Staphylococcus aureus: A Well-Armed Pathogen

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***Staphylococcus aureus* is a virulent pathogen that is currently the most common cause of infections in hospitalized patients. *S. aureus* infection can involve any organ system. The success of *S. aureus* as a pathogen and its ability to cause such a wide range of infections are the result of its extensive virulence factors. The increase in the resistance of this virulent pathogen to antibacterial agents, coupled with its increasing prevalence as a nosocomial pathogen, is of major concern. The core resistance phenotype that seems to be most associated with the persistence of *S. aureus* in the hospital is methicillin resistance. Methicillin resistance in nosocomial *S. aureus* isolates has been increasing dramatically in United States hospitals and is also associated with resistance to other useful antistaphylococcal compounds. Possible ways to decrease the incidence of nosocomial *S. aureus* infections include instituting more effective infection control, decreasing nasal colonization, developing vaccines, and developing new or improved antimicrobials.**

Staphylococcus aureus has been recognized as a major human pathogen ever since Sir Alexander Ogston [1] first proposed, in the 1880s, that it was the major cause of wound suppuration. Evidence for its virulence was shown in 1941, when Skinner and Keefer [2] reported that the mortality rate associated with *S. aureus* bacteremia in 122 patients at the Boston City Hospital was 82%. Furthermore, even though the introduction of β-lactam antibiotics into widespread clinical use markedly decreased mortality rates, 27% of patients with *S. aureus* bacteremia who were seen at the Johns Hopkins Hospital in the early 1960s died; these deaths occurred despite the fact that the patients' infecting organisms were susceptible in vitro to the antibiotics administered [3].

Currently, *S. aureus* is second only to coagulase-negative staphylococci as a cause of hospital-acquired bacteremia and is the leading potentially lethal cause of these infections [4]. In addition, for 1990 to 1992, *S. aureus* was identified by the National Nosocomial Infections Surveillance system as the leading overall cause of hospital-acquired infections [4]. Finally, the percentage of methicillin-resistant *S. aureus* (MRSA) in United States hospitals rose from 2.4% in 1975 to 29% in 1991, with a MRSA rate of 38% at large (>200 beds) hospitals. Furthermore, the increase in the prevalence of MRSA and multidrug-resistant *S. aureus* is not just a problem in the United States but is worldwide.

Thus, *S. aureus* is a virulent pathogen that is currently the most common cause of infections in hospitalized patients. Its increasing resistance to antibiotics indicates that its prevalence will continue to rise. Given the number and severity of *S. aureus* infections in the United States and in other countries, it is important to understand the nature and pathogenesis of infections and the current strategies available for therapy and prevention.

Spectrum of Infections

Those infections or syndromes that *S. aureus* can cause are listed in table 1 (the diseases in boldface are those for which *S. aureus* is the only or the most common pathogen). It is evident that the organism can involve any organ system, and the number of infections that it causes is matched by no other single pathogen.

Pathogenesis of Infection

The five stages in the pathogenesis of *S. aureus* infections are (1) colonization, (2) local infection, (3) systemic dissemination and/or sepsis, (4) metastatic infection, and (5) toxinosis. Approximately 30% of healthy individuals are colonized by *S. aureus*, usually in the anterior nares but also in the vagina and perianal area. The organism can be carried asymptomatically for weeks or months on mucous membranes but is only transiently carried on intact skin. Colonization is believed to precede infection. Local abscesses of skin or skin structures result when the organism is inoculated into the skin from a site of carriage. The infection can spread locally (e.g., carbuncle, cellulitis, impetigo bullosa, or wound infection) or can gain access to the blood.

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Once in the blood, the organism spreads widely to peripheral sites in distant organs, and septic shock can ensue. Without specific therapy, the mortality rate associated with disseminated infection is high. As a result of hematogenous dissemination, a number of specific staphylococcal infections can result (e.g., endocarditis, osteomyelitis, renal carbuncle, septic arthritis, or epidural abscess). Finally, even if the organism itself does not invade the bloodstream, specific syndromes can result from the local or systemic effects of specific toxins. Examples of these syndromes are toxic shock syndrome, scalded skin syndrome, and food-borne gastroenteritis. It is also apparent that certain underlying conditions or behaviors can predispose individuals to staphylococcal infections, including diabetes mellitus [3], indwelling intravenous catheters [5], intravenous drug abuse [6], and AIDS [7].

The success of the organism as a pathogen and its ability to cause such a wide range of infections are due to its extensive virulence factors. It displays a wider variety of virulence mechanisms than virtually any other human pathogen and is a model for the study of the pathogenesis of infectious diseases [8]. A list of those factors known to contribute to the virulence of the organism is shown in table 2 (the factors are grouped by their proposed pathogenetic mechanisms).

