*Staphylococcus aureus* is a bacterium found primarily on the skin and in the nose of humans. *S. aureus* belongs to the coccus family of bacteria. These bacteria have a spherical shape and appear as large round yellow clusters similar to grapes. *S. aureus* is an important human pathogen which causes a range of diseases ranging from minor issues such as minor skin infections to severe toxin mediated diseases (Online Textbook of Bacteriology, 2008).

Individuals most at risk of *S. aureus* infection are those who are frequently treated with antibiotics, as this produces opportunities for the development of multi – drug resistant *S. aureus* (Kluytmans, Belkum and Verbrugh, 1997). Hospital environments are one setting in which people living in close proximity to one another are administered numerous antibiotics, thus they are hotbeds for multi-drug resistant *S. aureus*. One particular strain responsible for the increasing number of in-hospital infections is methicillin resistant *S. aureus* (MRSA), which has evolved multidrug resistance to strong antibiotics such as oxacillin, penicillin and amoxicillin (Center for Disease Control and Prevention, 2006). These organisms are responsible for over half of the Staphylococcus infections experienced in hospital environments, often leading to serious illnesses such as pneumonia (Center for Disease Control and Prevention, 2006). The development of novel antibiotics as well as controlling and preventing overuse of certain antibiotics are of critical importance to stopping this emerging 'super-bug' (Center for Disease Control and Prevention, 2006).

This paper succinctly describes salient characteristics of *S. aureus*, and briefly outlines how MRSA is currently treated. One field of research which may improve the standard of care in MRSA patients is discussed.

## ***Staphylococcus aureus***

### Overview

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|---|---|
| Kingdom: | Bacteria |
| Phylum: | Firmucutes |
| Class: | Bacilli |
| Order: | Bacillales |
| Family: | Staphylococcaceae |
| Genus: | Staphylococcus |
| Species: | Staphylococcus aureus |

*Staphylococcus aureus* is a Gram-positive spherical bacteria found in small clusters which produce yellow coloured colonies (Online Textbook of Bacteriology, 2008). They are facultative anaerobes that can grow by aerobic respiration or lactic acid fermentation of glucose. *S. aureus* is catalase positive and can survive in NaCl concentrations of up to 15 percent (Online Textbook of Bacteriology, 2008). While most Staphylococci are coagulase-negative, *S. aureus* is coagulase positive. *S. aureus* produces several virulence factors, some of which affect the immune system (Online Textbook of Bacteriology, 2008).

### Surface Proteins

Protein A is a staphylococcal surface protein bound to peptidoglycan pentaglycine bridges (Schneewind, Fowler and Faull, 1995). The protein is anchored using sortase A, which is involved in the anchoring of several staphylococcal surface proteins (Zhu et al, 2008). The N-terminal of the protein is exposed and binds to immunoglobulins that cover bacterial surfaces during infection (Schneewind et al., 1995). Protein A has been found to contain 5 repeated units, each capable of binding to immunoglobulin G (Patel et al. 1987). Studies indicate that

protein A mutants showed reduced virulence, indicating that the protein plays a vital role in virulence. In fact, laboratory research shows that animals injected with protein A exhibit a variety of effects, including hypersensitivity and histamine release (Zhu et al, 2008).

Staphyloxanthin is a membrane bound orange-red caratenoid pigment that is believed to allow for protection against oxidative stress. It has also been found to be involved in neutrophil killing, indicating it is also virulence factor (Clauditz et al, 2006).

**Toxins and Pathogenicity**

*S. aureus* toxins can be categorized into the following groups: pyrogenic toxin superantigens (PTSAgs), exfoliative toxins, leukocidins, and other toxins. PTSAgs also involve staphylococcal enterotoxins (SE), SE-like toxins, and toxic shock syndrome toxin-1 (TSST-1) (Verkaik et al., 2009). These superantigens allow for the cross-linking of histocompatibility class II molecules to antigen presenting cells and T cell receptors. This in turn leads to over proliferation of T cells and cytokine release, resulting in the disproportionate inflammatory activity believed to cause food poisoning and toxic shock syndromes (Verkaik et al., 2009).

