CLINICAL IMPLICATIONS OF BASIC RESEARCH

Removing the Golden Coat of *Staphylococcus aureus*

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Infections caused by *Staphylococcus aureus*, particularly those that are resistant to methicillin and all available β-lactam antibiotics — the so-called methicillin-resistant *S. aureus* (MRSA) infections — have been declared a public health imperative. A recent report from the Centers for Disease Control and Prevention[1] estimated that 18,650 persons in the United States died from invasive MRSA infections in 2005. A new therapeutic approach to the management of these infections would therefore be welcome.

The development of new antibiotics to treat MRSA infections has slowed for complex reasons.[2] Some researchers have pointed to a lack of "new" microbial targets. Indeed, most antimicrobial agents currently in use are directed against bacterial cell-wall metabolism, the machinery of bacterial protein synthesis, or a biosynthetic pathway unique to bacteria. Targeting a pathway that is common to bacteria and humans may kill the bacteria but may also incur unacceptable adverse events.

Liu and colleagues[3] recently observed that the synthesis of staphyloxanthin, the carotenoid pigment that bestows the golden yellow color of clinical isolates of *S. aureus*, can be greatly diminished by a candidate inhibitor of human squalene synthase; this agent was previously developed to inhibit cholesterol synthesis. The inhibitor is likely to have few toxic effects, since only cholesterol synthesis is targeted and cholesterol is likely to be present in the serum or the diet. Liu et al. also observed that the human squalene synthase inhibitor greatly diminished staphyloxanthin biosynthesis in vitro. They inoculated mice intraperitoneally with a wild-type, pigmented *S. aureus* isolate called ATCC 27659 or an isogenic mutant that lacked the dehydrosqualene synthase gene. Only the mutant strain was cleared by the host. A comparison of experimental intranasal inoculation showed that the rate and magnitude of colonization for the two strains did not differ. Liu et al. also showed that treatment of mice with the dehydrosqualene synthase inhibitor after intraperitoneal inoculation resulted in enhanced bacterial killing, as evidenced by lower bacterial counts in the mouse kidney.

The success of this approach is largely dependent on a pathway (Fig. 1) used in the early steps of synthesis of both staphyloxanthin and squalene, which is a cholesterol precursor. Liu et al. posit that staphyloxanthin may be a critical virulence factor in *S. aureus* infections because of its ability to detoxify antibacterial molecular species such as the superoxide anion, hydrogen peroxide, and hypochlorous acid, which are generated mainly by neutrophils of the host's immune system.

The concept of countering pathogenicity by inhibiting the synthesis of a virulence factor is new. Whether it will be clinically applicable requires further testing, possibly including the

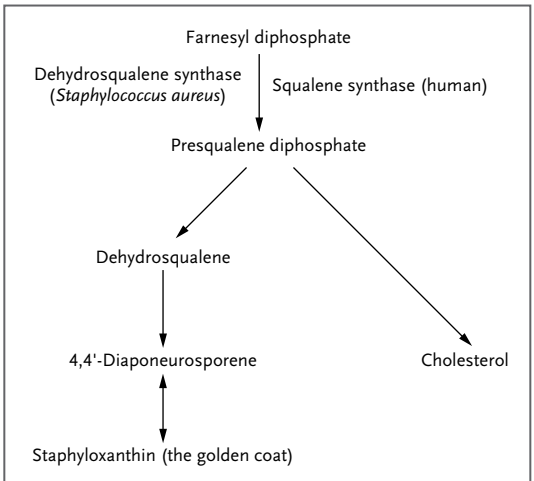


Figure 1. Biosynthetic Pathway of Staphyloxanthin Synthesis.

Selected steps common to the cholesterol synthesis pathway in humans and the staphyloxanthin synthesis pathway in *Staphylococcus aureus* are depicted. Squalene synthase is the enzyme inhibited by the compound recently described by Liu et al.[3] (Figure modified from Liu et al.[3])

