecules (including clumping factor A and B [ClfA, ClfB], collagen binding protein A [CNA], and fibronectin-binding proteins A and B [FnbpA, B], among others, help the organism colonize and invade host tissues. When used as vaccine candidates some of these molecules have demonstrated protective efficacy in laboratory animals.^{27–31}

IsdB is cell-wall anchored protein representing one of several *S. aureus* iron-regulated surface determinants (Isd). Antibodies evoked by this protein are opsonic and protected mice against challenge infections.³² Vaccination with IsdA or IsdH protected rats from nasal colonization by *S. aureus*.³³ More recently, a heteropolymer vaccine containing 4 antigens that are highly conserved among *S. aureus* strains [SdrD (a serine aspartate repeat protein), SdrEE, IsdA and IsdB] evoked protective immune responses in mice challenged with 4 of 5 *S. aureus* strains.³⁴ Lastly, a DNA vaccine containing the *mecA* gene that encodes penicillin binding protein 2a (PBP 2a) evoked protective antibodies reducing bacterial burden in mice.³⁵

Antibodies evoked by several surface-associated molecules have been tested in passive immunization studies. Tefibazumab (Aurexis®) is a humanized IgG₁ monoclonal antibody against clumping factor A (ClfA) that has been successful in a rabbit model of infection, but failed to promote a statistically significant response in humans.^{36, 37} Veronate® (INH-A21) a donor-selected human immunoglobulin containing antibodies against ClfA and SdrG, another MSCRAMM molecule, did not protect low birth weight neonates from staphylococcal infections.³⁸ Aurograb® is a single-chain antibody preparation against GrfA, an ATP-binding cassette transporter that is a drug efflux pump. Antibody against this protein increases vancomycin sensitivity. Although it has been shown to lower bacterial burden in MRSA challenged mice, its role in the treatment or prevention of human infection is not fully defined.³⁹

Several secreted toxins, including α -hemolysin (Hla), Panton-Valentine leukocidin (PVL), toxic shock syndrome toxin-1 (TSST-1) and staphylococcal enterotoxin, have been evaluated as vaccine candidates with variable success.^{40–42} Antibodies against Hla prevented injury to human lung epithelial cells during *in vitro* infection, suggesting a potential protective role in human infection.⁴⁰ A non-toxic Hla mutant (H35L) protected mice from lethal challenge infection,^{40, 43} but in another study a Hla toxoid failed to completely protect rabbits.⁴⁴ Several studies have evaluated the protective immunogenicity of staphylococcal superantigens. Non-toxic forms of staphylococcal enterotoxins have protected laboratory animals.^{41, 45, 46} Mixed results have been seen with TSST-1 as a vaccine candidate.^{42, 47} Passive immunization with antibodies evoked by PVL failed to protect mice.⁴⁰

Although a number of novel antigens are being studied, to date there is no effective staphylococcal vaccine for human use, and a number of key questions remain unanswered.^{27, 48–51} These include identifying measures of protective immunity, defining the most applicable animal models for testing vaccine efficacy and determining whether a vaccine can protect against nasal colonization and prosthetic device infection, among others. Novel approaches to antigen screening using sera from healthy controls (colonized and non-colonized) and from survivors of infection may identify differences in immune response that guide targeted efforts at vaccine development. Continued identification of virulence factors may allow for the development of a multi-component, efficacious vaccine.

Group B Streptococcus

Group B streptococcus (GBS) infection is a leading cause of neonatal sepsis. Serotypes Ia, III, and V are responsible for most of the cases in the United States and Europe. Currently, preventative strategies are based on intrapartum antibiotic prophylaxis.⁵² However, this antibiotic strategy is not universally protective, especially with late onset GBS disease, and carries with it the risks of antibiotic use.^{53–55} Of note, disease also occurs in non-pregnant adults, especially in those with chronic disease, adding to the need for safe and effective vaccine strategies.^{56, 57}

Vaccine strategies have focused on several surface-associated GBS molecules (Table 2).^{53, 54, 58} Interest in CP is based on the observation that low maternal anti-capsular antibody

concentration is correlated with neonatal susceptibility to infection.⁵⁹ CP, representing the more commonly observed clinical serotypes, coupled to an immunogenic protein (designed to improve the immunogenicity of the CPS) elicits protective immune responses in animal models.^{60, 61} GBS conjugate vaccines are immunogenic in non-pregnant women of childbearing years.^{62–64} Similarly, type III CP-tetanus toxin vaccine is well tolerated and evoked type-specific antibodies in pregnant women that are transplacentally delivered to the infants.⁶⁵ A type V CP conjugate is immunogenic in older adults, evoking type specific opsonophagocytic antibodies.^{66, 67} CPS conjugate vaccines representing all 9 currently identifiable GBS serotypes are being clinically evaluated.⁵⁴ Although each CPS serotype essentially only evokes type-specific immune responses, a multivalent vaccine could evoke immune responses broad enough to protect against prevalent serotypes.^{68, 69}

