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## Staphylococcus aureus

*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*[2] which can be found as part of the normal skin flora and in anterior nares of the nasal passages.[2][3] *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 skininfections, such as pimples, impetigo, boils (furuncles), cellulitis folliculitis, carbuncles, s calded skin syndrome, and abscesses, to life-threatening diseases such as pneumonia, meningitis, osteomyelitis, endocarditis, toxicshock
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

*S. aureus* (/ˈstæf l k k s ri s/, Greek               , "grape-cluster berry", Latin aureus, "golden") is a facultative anaerobic Gram-positivecoccal 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 asgrape-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 hydrogenperoxide (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 and that incorrect species identification can impact effective treatment and control measures.

Role in disease

*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. *S. aureus* can infect tissues when the skin or mucosal barriers have been breached. This can leadto 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 staphylococcalendocarditis (infection of the heart valves) and pneumonia.

Strains of *S. aureus* can host phages, such as 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

## Animal infections

*S. aureus* can survive on dogs, cats, and horses, and can cause bumblefoot in chickens. Some believe health-care workers' dogs should be considered a significant source of antibiotic-resistant *S. aureus*, especially in times of outbreak. *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.

## 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, staphylokinaseto dissolve fibrin and aid in spread, and beta-lactamase for drug resistance.

### 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.

### 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.

**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

**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**

ProteinA is anchored to staphylococcal peptidoglycan pentaglycine bridges(chainsoffive glycine residues)bythe transpeptidase sortase .A Prot -ein 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

**Staphylococcal Pigments**

Some strains of *S. aureus* are capable of producing staphyloxanthin — agoldencoloured 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 peroxidethan 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. 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 *S. aureus* pigmentation and disease progression in a mouse infection model.

## Classical diagnosis

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 *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,onthe,specieslevel, catalase (positiveforall *Staphylococcus* species), coagulase (fibrin clot formation, positive for*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 *S. aureus*. Recent genetic advances have enabled reliabl and rapid techniques for the identification and characterization of clinical isolates of *S. 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  -lactam antibiotic (for example, oxacillin or flucloxacillin). Combination therapy with gentamicin may be used to treat serious infections, such as endocarditis, but its use is controversial because of the high risk of damage to the kidneys 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%. Methicillin-resistant *S. aureus*,

 abbreviated **MRSA** andoften pronounced / m rs / or / m    s eɪ/, is one of a number of greatly feared strains of *S. aureus* which have become resistant to most   -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

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

**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 (SCC*mec*). 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.

Aminoglycoside antibioticssuchas 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  -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.

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 nowendemic

MRSA infections in both the hospital and community setting are commonly treated with non-  -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 iscurrently 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.

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 glycopeptides 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; but the first case of *S. aureus* truly resistant to glycopeptide antibiotics was only reported in 2002. Three cases of VRSA infection had been reported in the United States as of 2005.

## 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. 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.

## 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, 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 article on infection control for further details.

Recently, there have been myriad reported cases of *S. aureus* in hospitals across America. The pathogen has had facilitated transportation in medical facilities mainly because of insufficient healthcare worker

hygiene. *S. aureus* is an incredibly hardy bacterium, as was shown in a study where it survived on polyester for just under three months; 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 vaporin CO2 NAV-CO2 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.

 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 aschlorhexidine) 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. 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 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.

## Panton-Valentine leukocidin

**Panton-Valentine leukocidin** (PVL) is a cytotoxin—one of the  -pore-forming toxins. The presence of PVL is associated with increased virulence of certain strains (isolates) of *Staphylococcus aureus*. It is present in the majority  of community-associated Methicillin-resistant *Staphylococcus aureus* (CA-MRSA) isolates studied and is the cause of necrotic lesions involving the skin or mucosa, including necrotic hemorrhagic pneumonia. PVL creates pores in the membranes of infected cells. PVL is produced from the genetic material of a bacteriophage that infects *Staphylococcus aureus*, making it more virulent.

