Staphylococcus aureus

From Wikipedia, the free encyclopedia

*Staphylococcus aureus* is a bacterium that is a member of the Firmicutes, and is frequently found in the human respiratory tract and on the skin. Although *S. aureus* is not always pathogenic, it is a common cause of skin infections (e.g. boils), respiratory disease (e.g. sinusitis), and food poisoning. Disease-associated strains often promote infections by producing potent protein toxins, and expressing cell-surface proteins that bind and inactivate antibodies. *The emergence of antibiotic-resistant forms of pathogenic S. aureus* (e.g. MRSA) is a worldwide problem in clinical medicine.

*Staphylococcus* was first identified in 1880 in Aberdeen, United Kingdom, by the surgeon Sir Alexander Ogston in pus from a surgical abscess in a knee joint. This name was later appended to *Staphylococcus aureus* by Rosenbach who was credited by the official system of nomenclature at the time. It is estimated that 20% of the human population are long-term carriers of *S. aureus* which can be found as part of the normal skin flora and in anterior nares of the nasal passages. *S. aureus* is the most common species of staphylococcus to cause *Staph* infections and is a successful pathogen due to a combination of nasal carriage and bacterial immuno-evasive strategies. *S. aureus can cause* a range of illnesses, from minor skin infections, such as pimples, impetigo, boils (furuncles), cellulitis folliculitis, carbuncles, scalded skin syndrome, and abscesses, to life-threatening diseases such as pneumonia, meningitis, osteomyelitis, endocarditis, toxic shock syndrome (TSS), bacteremia, and sepsis. Its incidence ranges from skin, soft tissue, respiratory, bone, joint, endovascular to wound infections. It is still one of the five most common causes of nosocomial infections and is often the cause of postsurgical wound infections. Each year, some 500,000 patients in American hospitals contract a staphylococcal infection.
Microbiology

Gram stain of *S. aureus* cells which typically occur in clusters. The cell wall readily absorbs the crystal violet stain.

Yellow colonies of *S. aureus* on a blood agar plate, note regions of clearing around colonies caused by lysis of red cells in the agar (beta hemolysis).

*S. aureus* (/ˈsteɪfiʃəʊ ˈkɒks əriəs/, Greek σταφυλόκοκκος, "grape-cluster berry", Latin aureus, "golden") is a facultative anaerobic Gram-positive coccal bacterium, also known as "golden staph" and Oro staphira. In medical literature the bacteria is often referred to as *S. aureus* or *Staph aureus*. *Staphylococcus* should not be confused with the similarly named and medically relevant genus *Streptococcus*. *S. aureus* appears as grape-like clusters when viewed through a microscope, and has large, round, golden-yellow colonies, often with hemolysis, when grown on blood agar plates. *S. aureus* reproduces asexually by binary fission. The two daughter cells do not fully separate and remain attached to one another. This is why the cells are observed in clusters.

*S. aureus* is catalase-positive (meaning it can produce the enzyme catalase). Catalase converts hydrogen peroxide (H₂O₂) to water and oxygen. Catalase-activity tests are sometimes used to distinguish staphylococci from enterococci and streptococci. Previously, *S. aureus* was differentiated from other staphylococci by the coagulase test.
However it is now known that not all *S. aureus* are coagulase-positive[^5][^7] and that incorrect species identification can impact effective treatment and control measures. [^8]

**Role in disease**

*SEM of methicillin-resistant* *Staphylococcus aureus.*

*S. aureus* is responsible for many infections but it may also occur as a commensal. The presence of *S. aureus does not always indicate infection.* *S. aureus* can survive from hours to weeks, or even months, on dry environmental surfaces, depending on strain. [^9]

*S. aureus* can infect tissues when the skin or mucosal barriers have been breached. This can lead to many different types of infections including furuncles and carbuncles (a collection of furuncles).

*S. aureus* infections can spread through contact with pus from an infected wound, skin-to-skin contact with an infected person by producing hyaluronidase that destroys tissues, and contact with objects such as towels, sheets, clothing, or athletic equipment used by an infected person. Deeply penetrating *S. aureus* infections can be severe. Prosthetic joints put a person at particular risk of septic arthritis, and staphylococcal endocarditis (infection of the heart valves) and pneumonia. Strains of *S. aureus* can host phages, such as Φ-PVL (produces Panton-Valentine leukocidin), that increase virulence.

