

## Staphylococci

**General Description of Staphylococci:** Staphylococci are members of the Micrococcaceae family. They are classically considered extracellular, pyogenic pathogens because of their ability to induce abscess formation. The bacteria are nonmotile and tend to grow in clusters. They are extremely hardy and can survive for prolonged periods of time on environmental surfaces. This family includes *Staphylococcus aureus*, *epidermidis* and *saprophyticus*. The initial descriptions below refer to the most important pathogen of this family - *Staphylococcus aureus*. There is a brief discussion of the clinical role of coagulase negative staphylococci, such as *Staphylococcus epidermidis* at the end of the outline.

**Laboratory Identification:** Staphylococci are recognized in clinical samples by Gram stain and their characteristic morphology – Gram positive cocci in grape-like clusters. They form round often beta-hemolytic colonies on agar. The *aureus* refers to the gold color of the colonies. All staphylococci are catalase positive. The coagulase and manifold fermentation tests are used to distinguish *S. aureus* from other staphylococcal species.

**Biology:** There are a large number of surface components as well as secreted products of staphylococci. These are summarized below.

**Structural components:** The cell envelope of staphylococci is composed of a microcapsule and a cell wall consisting of alternating units of N-acetylglucosamine and N-acetyl muramic acid. Additional components of the cell wall include lipoteichoic acid and a family of structurally related surface proteins that facilitate bacterial adherence to host cell surfaces. These surface proteins facilitate attachment to molecules found in the extracellular matrix including fibronectin, fibrinogen, and collagen. They may help explain the tropism of this bacterial species to invade particular tissue sites. The combination of peptidoglycan and lipoteichoic acid has been implicated in animal models of sepsis as the bacterial components responsible for inducing the sepsis syndrome.

**Products secreted by *S. aureus*:**

**Enzymes produced by staphylococci:**

Catalase converts  $H_2O_2$  to  $H_2O$  and  $O_2$ .

Coagulase converts fibrinogen to fibrin and is the primary test used to distinguish *S. aureus* from the other staphylococcal species

Hyaluronidases hydrolyze hyaluronic acids and may contribute to tissue breakdown and spread of staphylococci across tissue barriers.

Beta-lactamases are released by staphylococci and can hydrolyze the beta-lactam ring of penicillins and cephalosporins rendering the antibiotics useless.

**Toxins produced by staphylococci:**

Superantigen family including toxic shock syndrome toxin-1 (TSST-1), enterotoxins and the epidermolytic toxins.

Membrane damaging toxins including leukocidin and alpha toxin. Leukocidin has been associated with soft tissue infections. Alpha toxin may play a role in producing the sepsis syndrome.

**Epidemiology:** Humans are the natural reservoir for staphylococci. Coagulase negative staphylococci are a part of the normal skin flora and are also found in the anterior nares. The anterior nares are colonized by *S. aureus* in 20-40% of the normal population. Carriage is increased in populations known to be at risk of staphylococcal disease including dialysis patients, diabetics and HIV-infected subjects. Staphylococci cause infection either as a result of autoinoculation or by transmission from a carrier to a patient. Most often this is the result of transient carriage although occasionally a carrier may be responsible for an outbreak of staphylococcal disease.

Staphylococci are among the most common causes of community and hospital-based infections. A particular concern in recent years has been the emergence of strains that are highly resistant to a large number of different antibiotics.

**Pathogenesis of disease:** Staphylococci cause disease either as the result of a mechanical breach in skin or mucosal barriers or by the elaboration of toxins.

Invasive infections: *S. aureus* are unlikely to cause either local or systemic disease in the absence of some trauma (albeit minor); rather they can persist as commensals on the skin or in the nose without causing damage. Because of their presence as commensals on the skin and other sites, both coagulase positive and negative bacteria frequently cause prosthetic device (e.g. intravascular catheters) related infections. Establishment of infection in general requires an ordered sequence of events that involves adherence, colonization, invasion, spread, as well as the host response to this process. The staphylococcal surface proteins, e.g. fibronectin-binding protein or collagen-binding protein, facilitate bacterial attachment to host tissue surfaces. Following adherence, staphylococci elaborate enzymes that provide nutrients for the bacteria and facilitate bacterial spread to adjacent tissue as well as spread to other organs. Staphylococci are noted for their ability to spread to other tissues establishing metastatic foci of infection.

The primary host response to staphylococcal infection is the polymorphonuclear leukocyte. Patients with qualitative or quantitative defects in leukocytes are at increased risk of staphylococcal infection.

Toxin-related diseases. In addition to the above-described pathogenetic mechanisms, staphylococci also cause disease via toxins. These include food poisoning, toxic shock syndrome (TSS) and the scalded skin syndrome. These illnesses may occur in the absence of a site of infection. For example in TSS, vaginal colonization rather than infection is the rule. TSS is a superantigen-mediated disease. The superantigens are T cell mitogens. Disease is due to the ability of these toxins to bind antigen presenting cells MHC 2 molecule outside the peptide groove. The superantigens then bind T cells via the variable region resulting in massive T cell activation and the release of large quantities of cytokines – a “cytokine storm” including IL-1, IL-2, TNF, and interferon gamma. The result is a multiorgan disease similar in clinical presentation to septic shock with significant morbidity and mortality.

TSS is caused by a 22kDa protein or one of the structurally related enterotoxins. The TSST-1 gene, *tst*, is on the chromosome and appears to be part of a mobile genetic element.

**Clinical manifestations of staphylococcal disease:** *Staphylococcus aureus* causes a variety of diseases. These include local skin and soft tissue infections, invasive systemic infections such as infective endocarditis, sepsis or metastatic infections and respiratory tract infections such as pneumonia. In addition there are toxin-related illnesses that include food poisoning or toxic shock syndrome.

### **Treatment and prevention of staphylococcal infections:**

Treatment: Most staphylococcal infections require antibiotic therapy. Selection of an appropriate antibiotic is based on antibiotic susceptibility testing. Recently an increasing number of staphylococci have become resistant to the beta-lactam antibiotics. They have also become less susceptible to the second line agents such as vancomycin. In addition, localized collections such as staphylococcal abscesses require surgical drainage.

Prevention: Several approaches have been used to prevent staphylococcal infections. These include using the topical application of antibiotics to the nares to eliminate nasal carriage of staphylococci in high-risk groups such as hemodialysis patients. A second approach has been the recent development of potential staphylococcal vaccines. These candidate vaccines include polysaccharide-protein conjugate products as well as surface ligand domain peptide vaccines. Both have proven effective in animal models of infection but their efficacy in humans is still under investigation.

### **Coagulase Negative Staphylococci**

*Staphylococcus epidermidis* is the most common of the coagulase negative staphylococci encountered in clinical infections. They are considerably less virulent as pathogens than the *aureus* species. These coagulase negative species are most commonly encountered in association with prosthetic devices. They have a unique ability to adhere to prosthetic material and establish infection. This appears to be in part due to the elaboration of an extracellular polysaccharide referred to as slime or biofilm. They are among the most common causes of intravascular catheter, prosthetic valve and prosthetic hip infections.

Over the past 20 years these different species have become increasingly resistant to different families of antibiotics. As a result treatment often requires the use of second or third line agents. In addition successful therapy of the prosthetic device infections usually requires removal of the device. An additional therapeutic dilemma with these species is that they are frequent contaminants. Because of their presence as part of the normal skin flora they are frequently isolated from blood or body fluids when they are not the true pathogens. This creates some difficulty in determining whether an isolate is genuine or a contaminant.

### **References**

Material covered in this lecture can be found in Murray, Chapter 22, page 221-236.