## History

It was initially discovered by Van deVelde in 1894 due to its ability to lyse leukocytes. It was named after Sir Philip Noel Panton and Francis Valentine when they associated it with soft tissue infections in 1932

## Mechanism of action

Exotoxins such as PVL constitute essential components of the virulence mechanisms of *S. aureus*. Nearly all strains secrete lethal factors that convert host tissues into nutrients required for bacterial growth.

PVL is a member of the synergohymenotropic toxin family that induces pores in the membranes of cells. The PVL factor is encoded in a prophage—designated as  -PVL—which is a virus integrated into the *S. aureus* bacterial chromosome. Its genes secrete two proteins—toxins designated LukS-PV and LukF-PV, 33 and 34 kDa in size. The structures of both proteins have been solved in the soluble forms, and are present in the PDB as ID codes1t5r and 1pvl respectively. See the PDBe article for more information on these structures.

LukS-PV and LukF-PV act together as subunits, assembling in the membrane of host defense cells, in particular, white blood cells, monocytes, andmacrophages. The subunits fit together and form a ring with a central pore through which cell contents leak and which acts as a superantigen.

## Clinical effects

PVL causes leukocyte destruction and necrotizing pneumonia, an aggressive condition that often kills patients within 72 hours. Comparing cases of staphylococcal necrotizing pneumonia, 85% of community-acquired (CAP) cases were PVL-positive, while none of the hospital-acquired cases were. CAP afflicted younger and healthier patients and yet had a worse outcome (>40% mortality.)  It has played a role in a number of outbreaks of fatal bacterial infections PVL may increase the expression of staphylococcal protein A, a key pro-inflammatory factor for pneumonia.

## Epidemiology

Panton-Valentine leukocidin (PVL) is one of many toxins associated with *S. aureus* infection. Because it can be found in virtually all CA-MRSA strains that cause soft-tissue infections, it was long described as a key virulence factor, allowing the bacteria to target and kill specific white blood cells known as neutrophils. This view was challenged, however, when it was shown that removal of PVL from the two major epidemic CA-MRSA strains resulted in no loss of infectivity or destruction of neutrophils in a mouse model.

 Genetic analysis shows that PVL CA-MRSA has emerged several times, on different continents, rather than being the worldwide spread of a single clone.

**P**anton-Valentine leukocidin (PVL) is one of many toxins produced by*Staphylococcus aureus.* Structurally similar to   haemolysin, this leukocidin comprises two subunits (F and S) that together are leukocidal and dermonecrotic. Intermixing of   haemolysin and the subunits of PVL produces toxin molecules with varying cellular affinities and destructive capability, even when the staphylococci may be otherwise sensitive to antibiotics such as methicillin. The death of a fit young soldier in the United Kingdom earlier this year from toxicity to PVL illustrated the extent of that capability

Infection with PVL producing staphylococci is rare. Fewer than 2% of clinical isolates of *S aureus* examined in the United Kingdom in 2002-3 had the genes to produce the leukocidin, although it was found in 4.6% of samples from infections of skin and soft tissue. Furthermore, "pure" disease caused by those *S aureus* bacteria that produce PVL is rarely life threatening. It presents as recurrent furunculosis or abscesses, it may be either sensitive or resistant to methicillin, and it can be difficult to eradicate among carriers. Three new and more virulent staphylococcal syndromes associated with the leukocidin—purpura fulminans, skin sepsis, and necrotising pneumonia—have been recognised recently, however.

Purpura fulminans due to PVL producing methicillin sensitive *S aureus* (MSSA) has a mortality of 60% despite such sensitivity. Skin sepsis due to community acquired methicillin resistant *S aureus* (MRSA) occurs in patients without recent contact with healthcare facilities or known risk factors for such infection. Transmission during close physical contact causes outbreaks in prisoners, military personnel, schoolchildren, and athletes. Although these bacterial strains are resistant to methicillin, they are, at least, usually sensitive to more antibiotics than hospital strains.

The third manifestation of more serious disease caused by PVL is necrotising pneumonia, which is often lethal. It has been reported in America, Australia, Europe, and the Far East. The pneumonia often arises from bloodborne spread of organisms from infected tissue and can follow viral respiratory infections, especially influenza.