**Atopic dermatitis**

*S. aureus* is extremely prevalent in atopic dermatitis patients. It is mostly found in fertile, active places, including the armpits, hair, and scalp. Large pimples that appear in those areas may exacerbate the infection if lacerated. This can lead to staphylococcal scalded skin syndrome (SSSS). A severe form of this, Ritter's disease, can be observed in neonates. [^10]

**Animal infections**

*S. aureus* can survive on dogs,[^11] cats,[^12] and horses,[^13] and can cause bumblefoot in chickens. [^14] Some believe health-care workers' dogs should be considered a significant
source of antibiotic-resistant *S. aureus*, especially in times of outbreak.\[11\] *S. aureus* is one of the causal agents of mastitis in dairy cows. Its large polysaccharide capsule protects the organism from recognition by the cow's immune defenses.\[12\]

**Virulence factors**

**Enzymes**

*Staphylococcus aureus* produces various enzymes such as coagulase (bound and free coagulases) which clots plasma and coats the bacterial cell to probably prevent phagocytosis. Hyaluronidase (also known as spreading factor) breaks down hyaluronic acid and helps in spreading of *Staphylococcus aureus*. *S. aureus* also produces DNAse (deoxyribonuclease) which breaks down the DNA, lipase to digest lipids, staphylokinase to dissolve fibrin and aid in spread, and beta-lactamase for drug resistance.\[16\]

**Toxins**

Depending on the strain, *S. aureus* is capable of secreting several exotoxins, which can be categorized into three groups. Many of these toxins are associated with specific diseases.\[17\]

**Superantigens**

(PTSAgs) have superantigen activities that induce toxic shock syndrome (TSS). This group includes the toxin TSST-1, enterotoxin type B, which causes TSS associated with tampon use. This is characterized by fever, erythematous rash, hypotension, shock, multiple organ failure, and skin desquamation. Lack of antibody to TSST-1 plays a part in the pathogenesis of toxic shock syndrome. Other strains of *S. aureus* can produce an enterotoxin that is the causative agent of *S. aureus* gastroenteritis. This gastroenteritis is self-limiting, characterized by vomiting and diarrhea one to six hours after ingestion of the toxin with recovery in eight to 24 hours. Symptoms include nausea, vomiting, diarrhea, and major abdominal pain.\[18\][19]

**Exfoliative toxins**

EF toxins are implicated in the disease staphylococcal scalded-skin syndrome (SSSS), which occurs most commonly in infants and young children. It also may occur as epidemics in hospital nurseries. The protease activity of the exfoliative toxins causes peeling of the skin observed with SSSS.\[19\]

**Other toxins**

Staphylococcal toxins that act on cell membranes include alpha toxin, beta toxin, delta toxin, and several bicomponent toxins. The bicomponent toxin Panton-Valentine leukocidin (PVL) is associated with severe necrotizing pneumonia in
children. The genes encoding the components of PVL are encoded on a bacteriophage found in community-associated methicillin-resistant *S. aureus* (MRSA) strains.

Other immunoevasive strategies

Protein A

Protein A is anchored to staphylococcal peptidoglycan pentaglycine bridges (chains of five glycine residues) by the transpeptidase sortase A. Protein A, an IgG-binding protein, binds to the Fc region of an antibody. In fact, studies involving mutation of genes coding for protein A resulted in a lowered virulence of *S. aureus* as measured by survival in blood, which has led to speculation that protein A-contributed virulence requires binding of antibody Fc regions.

Protein A in various recombinant forms has been used for decades to bind and purify a wide range of antibodies by immunoaffinity chromatography. Transpeptidases, such as the sortases responsible for anchoring factors like Protein A to the staphylococcal peptidoglycan, are being studied in hopes of developing new antibiotics to target MRSA infections.

*Staphylococcus aureus* on Tryptic Soy Agar. The strain is producing a yellow pigment staphyloxanthin.

Staphylococcal Pigments

Some strains of *S. aureus* are capable of producing staphyloxanthin — a golden coloured carotenoid pigment. This pigment acts as a virulence factor, primarily by being a bacterial antioxidant which helps the microbe evade the reactive oxygen species which the host immune system uses to kill pathogens.