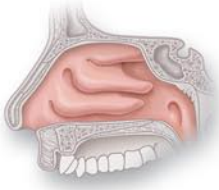
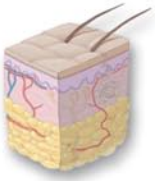
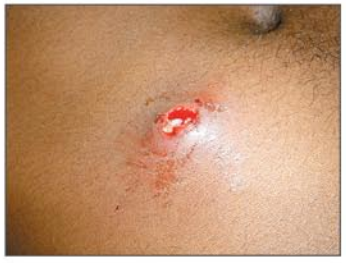
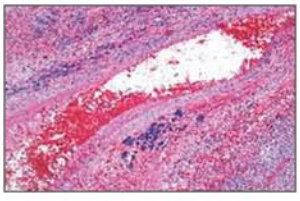
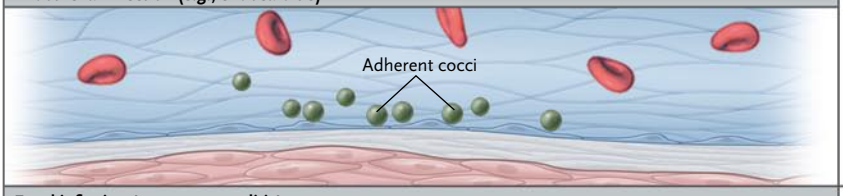
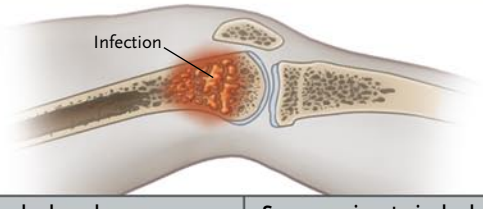
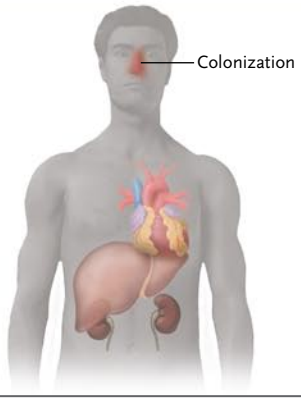
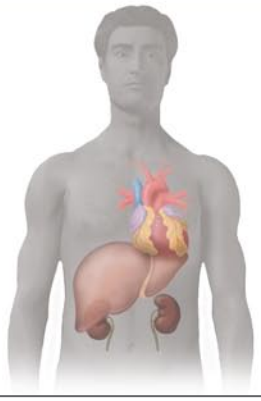
Clinical syndrome			Relative importance of neutrophil involvement
Asymptomatic colonization			
 Nose	 Skin	 Vagina	+
Skin and soft-tissue infection or abscess	**Pneumonia**		
	 Necrotizing *S. aureus* pneumonia		+++
Endothelial infection (e.g., endocarditis)			
			++
Focal infection (e.g., osteomyelitis)			
			+++
Severe sepsis or toxic shock syndrome without *S. aureus* infection	**Severe sepsis or toxic shock syndrome with *S. aureus* infection**		**Without *S. aureus* infection**
			+
			With *S. aureus* infection
			+++

Figure 2 (facing page). *Staphylococcus aureus* and Clinical Syndromes.

Different types of clinical syndromes characterize the interactions between *S. aureus* and humans. The involvement of neutrophils with the pathogenesis of each syndrome varies; thus, the efficacy of a squalene synthase inhibitor in each type of syndrome would also be expected to vary. Selected scenarios are depicted. Liu et al.[3] observed a major effect of a squalene synthase inhibitor after intraperitoneal challenge with *S. aureus;* this experimental scenario of infection resembles a bacteremia–sepsis syndrome in patients, possibly with associated endothelial infection.

targeting of other components of staphyloxanthin synthesis or other virulence factors, toxins, or adhesins. The relative importance of these factors remains to be seen.

Many steps would be required to translate this observation for use in the clinical arena. Liu et al. studied just one strain of *S. aureus;* its relationship to other currently circulating strains — epidemic MRSA strains in particular — is uncertain. Some clinical isolates do not produce staphyloxanthin, which is inferred from their lack of yellow pigment on solid mediums. A more thorough characterization of the animal model used by Liu et al. would be informative. The decrease in bacteria surviving in the kidney after parenteral inoculation observed by Liu et al. is consistent with a therapeutic effect, but other organs and other routes of inoculation should be tested. Moreover, the effect of renal bacteria on survival varied among the animals studied; identifying the causes of this variation may help to guide further research.

S. aureus is a commensal bacterium; it colonizes the skin and mucosal surfaces such as the nares, pharynx, and vagina. At any given time, approximately 25 to 40% of people are colonized with *S. aureus.* The mere presence of the organism in the nose or on the skin does not seem to provoke a host response; thus, the staphyloxanthin inhibitor used by Liu et al. had no effect on *S. aureus* in this setting.

Disease is produced by one of several mechanisms (Fig. 2). A breach in the mucosal barrier or skin may allow opportunistic multiplication of bacteria in the subcutaneous tissues and thereby result in an infection of the skin or soft tissue; invasive disease infrequently follows. Many neutrophils are recruited to the site of this event. An inhibitor of staphyloxanthin synthesis may halt the progression of a recognized skin and soft-tissue infection. Another route of infection is through inhalation; infection may establish a primary pneumonia that may be necrotizing. A preceding infection with a virus such as influenza may predispose persons to this form of infection. It is uncertain whether the production of staphyloxanthin would influence this scenario. Occasionally, severe disease (e.g., a systemic toxinosis such as toxic shock syndrome) may occur without the migration of *S. aureus* from its superficial mucosal perch; one of a variety of toxins or superantigens that can initiate a cascade of host responses may be secreted. It is unlikely that the enhanced killing of neutrophils would critically affect the course of such a toxinosis.

Although most *S. aureus* infections, on reaching the bloodstream, are probably self-limited by host defense mechanisms, an intravascular infection or metastatic infection may occur. The intraperitoneal inoculation route used by Liu et al. most closely resembles invasive disease, and it is in this context that their approach, perhaps in combination with another antiinfective agent such as a conventional antibacterial compound, shows the most promise.

S. aureus is a dynamic species, endowed with an array of adhesins and virulence factors, and thus it facilely adapts to a variety of environments. Therefore, it seems unlikely that the approach used by Liu et al. will singly solve the therapeutic dilemma created by antibacterial-resistant isolates. It does, however, open the door to a new line of clinically relevant research.

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