Specific factors are present that allow the organism to initially thwart opsonophagocytosis, walling off the infection to form an abscess; to invade through tissue from the initial site of infection; to induce the sepsis syndrome by promoting massive cytokine release; to move out of the blood into underlying tissue by attaching to and invading endothelial cells; and to produce specific syndromes by toxin production. There are also specific global regulatory systems, such as *agr* and *sar,* that determine which virulence factors are produced at specific times during growth and in response to the local environment [8].

It is apparent that the control of infections caused by a pathogen as virulent as *S. aureus* is of major importance. The increase in the resistance of this pathogen to antibacterial agents, coupled with its increasing prevalence as a nosocomial pathogen, is of major concern.

Table 1. Infections or syndromes for which *Staphylococcus aureus* is a prominent pathogen.

Furuncle or carbuncle
Impetigo bullosa
Cellulitis
Surgical wound infection
Pyomyositis
Botryomycosis
Hosptial-acquired bacteremia
Acute or right-sided endocarditis
Hematogenous osteomyelitis
Septic arthritis
Epidural abscess
Brain abscess
Hospital-acquired penumonia
Empyema
Septic shock
Toxic shock syndrome
Scalded skin syndrome
Food-borne gastroenteritis
Renal carbuncle

NOTE. Conditions in boldface are those for which *S. aureus* is the sole or most common etiologic agent.

Table 2. Virulence factors of *Staphylococcus aureus* and their proposed pathogenetic mechanisms.

Thwart host defenses
Microcapsule
Protein A
Coagulase
Fatty acid–metabolizing enzyme
Leukocidin and/or γ-toxin
Invade tissue
Proteases
Nucleases
Lipases
Hyaluronate lyase
Staphylokinase
Elicit sepsis syndrome
Toxic shock syndrome toxin
Enterotoxins
Cytolytic toxins (α, β, γ, and δ)
Induce specific toxinosis
Toxic shock syndrome toxin
Enterotoxin
Exfoliative toxin
Attach to endothelial cells and basement membrane
Binding proteins for fibrinogen, fibronectin, laminin, collagen, vitronectin, and thrombospondin

Resistance to Antimicrobial Agents

The core resistance phenotype that seems to be most associated with the persistence of *S. aureus* in the hospital is methicillin resistance. This resistance is due to the acquisition of a new penicillin-binding protein, PBP2a. This protein has low affinity for most β-lactam antibiotics and, therefore, mediates cross-resistance to all of these compounds.

Methicillin resistance in nosocomial *S. aureus* isolates has been increasing dramatically in United States hospitals and is also associated with resistance to other useful antistaphylococcal compounds [4, 9]. According to most surveys [10, 11], $>$50% of MRSA are also resistant to macrolides, lincosamides, fluoroquinolones, and aminoglycosides. The rate of resistance to trimethoprim-sulfamethoxazole often exceeds 30% [10]. This high level of resistance not only impedes successful therapy for infections but also allows the organism to persist in the hospital, expanding its reservoir. In addition, vancomycin is often the only effective agent available for therapy, and its extensive use may help promote colonization and infection with vancomycin-resistant enterococci.

Outlook for Therapy and Prevention

There are a number of possible options for decreasing the incidence of nosocomial *S. aureus* infections and for treating infections caused by MRSA that are also resistant to other antimicrobials.

1. *Instituting more effective infection control practices.* The new Centers for Disease Control and Prevention guidelines for preventing transmission of nosocomial pathogens [12] may help prevent transmission of staphylococci within the hospital. Although this practice is unlikely to decrease the reservoir, it may decrease patients' acquisition of *S. aureus* infection.

2. *Decreasing nasal colonization.* Since many wound infections are due to autoinoculation, decreasing nasal carriage by using either systemic or topical agents has been shown to reduce the incidence of *S. aureus* infections [13]. Studies should be performed to assess the role of widespread nasal decolonization in preventing nosocomial *S. aureus* infections.

3. *Development of S. aureus vaccines.* Although vaccination with various staphylococcal antigens or whole organisms has been used for some time to prevent infections in animals (such as bovine mastitis), there has been little success with vaccination for preventing human infections. However, a conjugate vaccine with *S. aureus* types 5 and 8 capsular polysaccharide coupled to *Pseudomonas* exotoxin A has been shown to be immunogenic in humans and provides some protection from challenge in animals [14]. Studies of additional antigens, including toxoids, are warranted.

4. *Development of new or improved antimicrobial agents.* With the increase in the prevalence of multidrug-resistant isolates, chemotherapy for *S. aureus* infections is becoming increasingly difficult. The pharmaceutical industry is responding either by modifying existing compounds to broaden their spectra or by developing novel compounds. The former includes modified tetracyclines (glycylcylines), fluoroquinolones, glycopeptides, and β-lactam agents (cephems and carbapenems). The latter includes oxazolidinones and a combination drug consisting of semisynthetic derivatives of streptogramin A (dalfopristin) with streptogramin B (quinupristin). Attempts to find other unique compounds that may attack new or novel bacterial targets are also under way.

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