The Journal of Infectious Diseases

EDITORIAL COMMENTARY

Towards a Monoclonal Antibody-Based Therapy for Prevention and Treatment of *Staphylococcus aureus* Infections

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Keywords. antibiotic resistance; monoclonal antibody; MRSA; *Staphylococcus aureus*; therapeutic; vaccine.

(See the Breif Report by Chen et al on pages 884–8.)

Staphylococcus aureus is an important human pathogen and a leading cause of bacterial infections worldwide. *S. aureus* causes a wide spectrum of diseases ranging from common skin and soft tissue infections (SSTIs) to severe life-threatening bacteremia. Indeed, *S. aureus* is one of the most common causes of bacteremia [1], and the most common cause of infective endocarditis in the industrialized world [2]. Furthermore, *S. aureus* is the predominant cause of osteoarticular infections and SSTIs [3]. *S. aureus* disease is intimately associated with existence as a human commensal, and the organism is well positioned to cause iatrogenic infections in individuals with predisposing risk factors such as indwelling device use and surgery. The epidemiology of *S. aureus* disease is influenced by the ability of the pathogen to rapidly develop antibiotic resistance. For example, methicillin-resistant *S. aureus* (MRSA) emerged nearly 70 years ago and has remained a significant problem in hospital settings worldwide [4]. In addition to a preeminent role in health care-associated disease, *S. aureus* is a major source of community-acquired infection in individuals with no apparent risk factors. For example, the emergence and rapid dissemination of CA-MRSA strain USA300 contributed to a remarkable rise in SSTIs that nearly tripled the number of emergency department visits in the United States between 1993 and 2005 [5]. More recently, nationwide surveillance of medical centers for MRSA infections indicated that USA300 is the predominant strain type in both community and health care settings in the United States, in all regions and at all infection sites [6]. The contribution of *S. aureus* to the overall burden of antimicrobial resistance is significant, and the pathogen has developed mechanisms of resistance to virtually all clinically useful agents. The problem is confounded by a limited number of microbicidal agents in the pharmaceutical development pipeline. Given the ability of *S. aureus* to rapidly develop antibacterial resistance, there is a critical need for alternative therapies for prevention and treatment of staphylococcal disease, such as vaccines. There currently exists no licensed *S. aureus* vaccine, despite numerous efforts to test both active and passive immunization, the majority of which failed to meet the pretrial endpoints. There are several potential reasons why vaccination strategies have been unsuccessful. Traditional approaches that are directed to enhance opsonophagocytosis are subject to the caveat that phagocytosis of *S. aureus* by neutrophils from healthy individuals is highly efficient [7]. In addition, CA-MRSA strains such as USA300 demonstrate enhanced intracellular survival and rapidly lyse human polymorphonuclear leukocytes following uptake [7]. Although unsuccessful to date, there are ongoing efforts to develop multivalent vaccines, including those directed against virulence factors and toxins [8]. The challenge remains to develop a vaccine against a microbe that has likely evolved with humans since antiquity.

Although *S. aureus* is notorious as an opportunistic pathogen, it is also a human commensal organism. For example, Gorwitz et al reported that approximately 28% of healthy people in the United States are colonized asymptomatically with *S. aureus* in the anterior nares [9], including colonization by MRSA in 1.5% of people surveyed. More recently, Albrecht et al (members of this same research group) identified *S. aureus* colonization in 38.8% of individuals reporting to emergency departments in the United States for something other than infection, and this included MRSA colonization in 9.5% of these individuals [10]. These studies also compared *S. aureus* colonization in individuals reporting to the emergency department for skin abscesses with control subjects (those at the emergency department for something other than

Received 12 November 2018; editorial decision 12 November 2018; accepted 13 November 2018; published online November 15, 2018.

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The Journal of Infectious Diseases® 2019;219:848–50

DOI: 10.1093/infdis/jiy667

infection), and they extended screening for colonization to include the throat, groin, and gastrointestinal tract (rectum) [10]. One notable finding reported by Albrecht et al is that the groin rather than nose was more often positive for colonization by USA300 (methicillin-sensitive *S. aureus* [MSSA] or MRSA), whereas the nose was most commonly colonized for all other lineages of *S. aureus*. Moreover, individuals with *S. aureus* infections with MRSA were typically colonized at multiple body sites, whereas those with MSSA infections were frequently colonized at a single location.