Several other GBS proteins have been investigated as potential vaccine candidates. The beta C protein (β CP) binds the Fc portion of human IgA allowing GBS to evade human immune responses and evokes protective immune responses in laboratory animals.⁷⁰ However, this peptide is not universally expressed in all strains of clinically important GBS, limiting its use as a protein-only vaccine component and suggesting that it may have greater utility as a carrier protein.⁵³ As an example, a β CP-type III CP conjugate vaccine elicited protective immune responses in mice.⁷¹ GBS C5a peptidase (ScpB) is a surface peptidase that inactivates human C5a, a human neutrophil chemoattractant, and is conserved at the gene level in the majority of GBS. Antibodies evoked by ScpB are opsonic.^{72, 73} Immunization of mice with ScpB improved lung clearance of bacteria following intranasal challenge infection⁷² and prevented maternal vaginal colonization and pup death.⁷⁴

Rib protein is another cell surface protein expressed in many strains of GBS that cause invasive infection.⁷⁵ Rib protein elicited protective immune responses when co-administered with the B subunit of cholera toxin intranasally in mice.⁷⁶ GBS immunogenic bacterial adhesin (BipA) is surface-exposed in some GBS and evokes protective, opsonic antibodies in mice.⁷⁷ Other peptides studied include laminin binding protein (Lmb), surface immunogenic peptide (Sip), and leucine-rich repeat protein antigen (LrrG), as reviewed.^{53, 54} More recent approaches have involved multi-genome analysis identifying conserved genes that would express highly conserved proteins such as Sip and surface-associated proteins (SAG), which could form the basis of a conjugate vaccine.^{54, 78–80} Using this technology, studies have demonstrated the broadly protective efficacy in mice of GBS pilus-based vaccines.^{81, 82} Other technologies, including further multi-genome screening and proteomics, may provide the template for additional vaccine candidates.⁵⁴

Despite progress, there are continued challenges in developing a globally effective anti-GBS vaccine. Geographic variability of serotypes will require a multivalent vaccine that includes the most relevant components. Because a primary vaccine target will be women in child-bearing years, it must be safe and non-teratogenic. This risk might be ameliorated by mucosal immunization strategies in which the protection of the infant might not require placental antibody transfer. The feasibility of this has been studied in several animal studies, as reviewed.⁵³ This approach should also provide life-long immunity, which is important in the face of the growing recognition of non-perinatal GBS infections. Large-scale vaccine trials are likely to be very expensive and face daunting legal and regulatory issues.

Group A Streptococcus

Group A streptococci (GAS) are ubiquitous human pathogens that cause a wide array of clinical illnesses. Acute infections range from uncomplicated pharyngitis, cellulitis, and pyoderma to necrotizing fasciitis, sepsis, pneumonia, and streptococcal toxic shock syndrome. The sequelae that may follow GAS infections include acute rheumatic fever (ARF) and post-streptococcal

glomerulonephritis (PSGN). There is a distinct dichotomy in the burden of GAS infections and their sequelae between economically developed and poor countries of the world. In the United States, Western Europe and other developed countries, the majority of these infections present as uncomplicated pharyngitis or pyoderma. In developing countries, the largest burden of disease caused by GAS infections is ARF and rheumatic heart disease (RHD). Previous estimates indicated that approximately 350,000 people die each year from complications of RHD, and approximately 12 million people currently suffer from RHD.⁸³ Recent studies of the prevalence of RHD in school-age children and young adults suggest that global morbidity and mortality from RHD may be 4 to 6 times higher than previous estimates.^{84, 85} Primary and secondary prevention strategies based on antibiotic administration have only been marginally successful in developing countries. In developed and developing countries, invasive GAS infections may account for an additional 160,000 deaths annually.⁸³ Thus, there is a significant need for safe and effective vaccines that would prevent acute GAS infections including serious invasive infections, ARF and RHD. GAS vaccine development has been ongoing for more than 80 years.^{86, 87} Early clinical trials of vaccines containing whole heat-killed organisms, “toxins” and crude or purified proteins were conducted from the 1920s through 1979 and involved thousands of volunteers.^{88, 89} Most of these approaches focused on the central role of M protein in the pathogenesis of infection based on Lancefield’s original observation that type-specific immunity directed against the M protein was bactericidal and protective in animals.⁹⁰ Landmark studies by Fox *et al*^{91, 92} and by Beachey *et al*⁹³ demonstrated that highly purified preparations of M protein elicited protective immune responses in humans. Current strategies for vaccine development are based on our understanding of the molecular pathogenesis of GAS infections and some of the known virulence determinants that contribute to pathogenesis (Table 3), as well as newer approaches that involve mining GAS genomes and reverse vaccinology.⁸⁰ For the sake of discussion, the candidate vaccine antigens of GAS can be divided into M protein-based and non-M protein vaccines.

