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Staphylococcus aureus: an introduction

Ian A. Myles and **Sandip K. Datta**
Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA

Shortly after finishing his undergraduate studies at the University of Aberdeen in Scotland and embarking on his career as a surgeon, Alexander Ogston presented in 1880 at the Ninth Surgical Congress in Berlin his work establishing the causative role of bacteria in wound infection and subsequent septicemia. Building on the teachings of his senior contemporaries, Louis Pasteur and Joseph Lister, Ogston had observed pus from 88 human abscesses under his microscope and noted Gram-positive spherical "micrococci" [1]. Taking from the Greek word for "bunches of grapes," he named the organism *Staphylococcus*. After injecting the isolated bacteria into healthy guinea pigs and mice and recreating the abscesses from which the isolates were derived, he had conclusively introduced the world to the infectious agent, now known as *Staphylococcus aureus* due to its golden color in culture, that continues to burden human health today [1].

For decades, treatment options were limited to the topical application of carbolic acid (phenol), the same antiseptic technique introduced by Lister and promoted by Ogston [2]. The excitement that accompanied the introduction of penicillin in the 1940s turned into concern only 2 years later when resistance to the once-heralded miracle drug first appeared in penicillinase-producing strains of *S. aureus*, and then into surrender by 1950 when the frequency of resistance mandated alternative therapy [3–7]. Strains of *S. aureus* with an altered penicillin-binding protein soon countered the semi-synthetic beta-lactam antibiotics that had replaced penicillin, with methicillin-resistant *Staphylococcus aureus* (MRSA) first described in 1961 [5, 8]. After decades of being a predominantly hospital-associated infection, in the twenty first century, MRSA has spread beyond hospitals to become a significant "community-associated" public health burden, as outlined by Fowler and colleagues in this special issue, that threatens to once again outpace antibiotic development.

Beyond antibiotic resistance, the success of *S. aureus* as a human pathogen stems from the arsenal of virulence factors it has evolved to combat host defense mechanisms. The battle over metal ions is an often-overlooked case in point, detailed here by Skaar and colleagues. For example, the body sequesters essential iron to limit bacterial growth [9–11]. However, staphylococcal siderophores overcome host attempts to starve it of iron from both heme [12] and transferrin [13]. *S. aureus* also uses the pore-forming toxin alpha-hemolysin to lyse red blood cells and access hemoproteins [14, 15]. Similarly, *S. aureus* has evolved incompletely examined mechanisms to circumvent host sequestration of other essential nutrients such as manganese, zinc, and copper.

The more conventional battle at the front lines of innate immunity places neutrophils at the center of the host response. *S. aureus* infection promotes neutrophil recruitment through induction of a variety of cytokines, chemokines, and chemokine receptors, such as IL-17 [16], CXCL8 [17], and CXCR2 [18]. Once engaged, neutrophils can phagocytose opsonized

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bacteria and trigger oxidative killing and other antimicrobial mechanisms [19], reviewed here by DeLeo and colleagues. The importance of neutrophils in the defense against staphylococcal infections is apparent in the increased susceptibility of patients with abnormalities in neutrophil numbers, such as congenital or chemotherapy-induced neutropenia [20–22]. Other susceptible patients include those with defects in functional oxidative burst (chronic granulomatous disease [20], myeloperoxidase deficiency [22], specific granule deficiency [23]), chemotaxis (leukocyte adhesion deficiency type I [22]), or both (diabetes mellitus [24], end-stage renal failure [25]). To counter neutrophil attack, *S. aureus* produces factors to limit chemotaxis [26], extravasation [27], and superoxide function [28]. It can induce neutrophil apoptosis with its Panton–Valentine leukocidin [29, 30], whose contribution to the virulence of epidemic community-associated clones has generated recent controversy that is addressed in several articles in this issue. Inside neutrophils, *S. aureus* can survive for days before lysing the cell and escaping back into the surrounding tissue [29]. Even the golden color seen in culture that inspired the “aureus” namesake has revealed itself to be an antioxidant virulence factor that neutralizes oxidative killing by neutrophils [31].