Colonization is seemingly nonproblematic for healthy individuals; however, it is associated with infection in people with risk factors for infection and/or comorbidities. In a landmark study published in 2001, von Eiff and colleagues reported that *S. aureus* bacteremia is associated with nasal colonization — that is, organisms recovered from blood were identical to those isolated from the nose in 82%–85% of patients [11]. Consistent with these findings, Albrecht et al found that *S. aureus* isolated from skin abscesses were most often (approximately 88% of the time) identical by molecular typing to that from colonized body sites [10]. Work from several research groups has shown that colonization with MRSA is a risk factor for subsequent MRSA infection [12, 13] (reviewed by Wertheim et al [14]). The implication of these studies collectively is that colonization with *S. aureus* (also termed carriage) is a major determinant for subsequent infection. Inasmuch as *S. aureus* carriage is linked to infection in susceptible individuals, and the global burden of MRSA is relatively high, some health care facilities have tested whether decolonization of *S. aureus* in the nose is effective at preventing infections [15]. Results have met with varied success, but this variability could be attributed in part to colonization at sites other than the nose. Nasal decolonization is typically achieved by administration of a topical antibiotic (mupirocin) ointment in the anterior nares [16]. Although this approach can work well for reduction of the *S. aureus* burden in the nose, it does not reduce bacterial burden at other sites colonized with *S. aureus*, including the groin and gastrointestinal tract. More extensive decolonization protocols eliminate *S. aureus* carriage from all body sites, but involve bathing with chlorhexidine soap for several days and taking oral antibiotics [17]. A prophylactic or therapeutic vaccine could be designed to promote complete (whole body) *S. aureus* decolonization. Such a vaccine might be a major advance for prevention of *S. aureus* infections in at-risk individuals and would be more practical for use in the clinic.

In this issue of the *Journal of Infectious Diseases*, Chen et al show that targeting *S. aureus* protein A (SpA) with monoclonal antibodies (Mabs) significantly decreases *S. aureus* colonization of the mouse nasopharynx and intestinal tract [18]. The reduced *S. aureus* colonization following treatment with anti-SpA Mab was accompanied by increased serum antibodies specific for several *S. aureus* molecules known to promote adherence to host tissues. These studies extend an intriguing line of investigation by this research group on the ability of SpA to function as an immune modulator.

Previously, the authors reported that mice immunized with a SpA mutant protein—one that is in incapable of binding the antibody Fc region—produce SpA neutralizing antibodies [19]. Animals immunized with the mutant, but not wild-type, SpA were protected against *S. aureus* infection. These findings led the authors to propose a model whereby wild-type SpA inhibits production of antibodies that would otherwise protect against *S. aureus* infection. With that idea in mind, the group generated mouse monoclonal antibodies, including one named hMab 3f6, which is an IgG2a that inhibits the ability of SpA to block generation of antibodies specific for *S. aureus* [20]. Notably, hMAb 3f6 protects mice from lethal bacteremia, and underscores the idea that SpA is a potential target for therapeutics.

In their current work, Chen et al created a more stable recombinant monoclonal antibody (rMab 363) by cloning and expression of Mab 363 in HEK293 F cells [18]. rMab 363 expressed by HEK293 F cells and hMab 363 expressed by mouse hybridoma cells had comparable ability to neutralize SpA, promote bactericidal activity in blood, and decrease *S. aureus* burden in a mouse infection model. The authors then demonstrated that intraperitoneal administration of rMab 363 prevents colonization of the mouse pharynx by *S. aureus* strain WU1 (a strain known to persistently colonize the mouse nasopharynx and gastrointestinal tract) or promotes decolonization within a few days after administration. Most notably, there was a concomitant increase in antibodies specific for *S. aureus* virulence molecules, including those known to be involved in host cell adhesion and colonization.

The anti-SpA Mab approach has the potential to solve two important problems associated with *S. aureus* carriage. First, the ability to decolonize target populations without using antibiotics would be a major breakthrough for *S. aureus* prophylaxis. Also, many previous *S. aureus* vaccine approaches were directed in part to promote opsonophagocytosis, whereas that by Chen et al enables adaptive immunity against *S. aureus* [18]. Therefore, a second important benefit of the anti-SpA Mab approach is the development of protective immunity against *S. aureus*. Whether results in the animal models translate to similar outcomes in humans remains to be determined, but the studies by Chen et al are an important step forward in our efforts to develop a *S. aureus* vaccine.

Notes

Financial support. This work was supported by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Potential conflicts of interest. Both authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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