Mutant strains of *S. aureus* modified to lack staphyloxanthin are less likely to survive incubation with an oxidizing chemical, such as hydrogen peroxide than pigmented strains. Mutant colonies are quickly killed when exposed to human neutrophils, while many of the pigmented colonies survive. In mice, the pigmented strains cause lingering abscesses when inoculated into wounds, whereas wounds infected with the unpigmented strains quickly heal.
These tests suggest the Staphylococcus strains use staphyloxanthin as a defence against the normal human immune system. Drugs designed to inhibit the production of staphyloxanthin may weaken the bacterium and renew its susceptibility to antibiotics.\[26\] In fact, because of similarities in the pathways for biosynthesis of staphyloxanthin and human cholesterol, a drug developed in the context of cholesterol-lowering therapy was shown to block \textit{S. aureus} pigmentation and disease progression in a mouse infection model.\[27\]

**Classical diagnosis**

Typical Gram-positive cocci, in clusters, from a sputum sample, Gram stain

Depending upon the type of infection present, an appropriate specimen is obtained accordingly and sent to the laboratory for definitive identification by using biochemical or enzyme-based tests. A Gram stain is first performed to guide the way, which should show typical Gram-positive bacteria, cocci, in clusters. Second, the isolate is cultured on mannitol salt agar, which is a selective medium with 7–9% NaCl that allows \textit{S. aureus} to grow, producing yellow-colored colonies as a result of mannitol fermentation and subsequent drop in the medium's pH.

Furthermore, for differentiation on the species level, catalase (positive for all \textit{Staphylococcus} species), coagulase (fibrin clot formation, positive for \textit{S. aureus}), DNase (zone of clearance on DNase agar), lipase (a yellow color and rancid odor smell), and phosphatase (a pink color) tests are all done. For staphylococcal food poisoning, phage typing can be performed to determine whether the staphylococci recovered from the food were the source of infection.

**Rapid diagnosis and typing**

Diagnostic microbiology laboratories and reference laboratories are key for identifying outbreaks and new strains of \textit{S. aureus}. Recent genetic advances have enabled reliable and rapid techniques for the identification and characterization of clinical isolates of \textit{S.}
*Staphylococcus aureus* in real time. These tools support infection control strategies to limit bacterial spread and ensure the appropriate use of antibiotics. Quantitative PCR is being increasingly employed in clinical laboratories as a technique to identifying outbreaks.

### Treatment and antibiotic resistance

The treatment of choice for *S. aureus* infection is **penicillin**; in most countries, however, **penicillin resistance is extremely common**, and first-line therapy is most commonly a penicillinase-resistant β-lactam antibiotic (for example, oxacillin or flucloxacillin). Combination therapy with **gentamicin** may be used to treat serious infections, such as endocarditis,[^30][^31] but its use is controversial because of the high risk of damage to the kidneys.[^32] The duration of treatment depends on the site of infection and on severity.

Antibiotic resistance in *S. aureus* was uncommon when penicillin was first introduced in 1943. Indeed, the original petri dish on which Alexander Fleming of Imperial College London observed the antibacterial activity of the *Penicillium* fungus was growing a culture of *S. aureus*. By 1950, 40% of hospital *S. aureus* isolates were penicillin-resistant; and, by 1960, this had risen to 80%.[^33]

Methicillin-resistant *S. aureus*, abbreviated **MRSA** and often pronounced /mɜrəsə/, is one of a number of greatly feared strains of *S. aureus* which have become resistant to most β-lactam antibiotics. MRSA strains are most often found associated with institutions such as hospitals, but are becoming increasingly prevalent in community-acquired infections. A recent study by the Translational Genomics Research Institute showed that nearly half (47%) of the meat and poultry in U.S. grocery stores were contaminated with *S. aureus*, with more than half (52%) of those bacteria resistant to antibiotics.[^34]

Researchers from Italy have identified a bacteriophage active against *S. aureus*, including methicillin-resistant strains (MRSA), in mice and possibly humans.[^35]

### Mechanisms of antibiotic resistance

Staphylococcal resistance to penicillin is mediated by **penicillinase** (a form of β-lactamase) production: an enzyme that cleaves the β-lactam ring of the penicillin molecule, rendering the antibiotic ineffective. Penicillinase-resistant β-lactam antibiotics, such as *methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, and flucloxacillin*, are able to resist degradation by staphylococcal penicillinase.