Strains of *S aureus* that produce PVL have a particular affinity for basement membrane exposed by desquamated ciliated epithelium, and they rapidly establish themselves in the lung, producing the leukocidin. Membrane piercing PVL then destroys newly recruited polymorph cells, liberating inflammatory mediators. Alveolar macrophages, with depleted phagocytic ability owing to viral infection, then allow unhindered bacterial multiplication: at postmortem examination usually few neutrophils are found. Necrotising vasculitis with massive areas of pulmonary infarction and haemorrhage follows. Sheets of staphylococci cover ulcerated remnants of tracheal and bronchial epithelium. Mortality due to such necrotising pneumonia is nearly 75%.The first British case of necrotising pneumonia associated with PVL was in

2003, and I am aware of six cases managed by colleagues in the UK in the past nine months. Because postmortem specimens are rarely cultured and the disease is not notifiable, its true incidence remains unknown. No particular strain of *S aureus* predominates, and there is no predictable pattern of geographical variation.

Early diagnosis of necrotising pneumonia is very difficult, especially in young, fit people. Pyrexia, myalgia, chills, and occasionally diarrhoea imply non-specific viral illness but, equally, can indicate the production of other staphylococcal toxins. Typically, a previously young, fit patient, presents in the community with a recent flu-like illness. Classically he or she has a fever of > 39°C; tachycardia of > 140 beats per minute; and marked haemoptysis, hypotension, and leucopenia. Very high serum concentrations of C reactive protein (> 400 g/l) may occur too, reflecting gross tissue destruction, thrombosis, and sepsis. Multilobular alveolar infiltrates are usual and, unlike in hospital acquired MRSA pneumonia, the lungs often cavitate. Effusions commonly develop.

 The initial management of necrotising pneumonia is supportive, with intensive care and aggressive treatment with antibiotics. In addition to routine infection control precautions, it may be advisable to use masks when clearing patients' airways with suction because infection among close contacts has been reported. Having said that, screening of close contacts for PVL positive *S aureus* has not been recommended to date. In the face of such high mortality, treatment with high doses of potent, penetrating, anti-staphylococcal antibiotics is justifiable to try to block the production of toxins. Conventional doses of vancomycin produce inadequate lung concentrations to kill MRSA in many patients, and vancomycin will not suppress toxin formation. Empirical therapy must cover MRSA, since 47% of PVL positive clinical isolates of *S aureus* from various sources were resistant to methicillin. Furthermore, isolates of *S aureus* that seem to be resistant to erythromycin but sensitive to clindamycin should be checked ("D tested") to exclude inducible resistance to clindamycin. Clindamycin and linezolid have the advantage of switching off toxin production, and linezolid is also active against MRSA. This combination may be synergistic and has been used as initial therapy, pending the results of testing for antibiotic sensitivity. With no evidence based guidelines for treating necrotising pneumonia, and no dosage recommendations for intravenous dosages of clindamycin in this situation, 1.2 g given at six hourly intervals seems reasonable. This is

similar to the regimen recommended for streptococcal necrotising fasciitis.

Rifampicin, flucloxacillin, and cephalosporins have also been used, with varying degrees of success. Intravenous immunoglobulin, 2 g/kg, may have a beneficial immunomodulatory action, especially in toxic shock, neutralising superantigens, and circulating toxins. Anecdotal reports indicate a possible role for activated protein C. The key to improved survival may be the inactivation of the toxins that continue to drive the necrosis even after the bacteria have died. Potential treatments needing further research include nebulised immunoglobulin, glycerol monolaurate, staphylococcal vaccination, and it may be worth revisiting old treatments such as leukocidin toxoid.

Depressingly, even with what seems to be appropriate initial treatment with antimicrobial drugs, the maximal survival from necrotising pneumonia is 30%.During the 1919 influenza outbreak in Fort Jackson in the United States, when hundreds of troops were dying—almost certainly of PVL related necrotising pneumonia—doctors reported that "the treatment of *Staphylococcus aureus* infection of the lung is extremely ineffectual."