The recruitment and activation of neutrophils during staphylococcal infection is triggered by the activation of pattern recognition receptors, such as toll-like receptors (TLR), on keratinocytes and other cells involved in the innate immune response [32]. Upon activation, these cells also secrete directly bactericidal products such as human beta defensins [33], cathelicidin (LL-37) [34], and RNase 7 [35]. Atopic dermatitis is associated with both decreased levels of these antimicrobial peptides as well as increased rates of *S. aureus* colonization and infection, highlighting the potential clinical importance of these compounds in combating *S. aureus* [36]. Susceptibility to staphylococcal infections in patients with deficiencies in the IL-1 receptor/ TLR-associated signaling molecules IRAK4 [37] or MyD88 [38] further demonstrates the contribution of this critical innate immunity pathway to control of this pathogen in humans.

While there is a vast literature on measuring the adaptive immune responses to *S. aureus*, few, if any, have found evidence that such responses are protective against subsequent infections [39]. Clinical phenotypes seen in Hyper IgE syndrome (STAT3 [40, 41] or DOCK8 [42, 43] deficiency), mucocutaneous candidiasis [44], APECED [45], HIV [46], and atopic dermatitis [47] suggest that altered T cell responses predispose to staphylococcal infections, in particular implicating a protective role for IL-17-secreting CD4 helper T cells (Th17 cells). In contrast, patients suffering from psoriasis have higher levels of IL-17 in their skin and are relatively protected from staphylococcal infections [47]. Further supporting a role for T cells in the response to *S. aureus* are the bacterial mechanisms that have evolved to counter adaptive cellular immunity. Enterotoxins shift the T cell response away from Th1/Treg and towards Th2 [48]. Superantigens such as toxic shock syndrome toxin function to induce non-specific and thus non-targeted T cell excitation [49], and protein A causes similarly non-targeted expansion of B cells [50]. Protein A, among other factors, also helps negate protective effects mediated by complement [51], TNF receptor [52], and the epidermal growth factor receptor [53].

Staphylococcal infection presents most commonly in the skin and soft tissues. These infections cause over ten million outpatient visits and nearly a half-million hospital admissions per year in the USA [54]. Interestingly, nearly a third of people are colonized with *S. aureus* [55]. Although this is a risk factor for subsequent infection [56], it is notable that so many people have a seemingly peaceful co-existence with this potentially lethal organism. Furthermore, the ubiquitous colonization of people with less virulent *Staphylococcus* species, such as *Staphylococcus epidermidis* and other coagulase-negative staphylococci, suggests that we can gain insights into *S. aureus* virulence by studying the

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colonization and virulence strategies of these closely related organisms, reviewed here by Otto. Miller and colleagues examine recent discoveries that elucidate the role of innate and adaptive immune mechanisms in cutaneous host defense against *S. aureus*.

Breach of skin and mucosal defenses predisposes toward potentially life-threatening invasive staphylococcal infection. Most commonly presenting as pneumonia and blood-stream infections, these invasive infections are becoming more prevalent [57–59], primarily as an iatrogenic consequence of increasingly complex medical procedures and therapies. Furthermore, an increased incidence of pneumonia has been seen during the ongoing epidemic of community-associated MRSA infection [59]. The pathogenesis of staphylococcal pulmonary infection is detailed in the chapter by Prince and colleagues, highlighting the role of the previously mentioned immunomodulatory virulence mechanisms [52, 60–62] as well as factors that aid in adhesion such as collagen-binding protein [63] and clumping factors A and B [64, 65]

In recent years, new reservoirs for drug-resistant *S. aureus* have been recognized, with a large proportion of both US meat and poultry samples [66] as well as Brazilian food products [67] testing positive for MRSA. The threats posed by this consequence of widespread agricultural and medical antibiotic use have ironically led to efforts to expand the antibiotic armamentarium against *S. aureus*, as reviewed here by Fowler and colleagues. Topical treatments aimed at colonization, such as mupirocin [68] and chlorhexadine [69], have also gained interest, revisiting mechanisms to kill *S. aureus* that are practically identical to that of carbolic acid used in the 1900s [70, 71]. In this issue, Liu and colleagues consider targeting staphylococcal virulence factors and host defense mechanisms as alternative treatment strategies to supplement traditional antibiotics. Schneewind and colleagues take a similar approach to consider novel vaccine targets. Spellberg and Daum reflect on the multiple past failures and future prospects for a successful vaccine, which still remains the holy grail for controlling infectious pathogens, especially one that has proven adept at outmaneuvering antibiotics and host defenses. This special issue comprises articles from a collection of experts that aim to capture our current knowledge of staphylococcal virulence and host defense as we work to understand this human commensal and formidable pathogen.

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