Exfoliative toxins are believed to be the cause of illnesses such as staphylococcal scalded skin syndrome and bullous impetigo. Leukocidal toxins are pore forming toxins made up of two components (S and F proteins), and the toxic effects depend on the interaction of these proteins with neutrophils and erythrocytes (Verkaik et al., 2009). Members of this toxin family include LukD, LukE, LukM, γ hemolysin, and Panton-Valentine leukocidin (PVL). PVL is responsible for necrotizing pneumonia, bone and joint infections, and abscesses. This toxin belongs to the 'epidermal cell differentiation inhibitor' group of toxins. These toxins function by inactivating GTPases, and by blocking chemotaxis and phagocytosis which are important immune cell functions (Verkaik et al., 2009).

Several pathogenicity factors of *S. aureus* are believed to be controlled by regulatory systems involving two component regulatory mechanisms. An important gene in these systems is *agr,* which is involved in quorum sensing and in the activity of transcription factors for genes such as the superantigen genes *tst* and *seb*. These regulatory genes are believed to act in a time and population density dependant manner (Novick, 2003).

**Phylogenetics**

Staphylococci consist of over 30 taxa. In order to analyze 38 taxa belonging to the Staphylcocci genus, the nucleotide sequences of the 16s rRNA gene were compared (Takahashi, Satoh and Kikuchi, 1999). The staphylococci were divided into 12 cluster groups, which were in agreement with DNA-DNA reassociation studies. *S. aureus* was found to be most closely associated with the *Staphylococcus epidermidis* species (Takahashi, Satoh and Kikuchi, 1999).

## Current Treatment and Research

**Treatment of MRSA**

The antibiotic vancomycin in combination with other intravenous antibiotics such as linezolid and rifampin

remains to be the main treatment for MRSA, however treatment failures attributed to partially resistant bacteria are commonly reported (Bouza, 2009). Drainage of abscesses caused by MRSA is a standard procedure, especially as an adjunct treatment following antibiotic therapy; however, without effective medication therapy this treatment has minimal use. To remain control over MRSA infections, new treatments are regularly developed and tested in clinical settings (Bouza, 2009).

Newer treatments which hold promise include second generation glycolipopeptides (such as daptomycin, dalbavancin, and telavancin), the glycylcycline class antibiotic tigecycline, and beta-lactam antibiotics (such as ceftobiprole and ceftaroline) (Bouza, 2009).

**Systems Biology Research**

*S. aureus* is a rapidly adapting bacterium and therefore a major concern in hospital environments. This is especially true of the methicillin resistant *S. aureus* (MRSA) strains which are quickly becoming multidrug resistant. Thus, it is important to able to quickly isolate and detect various resistant strains of this bacterium so that the spread can be reduced and the infection can be treated with the appropriate antibiotics. Five major lineages of MRSA have been seen since the implementation of methicillin to treat *S. aureus* (Robinson and Enright, 2003). This resistance to methicillin is carried on the staphylococcal cassette chromosome *mec* which carries the *mecA* gene responsible for conferring reduced susceptibility to methicillin. Evolutionary models for each lineage have been developed through the use of a parsimony approach (Garza-Gonzalez et al., 2010).

Current research also involves the study of *S. aureus* metabolomics. Recent research has indicated a link between virulence factor synthesis and tricarboxylic acid synthesis (Meyer et al, 2010). Studies have been done to determine techniques to prevent pitfalls such as the leakage of metabolites while quenching and complete splitting of intra-and extra-cellular metabolites in *S. aureus* (Meyer et al, 2010). By developing novel approaches to decipher the *S. aureus* metabolome and combining the data with transcriptome and proteome data in a holistic sense, a systems biology approach to studying this organism can be developed (Meyer et al, 2010).

Future experiments should look at the effects of antibiotics and other agents on *S. aureus* physiology at the metabolic level, and methods should be developed to use similar protocols in related bacterial species (Meyer et al, 2010).

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