Multivalent type-specific M protein-based vaccines

M protein is one of the major immunogenic surface proteins of GAS. It is organized as a coiled-coil dimer that emanates from the cell wall and is composed of a unique, type-specific N-terminus and internal tandem repeats designated A, B and C.⁹⁴ Molecular characterization of streptococcal M proteins has shown that the type-specific amino-terminal region elicits antibodies with the greatest bactericidal activity and can be separated from potentially harmful tissue cross-reactive epitopes.⁹⁵ In order to include multiple serotypes in a single vaccine construct, 1 approach has been to engineer recombinant fusion proteins containing N-terminal peptides linked in a tandem array. A prototype vaccine was constructed containing N-terminal fragments from 6 GAS M types of clinical importance.⁹⁶ A Phase 1 clinical trial in normal adult volunteers demonstrated that this vaccine was well-tolerated, did not induce tissue cross-reactive antibodies, and stimulated vigorous immune responses with opsonic activity when given as a 3-dose regimen to healthy adults.⁹⁷ To address the majority of prevalent M types in North America and Western Europe,⁹⁸ a 26-valent vaccine was constructed using a similar strategy.⁹⁹ A phase 1/2 trial in adult volunteers showed that the vaccine was well-tolerated, safe, highly immunogenic and evoked bactericidal antibodies against all of the vaccine serotypes.¹⁰⁰

Over 80 M serotypes have been identified and more than 150 types have been elucidated by *emm* (gene for M protein) sequence analysis. Many types can circulate in a community simultaneously, and both temporal and geographic variation has been observed. Nonetheless, recent surveillance in North America indicated that 80 – 90% of serotypes that cause invasive infections or pharyngitis are included in the 26-valent vaccine.^{98, 101} In contrast, previous studies suggest that the vaccine coverage would be less complete in other geographic areas,^{102, 103} and there is limited information regarding the distribution of M types in developing

countries.¹⁰⁴ Introduction of multivalent vaccines may face other issues, such as emergence of new *emm* types and the possibility that non-vaccine serotypes of clinical importance may replace those contained in the vaccine. To circumvent some of the potential issues related to type-specific multivalent vaccines, other more recent vaccine strategies involve the use of conserved M protein epitopes or conserved non-M antigens.

Previous studies have shown that the C-repeat region of M protein is surface-exposed and contains epitopes that are shared by most GAS.¹⁰⁵ There are currently several approaches to incorporate C-repeat epitopes into vaccine formulations, including a synthetic peptide copying a minimal B cell epitope (J8),¹⁰⁶ synthetic peptides representing an entire C-repeat peptide,^{107, 108} and synthetic peptides and recombinant proteins incorporating selected B and T cell epitopes from the C-repeat region.¹⁰⁹ In addition, the oral commensal bacterium *Streptococcus gordonii* has been evaluated in humans as a mucosal vector with the overall goal of expressing the conserved fragment of M protein on its surface.¹¹⁰ In animal models, mucosal vaccination with C-repeat epitopes induced antibodies that do not cross-react with human myocardium and protect against challenge with both homologous and heterologous GAS M types.^{105, 106, 111} Extensive studies of the J8 vaccine in animals have demonstrated protection against systemic challenge infections following active and passive immunization.^{106, 112} The relative potency of opsonic antibodies against this region of the M protein has been variable^{105, 107, 111} and may be influenced by the binding of human plasma components such as fibrinogen and albumin that block the binding of C-repeat epitopes in blood or exudate.¹¹³