Until the toxins and inflammatory intermediaries responsible for the necrosis can be neutralised earlier, the outlook will remain bleak

Panton-Valentine Leukocidin (PVL) is a toxin which destroys white blood cells and is a virulence  factor in some strains of Staphylococcus aureus. Strains of S. aureus producing a new pattern  of disease have emerged in the UK and world-wide. In the UK the genes encoding for PVL are  carried by less than 2% of clinical isolates of S. aureus whether meticillin-sensitive (MSSA) or  meticillin-resistant (MRSA)

## Clinical features of PVL–SA

In common with S. aureus infections in general, PVL-SA predominantly cause skin and soft  tissue infections, but can also cause invasive infections, the most serious of which is a necrotising haemorrhagic pneumonia with a high mortality, and often follows a flu-like illness. It may affect otherwise healthy young people in the community.

## Skin and soft tissue infections (SSTI)

These are often recurrent and can comprise:

• Boils (furunculosis), carbuncles, folliculitis, cellulitis

• Cutaneous lesions 5cm or larger in diameter are not uncommon

• Pain and erythema that seem out of proportion to severity of cutaneous findings may occur

• Necrosis is an indicator of possible PVL-SA infection

Invasive infections

• Necrotising pneumonia

• Necrotising fasciitis

• Osteomyelitis, septic arthritis and pyomyositis

• Purpura fulminans

Patients who develop necrotising pneumonia commonly have a preceding "flu-like" illness. It is not known what percentage are genuinely of viral aetiology. It is recommended that co-infection with a respiratory virus, including influenza A is investigated.

**Treatment of Panton-Valentine leukocidin (PVL)-associated staphylococcal pneumonia.**

Panton-Valentine leukocidin (PVL)-producing Staphylococcus aureus is emerging as a serious problem worldwide. Whilst usually causing skin and soft-tissue infections, particularly recurrent abscesses, there has in the last 10 years been an increase in the incidence of an associated devastating pneumonia affecting previously healthy young people and associated with a very high mortality. There are no evidence-based guidelines to consult for the management of PVL-associated staphylococcal pneumonia. The literature contains less than 100 cases, with widely differing antimicrobial therapies and the occasional use of other adjunctive therapies such as intravenous immunoglobulin, activated protein C and extracorporeal membrane oxygenation. This literature review focuses on the salient features of diagnosis and management, with particular attention to the choice of antimicrobials.

**What is PVL-SA?**

PVL is a toxin produced by certain types of the bacteria Staphylococcus Aureus. PVL-SA can kill white blood cells and cause tissue damage.

## What causes PVL-SA infections?

This type of bacteria is most often found in the community and the risk of acquiring the infection is increased with the five C's:

1. Close Contact – playing contact sports such as rugby or skin-to-skin

contact with an infected family member or friend.

2. Contaminated items – touching something which is contaminated with

the bacteria, e.g. gym equipment, towels or razors.

3. Crowding – living in crowded conditions increases the chance of

passing on the infection, e.g. military accommodation, prisons and boarding schools

4. Cleanliness – an unclean environment will encourage the bacteria to spread.

5. Cuts and grazes – having a cut or graze will allow the bacteria to enter the body.

## What are the symptoms of PVL-SA?

PVL-SA infection mainly occurs in young, healthy individuals. If PVL-SA enters the body through a graze or wound it can attack the skin and may rarely enter the blood stream, causing more serious problems. The symptoms include recurrent and painful spots/red areas on the skin, often at multiple sites which can persist despite appropriate antibiotic treatment. The affected area is often more painful than the size of the lesion would suggest.

## What does PVL-SA look like?

PVL-SA infected skin is generally red and inflamed with pus. It can have different appearances and may present as cellulitis (infection of deeper layers of skin), abscesses, boils, folliculitis (inflammation of the hair follicle) or an infected wound.