Resistance to methicillin is mediated via the **mec operon**, part of the staphylococcal cassette chromosome mec (SCCmec). Resistance is conferred by the mecA gene, which codes for an altered penicillin-binding protein (PBP2a or PBP2') that has a lower affinity...
for binding β-lactams (penicillins, cephalosporins, and carbapenems). This allows for resistance to all β-lactam antibiotics, and obviates their clinical use during MRSA infections. As such, the glycopeptide vancomycin is often deployed against MRSA.

Bacterial cells of *Staphylococcus aureus*, which is one of the causal agents of mastitis in dairy cows. Its large capsule protects the organism from attack by the cow's immunological defenses.

Aminoglycoside antibiotics, such as kanamycin, gentamicin, streptomycin, etc., were once effective against staphylococcal infections until strains evolved mechanisms to inhibit the aminoglycosides' action, which occurs via protonated amine and/or hydroxyl interactions with the ribosomal RNA of the bacterial 30S ribosomal subunit. There are three main mechanisms of aminoglycoside resistance mechanisms which are currently and widely accepted: aminoglycoside modifying enzymes, ribosomal mutations, and active efflux of the drug out of the bacteria.

Aminoglycoside-modifying enzymes inactivate the aminoglycoside by covalently attaching either a phosphate, nucleotide, or acetyl moiety to either the amine or the alcohol key functional group (or both groups) of the antibiotic. This changes the charge or sterically hinders the antibiotic, decreasing its ribosomal binding affinity. In *S. aureus*, the best-characterized aminoglycoside-modifying enzyme is aminoglycoside adenylyltransferase 4’ IA (ANT(4’)IA). This enzyme has been solved by x-ray crystallography. The enzyme is able to attach an adenyl moiety to the 4’ hydroxyl group of many aminoglycosides, including kamamycin and gentamicin.

Glycopeptide resistance is mediated by acquisition of the vanA gene. The vanA gene originates from the *enterococci* and codes for an enzyme that produces an alternative peptidoglycan to which vancomycin will not bind.
Today, *S. aureus* has become resistant to many commonly used antibiotics. In the UK, only 2% of all *S. aureus* isolates are sensitive to penicillin, with a similar picture in the rest of the world. The β-lactamase-resistant penicillins (methicillin, oxacillin, cloxacillin, and flucloxacillin) were developed to treat penicillin-resistant *S. aureus*, and are still used as first-line treatment. Methicillin was the first antibiotic in this class to be used (it was introduced in 1959), but, only two years later, the first case of MRSA was reported in England.\(^{[38]}\)

Despite this, MRSA generally remained an uncommon finding, even in hospital settings, until the 1990s, when there was an explosion in MRSA prevalence in hospitals, where it is now endemic.\(^{[39]}\)

MRSA infections in both the hospital and community setting are commonly treated with non-β-lactam antibiotics, such as clindamycin (a lincosamine) and co-trimoxazole (also commonly known as trimethoprim/sulfamethoxazole). Resistance to these antibiotics has also led to the use of new, broad-spectrum anti-Gram-positive antibiotics, such as linezolid, because of its availability as an oral drug. First-line treatment for serious invasive infections due to MRSA is currently glycopeptide antibiotics (vancomycin and teicoplanin). There are number of problems with these antibiotics, such as the need for intravenous administration (there is no oral preparation available), toxicity, and the need to monitor drug levels regularly by blood tests. There are also concerns glycopeptide antibiotics do not penetrate very well into infected tissues (this is a particular concern with infections of the brain and meninges and in endocarditis). Glycopeptides must not be used to treat methicillin-sensitive *S. aureus* (MSSA), as outcomes are inferior.\(^{[40]}\)

Because of the high level of resistance to penicillins and because of the potential for MRSA to develop resistance to vancomycin, the U.S. Centers for Disease Control and Prevention has published guidelines for the appropriate use of vancomycin. In situations where the incidence of MRSA infections is known to be high, the attending physician may choose to use a glycopeptide antibiotic until the identity of the infecting organism is known. After the infection is confirmed to be due to a methicillin-susceptible strain of *S. aureus*, treatment can be changed to flucloxacillin or even penicillin, as appropriate.

