Bacterial Infections: Gram-Positive Cocci

Although there are countless types of bacteria, it is important for a physician to know the most common ones - about the typical clinical picture they cause, as well as basics about their structure, virulence, morphology, and bacterial culture in order to be able to recognize and distinguish them from other bacteria and target them properly.

Staphylococci

Staphylococci are bacteria that turn blue during gram-staining and arrange themselves in grape-like clusters of cocci. They are generally catalase-positive, do not form spores, and are not encapsulated. Staphylococci are facultative anaerobes.

*Staphylococcus aureus*
Morphology and culture

*S. aureus* appears in gram-staining as blue grape-like clusters of spherical bacteria. A culture can be grown on blood agar plates. There, *S. aureus* appears as yellow-pigmented colonies that show areas of partial hemolysis around them.

Virulence factors

The virulence factors of *S. aureus* include hyaluronidases, lipases, and DNases which allow invasion into a tissue. The clumping factor ensures adhesion to tissue. Hemolysins have a toxic effect.

Diagnostics

*S. aureus* is part of the catalase-positive and clumping-factor-positive staphylococci. This can be proven in a test for the clumping factor. The clumping factor is a protein that belongs to the cell wall of *S. aureus*. During the coagulase-test, colony material and rabbit plasma are mixed. If the colony contains *S. aureus*, clumping in the plasma will appear. If there is no *S. aureus* in the colony and, instead, another coagulase-negative pathogen is present, the plasma will remain liquid with generalized turbidity.

Clinical picture

*S. aureus* causes many diseases. Among these are infections of the skin and soft tissue, e.g., boils, wound infections, sinusitis, otitis media, infections of the eyelid, diabetic foot ulcers, osteomyelitis, impetigo contagiosa, and infections that are associated with foreign bodies.
In addition to this, systemic diseases, such as sepsis, pneumonia, and endocarditis, can occur. Toxic diseases, such as foodborne infections, staphylococcal scalded skin syndrome (SSSS) and toxic shock syndrome (TSS), can also be caused by *S. aureus*.

**Treatment**

There are various therapeutic options that are determined mainly by the sensitivity of *S. aureus* to certain antibiotics. It is always helpful to employ an antibiogram in order to prevent antibiotic resistance. Drugs of choice are penicillinase-resistant β-lactam antibiotics such as flucloxacillin, the application of which is restricted to staphylococci ("staphylococcal penicillin"), or first or third-generation cephalosporins.

Furthermore, when combined with inhibitors of beta-lactamase, aminopenicillins can also be administered. The above-mentioned antibiotics are, however, not suitable for the treatment of methicillin-resistant *S. aureus* (MRSA). In such a case, vancomycin and linezolid can be used. In any case, it is essential to find and remove the source of infection.

*Staphylococcus epidermidis*

In gram staining, *S. epidermidis* shows a blue color and is arranged in grape-like clusters. Culture shows small colonies which are whitish or yellowish pigments. Usually, hemolysis is absent.
Virulence factors

Usually, there is no risk of *S. epidermidis* infection. It is part of the normal human skin flora.

**Diagnosis**

Unlike *S. aureus*, *S. epidermidis* does not have a coagulase and is, therefore, a coagulase-negative staphylococci. Hence, generalized turbidity is seen in the clumping factor test. To distinguish *S. epidermidis* from other staphylococci species, one can perform a sensitivity test for desferrioxamine.

**Clinical picture**

While *S. epidermidis* is usually not harmful to healthy people, it causes disease in immunocompromised patients. It is often the cause of nosocomial infections. Examples include catheter-related and foreign body-related sepsis, endophthalmitis, as well as endocarditis associated with a prosthetic valve or endocarditis lenta.

**Treatment**

*S. epidermidis* shows resistance to numerous antibiotics, most prominently, to penicillin and methicillin. An antibiogram is therefore always required. A combination of vancomycin + aminoglycoside + rifampin can be a reasonable treatment.

*Staphylococcus saprophyticus*

**Morphology and culture**

Like other staphylococci, *S. saprophyticus* appears as blue grape-shaped clusters of cocci when viewed through a microscope. Colonies of *S. saprophyticus* grow on blood agar and are whitish or yellowish without hemolysis. *S. saprophyticus* does not form spores.

**Virulence factors**

*S. saprophyticus* adheres to the urothelium where it produces ureases. These are enzymes that hydrolyse urea into carbon dioxide and ammonia.

**Diagnostics**

*S. saprophyticus* is a coagulase-negative staphylococcus, yielding a negative result when
tested for the clumping factor. To distinguish it from other coagulase-negative staphylococci, in particular from *S. epidermidis*, one can take advantage of its resistance to novobiocin. The test is simple: by putting a tablet of novobiocin on the agar and measuring the zone of inhibition, one can easily detect novobiocin-resistance.

**Clinical picture**

*S. saprophyticus* is particularly associated with urinary tract infections. It is responsible for 10–20% of uncomplicated cystitis and urethritis in young women, while it can cause unspecific urethritis in men. It is also a trigger of the so-called honeymoon cystitis since its occurrence is associated with sexual intercourse.