## How can PVL-SA be treated?

**Minor skin infections**

- Abscesses need to be incised and drained – this involves making a small cut in the skin with a sterile instrument and allowing the pus to drain from the abscess.

- Prevent spread by decontamination as outlined below.

**Moderate skin and soft tissue infections**

- Incision and drainage of abscesses. ·
- Oral antibiotic treatment – different antibiotics will be given depending on the susceptibility of the bacteria

**Severe skin and soft tissue infections**

- Intravenous antibiotics will need to be administered in hospital via a drip for 10-14 days.

**How do I stop the bacteria from spreading?**

Once the infection has resolved, your body must be cleared of any PVL-SA. Your doctor will prescribe a topical treatment, e.g. chlorhexidine, to wash yourself with and an antibacterial nasal ointment both to be used for 5-7 days. Your family members may also have to follow this system.

Panton-Valentine leukocidin (PVL) is a cytotoxin that can destroy white blood cells and cause extensive tissue necrosis and severe infection. The toxin was first described by Panton and Valentine in 1932

Some *Staphylococcus aureus* strains carry genes for PVL and at least 14 strains of PVL-positive *S. aureus* are known  It is carried by <2% of isolates of *S. aureus*, both meticillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA).

PVL-positive *S. aureus* strains are usually associated with community-acquired infections and generally affect previously healthy young children and young adults. Most infection has been associated with PVL-positive MSSA so far in the UK. Community-acquired MRSA is more likely to produce PVL than hospital-acquired MRSA. Carriage of the PVL gene alone may not be the main virulence factor. Factors that up-

regulate toxin synthesis in vivo could also contribute to more severe disease and worse outcomes

**Presentation**

There is an asymptomatic carrier status.

Infection with PVL-positive *S. aureus* most commonly causes:[10]

- Necrotising pyogenic skin infections.
- Cellulitis.
- Tissue necrosis.

It can also cause:

- Septic arthritis.
- Osteomyelitis.
- Pyomyositis.
- Bacteraemia.
- Purpura fulminans (typically characterised bydisseminated intravascular coagulation and purpuric skin lesions).[11]
- Community-acquired necrotising pneumonia.[12][13]

Clinical infection tends to accompany other risk factors such as:

- Overcrowding.
- Engagement in close contact sports (which can cause skin abrasions), eg rugby, wrestling.
- Being in military, residential home and school settings.
- Using contaminated articles: sharing towels, razors.
- Poor hand hygiene.
- Damaged skin, eg eczema.
- Illicit drug use.[14]

**Skin infection**

- Consider screening in anyone if there are recurrent abscesses/furunculosis.
- Management includes drainage of abscesses and sensitivity testing to find appropriate antibiotics.
- Swabs should be taken as indicated and, if there is specific reason to suspect PVL-positive *S. aureus* such as recent contact, it should be stated on the request form.
- If either MSSA or MRSA is isolated (the latter usually ciprofloxacin susceptible), refer to the Staphylococcal Reference Unit at Colindale for PVL-testing.
- A polymerase chain reaction (PCR) test for PVL virulence genes and simultaneous discrimination of MRSA from MSSA has recently been

developed The unit at Colindale can provide a result within the working day.

- Mild infections may resolve without treatment.
- Moderate infections should be treated with flucloxacillin, erythromycin or clindamycin
- If community-acquired MRSA-PVL infection occurs and hospitalisation is not thought appropriate, consider a 5-7-day course of one of the following, depending on microbiological susceptibility:
  - Rifampicin 300 mg bd PLUS doxycycline (100 mg bd - not for children <12 years).
  - Rifampicin 300 mg bd PLUS fusidic acid 500 mg tds.
  - Rifampicin 300 mg bd PLUS trimethoprim 200 mg bd.
  - Clindamycin 450 mg qds.
- Infection control measures include screening of patients for *S. aureus* carriage (swab nose, throat, perineum, axilla, skin lesions). Decolonisation may be needed as with MRSA.