Non-M Protein Vaccine Candidates

Several other conserved antigens of GAS show promise as protective immunogens in preclinical studies (Table 3). SCPA (C5a peptidase) is expressed by virtually all GAS strains and inhibits phagocyte migration into sites of infection by specifically cleaving the potent chemoattractant C5a. Antibodies against SCPA neutralize the enzymatic activity of the molecule and protect mice against challenge infections with multiple M types after intranasal or subcutaneous immunization.^{114, 115} Serum opacity factor (SOF) is a virulence determinant expressed by approximately half of all serotypes of GAS and has been shown to evoke bactericidal antibodies against heterologous types.¹¹⁶ Similarly, M-related proteins (MRP) are present on a number of different serotypes of GAS and contain cross-reactive epitopes that evoke bactericidal antibodies.¹¹⁷ Heterologous protection in animals has also been demonstrated following vaccination with SpeB, the precursor of cysteine protease.¹¹⁸ Several surface-expressed fibronectin-binding proteins have been reported to induce protective immunity.^{119, 120} Toxoids derived from the streptococcal pyrogenic exotoxins (SPEs) have been shown to protect against streptococcal toxic shock syndrome.¹²¹ GAS carbohydrate is another potential vaccine component that induces bactericidal antibodies that protect mice from intranasal and systemic challenge infections.^{122, 123} One of the most recent additions to the list of potential GAS vaccine candidates are streptococcal pili, which are long fibrous structures composed of subunits, 1 of which is the T antigen.¹²⁴ Systemic immunization of mice with pilus-subunit proteins confers protection against intranasal challenge infections in mice.¹²⁵ Pilus structures are semi-conserved among GAS, and recent analyses suggest that broad protection can be conferred using a vaccine containing 12 pilus subunit variants.¹²⁴ New approaches involving genomics, proteomics and reverse vaccinology are also being applied to the discovery of additional GAS vaccine candidates,^{126–129} which should add significantly to the list of known virulence determinants described above.

The overall goal of GAS vaccine development is to introduce vaccines that will significantly impact the global burden of disease. As summarized above, multivalent vaccines may prove to be efficacious in North America, Europe and other developed countries where the epidemiology of GAS infections is similar and prevention of common acute infections and

invasive infections may be achievable. The larger challenge will be to develop vaccines that address the global need and are effective in preventing the infections that may trigger ARF and RHD as well as serious invasive infections. This will likely require a systematic experimental approach to develop combination vaccines containing type-specific M peptides representing a finite number of epidemiologically significant serotypes of GAS plus several common protective antigens to achieve the desired level of protective immunity. Successful global deployment of safe and affordable vaccines could have a significant impact on the morbidity and mortality attributable to GAS infections.

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Table 1Virulence determinants of *Staphylococcus aureus* as potential immune targets

Determinant	Role in Infection	Efficacy in	
		Animals	Humans
Whole cell or lysates		yes/no	yes/no
Cell surface associated components			
Capsular polysaccharide	antiphagocytic	yes	yes/no
Adhesins	adherence/attachment		
Clumping factor		yes	unknown
Fibronectin binding proteins		yes	unknown
Lipoteichoic acid			unknown
Iron regulated surface determinants (Isd)	acquisition of iron	yes	unknown
Poly-N-acetylglucosamine (PNAG)	adhesion/antiphagocytic	yes	unknown
GrfA (ABC transporter)	drug efflux pump	yes	unknown
Serine aspartate repeat proteins	unknown	yes	unknown
Toxins / Enzymes / Evasion	evasion of host defenses		
Toxic shock syndrome toxin-1 (TSST-1)		yes/no	unknown
Staphylococcal enterotoxin		yes	unknown
α -hemolysin		yes	unknown
Panton-Valentine leukocidin		no	unknown

Table 2

Potential candidates for an effective group B streptococcal (GBS) vaccine

Vaccine Target	Advantages	Limitations
Capsular carbohydrate	non-reactogenic, specific serotypes linked to disease prevalence	weakly immunogenic without carrier, must be part of a multivalent vaccine
β -C Protein	protective immunogenicity in animals	not conserved among all GBS strains
C5a peptidase	highly conserved among GBS strains, evokes opsonic antibodies	efficacy in humans unknown
Rib protein	expressed on most GBS strains	may evoke strain specific immune responses
Surface immunogenic peptide (Sip)	expressed on most GBS strains; evokes non-strain specific immune responses	biological function not well understood
Immunogenic bacterial adhesin (BipA)	widely expressed on GBS strains, induces opsonic antibodies	efficacy in humans not known
Pilin	widely distributed among GBS strains; protective in mice	role in humans not known

Table 3

Partial list of potential group A streptococcal vaccine candidates

Vaccine Candidate	Protection in animals
<i>M protein-based antigens</i>	
M type-specific (multivalent)	Lethal challenge (Active)
Conserved region of M protein (C-repeats)	Protection following IN and IP challenge (Active)
<i>Shared antigens</i>	
C5a peptidase (SCPA)	Colonization and clearance following IN challenge (Active)
Cysteine protease (SpeB)	Lethal IP challenge (Passive-Active)
Streptococcal pyrogenic exotoxin A (SpeA)	Prevention of toxic shock
Fibronectin binding proteins (Sfb/prtF and FPB54)	Lethal IP challenge (Passive and Active)
Serum opacity factor (SOF)	Lethal IP challenge (Active)
M-related proteins (MRP)	Not demonstrated
Group A carbohydrate	Lethal IP challenge (Passive and Active)
Pili (T protein)	Lethal IN challenge

Abbreviations: IN (intranasal), IP (intraperitoneal)