*Vancomycin-resistant S. aureus* (VRSA) is a strain of *S. aureus* that has become resistant to the glycopeptides. The first case of vancomycin-intermediate *S. aureus* (VISA) was reported in Japan in 1996;\(^{[41]}\) but the first case of *S. aureus* truly resistant to glycopeptide antibiotics was only reported in 2002.\(^{[42]}\) Three cases of VRSA infection had been reported in the United States as of 2005.\(^{[43]}\)

**Carriage of *Staphylococcus aureus***

The carriage of *Staphylococcus aureus* is an important source of nosocomial infection and community-acquired methicillin-resistant *S. aureus* (MRSA). Although *S. aureus* can be present on the skin of the host, a large proportion of its carriage is through the anterior nares of the nasal passages.\(^{[2]}\) The ability of the nasal passages to harbour *S. aureus*
results from a combination of a weakened or defective host immunity and the bacteria's ability to evade host innate immunity.\[44\]

**Infection control**

Spread of *S. aureus* (including MRSA) generally is through human-to-human contact, although recently some veterinarians have discovered the infection can be spread through pets,\[45\] with environmental contamination thought to play a relatively unimportant part. Emphasis on basic hand washing techniques are, therefore, effective in preventing its transmission. The use of disposable aprons and gloves by staff reduces skin-to-skin contact and, therefore, further reduces the risk of transmission. Please refer to the main article on infection control for further details.

Recently, there have been myriad reported cases of *S. aureus* in hospitals across America. Transmission of the pathogen is facilitated in medical settings where healthcare worker hygiene is insufficient. *S. aureus* is an incredibly hardy bacterium, as was shown in a study where it survived on polyester for just under three months;\[46\] polyester is the main material used in hospital privacy curtains.

The bacteria are transported on the hands of healthcare workers, who may pick them up from a seemingly healthy patient carrying a benign or commensal strain of *S. aureus*, and then pass it on to the next patient being treated. Introduction of the bacteria into the bloodstream can lead to various complications, including, but not limited to, endocarditis, meningitis, and, if it is widespread, sepsis.

Ethanol has proven to be an effective topical sanitizer against MRSA. Quaternary ammonium can be used in conjunction with ethanol to increase the duration of the sanitizing action. The prevention of nosocomial infections involves routine and terminal cleaning. Nonflammable alcohol vapor in CO\textsubscript{2} NAV-CO\textsubscript{2} systems have an advantage, as they do not attack metals or plastics used in medical environments, and do not contribute to antibacterial resistance.

An important and previously unrecognized means of community-associated MRSA colonization and transmission is during sexual contact.\[47\]

Staff or patients who are found to carry resistant strains of *S. aureus* may be required to undergo "eradication therapy", which may include antiseptic washes and shampoos (such as chlorhexidine) and application of topical antibiotic ointments (such as mupirocin or neomycin) to the anterior nares of the nose.

*S. aureus* is killed in 1 minute at 78 °C and 10 minutes at 64 °C.\[48\]

The nonprotein amino acid L-homoarginine is a growth inhibitor of *S. aureus* as well as *Candida albicans*. It is assumed to be an antimetabolite of arginine.
Biological control might be a new possible way to control *Staphylococcus aureus* in body surfaces. Colonization of body surfaces (especially in the nose) by *Staphylococcus epidermidis* (inhibitory strain JK16) impairs the establishment of *S. aureus*.

A 2011 study[^49] points to this new possible way to control *S. aureus*. This study was performed from observations of the nasal microbial flora of a diverse group of people. It was discovered that there are two different strains of *S. epidermidis*, one that inhibits biofilm formation by *S. aureus*, *S. epidermidis* strain JK16 (inhibitory type), and one that does not (non-inhibitory type) *S. epidermidis* strain JK11. In this study they observed that there were some patients that were not affected by *Staphylococcus aureus*; this was because these patients had *S. aureus* together with *S. epidermis* (inhibitory type), in their nasal microbial flora. This is due to an amensalistic relationship between these microorganisms, the inhibitory strain of *S. epidermidis* and *Staphylococcus aureus*.

These findings open the way to a biological control therapy to help in the treatment of *S. aureus* infections which are becoming a growing threat due to the rise of resistance to conventional antibiotic treatments.