**Necrotising pneumonia**

**General points**:

- Can arise from blood-borne spread of organisms from infected tissue but can also follow viral respiratory infections. A preceding flu-like illness is common
- Necrotising vasculitis with massive areas of pulmonary infarction and haemorrhage can occur
- Infection tends to be rapidly progressive and in young, immunocompetent individuals
- There is a high fatality rate.
- Some cases have also been identified in people with pre-existing lung disease, egcystic fibrosis


**Panton-Valentine Leukocidin Genes in *Staphylococcus aureus***

Panton-Valentine Leukocidin Genes in *Staphylococcus aureu*In 1932, Panton and Valentine described PVL as a virulence facto belonging to the family of synergohymenotropic toxins (*4*). These toxins form pores in the membrane of host defense cells by synergistic action of 2 secretory proteins, designated LukS-PV and LukF-PV, which are encoded by 2 cotranscribed genes of a prophage integrated in the *S.aureus* chromosome (*5*). PVL is mostly associated with community-acquired methicillin-resistant *S. aureus* (MRSA) infections and distinguishable from nosocomial MRSA by nonmultidrug resistance and carriage of the type IV staphylococcal chromosome cassette element (SCC*mec* type IV) Despite the presumed importance of PVL as a virulence factor, few data are available on its prevalence among *S. aureus* isolates from the nares of

healthy persons compared with stains isolated from infections. This lack of data led us to investigate the frequency of PVL gene–positive *S. aureus* strains obtained from the nares of healthy carriers in the community. For this purpose, a single polymerase chain reaction method was used to detect both *lukS-PV* and *lukF-PV* genes In a previous study, the population structure of *S. aureus*, isolated from the nares of healthy persons in the Rotterdam area, the Netherlands, was elucidated Strains were obtained from healthy children (<19 years) and elderly persons (>55 years). Invasive strains (blood culture, skin and soft tissue infections, and impetigo isolates) were included in this study (Table). All carriage and clinical isolates (n = 1,033) were *mecA* negative. We used the same strain collection to study the PVL prevalence in carriage and invasive isolates of *S. aureus* from a single geographic region.Five PVL-positive *S. aureus* strains (0.6%) were found in the carriage group (n = 829), and 3 (2.1%) of 146 blood-culture isolates carried the PVL gene). This finding is in agreement with previously reported low PVL prevalences by Prevost et al. (0% in 31 carriage isolates and 1.4% in 69 blood-culture isolates) and Von Eiff et al. (1.4% in 210 carriage isolates and 0.9% in 219 blood-culture isolates). However, a higher prevalence of PVL (38.9%) was found in *S. aureus* strains causing abscesses and arthritis (Fisher exact test, p <0.0001) .This finding is also in agreement with the proposed involvement of PVL in severe and invasive (soft tissue) staphylococcal infections (*1–3*). No significant differences were found in the presence of PVL when carriage isolates were compared with invasive blood-culture isolates. PVL was found in each major genomic amplified fragment length polymorphism (AFLP) cluster, indicating that PVL has been introduced in distinct phylogenetic subpopulations of *S. aureus* (Figure). Multilocus sequence typing analysis of a subset of the strain collection showed that the 15 PVL-positive strains were within clonal complex (CC) 30 (n = 7), CC 121 (n = 3), CC 1 (n = 2), CC 8 (n = 1), CC 22 (n = 1), and CC 45 (n = 1) Although PVL was found among several staphylococcal genotypes, it was slightly overrepresented in AFLP cluster IVb (CC 121) compared with major clusters I and III. Whether the prevalence of PVL in carriage- and blood-culture isolates is higher and differs among distinct genetic clusters of *S. aureus* in countries with endemic CA-MRSA has to be investigated further.In conclusion, we have shown that the PVL-encoding phage has entered distinct staphylococcal lineages, although its prevalence differs per clonal group. PVL is associated with skin and soft tissue infections but not with bacteremia, which suggests that PVL is not likely to be involved in the pathogenesis of bacteremia. Infections caused by PVL-positive *S. aureus* strains have been documented since the 1930s. Expansion and increased incidence of such infections, however, are more recent, and

further epidemiologic studies for tracking this phenomenon are still warranted.