**Treatment**

*S. saprophyticus* is naturally resistant to several common antibiotics. It is, however, most sensitive to cotrimoxazole, which is therefore frequently used as a treatment.

**Streptococci**

Streptococci are gram-positive bacteria with an oval or round shape that grows in chains or pairs. They are catalase-negative, do not form spores, and are non-motile. Their classification is based on the grade of hemolysis when grown on blood agar and on their so-called Lancefield antigen. Lancefield antigens are different carbohydrate polymers in the cell wall of some bacteria.

The following table shows a classification of the most important streptococcal pathogens:

<table>
<thead>
<tr>
<th>Hemolysis pattern</th>
<th>Lancefield antigen</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>β (large, yellowish zone of hemolysis)</td>
<td>A antigen</td>
<td><em>S. pyogenes</em></td>
</tr>
<tr>
<td></td>
<td>B antigen</td>
<td><em>S. agalactiae</em></td>
</tr>
<tr>
<td>α (green hemolysis)</td>
<td>No antigen</td>
<td>Viridans streptococci, pneumococci</td>
</tr>
<tr>
<td>γ (no hemolysis)</td>
<td>D antigen</td>
<td>Enterococci</td>
</tr>
</tbody>
</table>

**Group A: Streptococcus pyogenes**

Microscopy reveals blue cocci that are sized 1 μm and arranged in chains. Blood agar reveals cultures with a surrounding yellowish zone of hemolysis. This pattern of hemolysis is called beta-hemolysis. Attached to the murein in its cell wall are carbohydrates of serogroup A.
**Virulence factors**

*S. pyogenes* has several virulence factors. Among them, one can find streptolysin O and S, which are able to cause beta-hemolysis but are especially known for their ability to destroy cell membranes. The streptococcal pyrogenic exotoxins A, B, and C are so-called exogenous superantigens. They induce the synthesis of cytokines and are, among others, responsible for the exanthema that accompanies some scarlet fever infections.

Furthermore, *S. pyogenes* possess an enzyme called streptokinase which is able to digest fibrin and thus helps the bacteria to spread through tissue. Hyaluronidases also support this process.

**Diagnostics**

For diagnosis purposes, one can use group A antigen. If mixed with antibody-coated particles, an agglutination can be noted, provided the A antigen is present in the tested substance. The same principle is used in the rapid strep test in practice and can help to diagnose e.g. streptococcal tonsillitis. Nevertheless, culture remains the golden standard.

**Clinical picture**

Infection with *S. pyogenes* causes acute diseases, as well as sequelae. Acute infections include pharyngitis, tonsillitis, and scarlet fever. Typical are also skin infections like erysipelas, phlegmon, and necrotizing fasciitis.

Acute glomerulonephritis, rheumatic fever, and heart diseases such as endocarditis, pericarditis, and myocarditis are classified as potential sequelae. Rheumatoid arthritis and CNS inflammation such as Sydenham’s chorea can also follow infection with *S. pyogenes*.

**Treatment**

Penicillin G or V is the drug of choice for *S. pyogenes*. First to 3rd-generation cephalosporins, or macrolides can also be used.

**Group B: Streptococcus agalactiae**

**Morphology and culture**

Like *S. pyogenes*, a culture of *S. agalactiae* shows a large yellowish zone of hemolysis and is thus also classified as streptococci with beta-hemolysis. As it has the B antigen in its cell wall, it is part of the group B streptococci.

**Virulence factors**

Primarily, *S. agalactiae* causes infections in animals. In humans, it is particularly dangerous during pregnancy and childbirth. Its virulence factors include hemolysin, a surrounding capsule, and laminin-binding proteins.

**Diagnostics**

*S. agalactiae* can easily be grown on blood agar plates. By adding CAMP factor, it shows a more pronounced hemolysis pattern. For final evidence, it is useful to prove the presence of the B antigen with the help of antibody-coated particles.

**Clinical picture**

*S. agalactiae* is well-known for its association with septicemia in newborns. It is believed
that colonization of the female vagina by B streptococci can be proven in 5–20% of all cases. During childbirth, they can be transmitted to the child and cause septicemia in newborns and meningitis.

Those infections are divided into an ‘early onset’ infection, which occurs in the 1st few hours to days, and a ‘late-onset’ infection, which manifests several days to weeks after birth. The lethality rate of early-onset infection in premature infants is 50%, that of a late-onset infection at 25%.

**Treatment**

If there is prenatal proof of B streptococci infection, it is possible to reduce the risk of newborn infection through antibiotic prophylaxis with penicillin. A manifest *S. agalactiae* infection can be treated with ampicillin, cefotaxime, and gentamicin.

**Group C**

*S. anginosus* is an example of a group C streptococci. It is part of the commensal pharyngeal flora, but can also cause wound infections and peritonsillar abscesses. The C antigen can also be found in cell walls of *S. dysgalactiae*, along with antigens G and L. Its virulence factors are similar to those of *S. pyogenes*. However, this group is of less importance and will not be reviewed further.

**Group D: Enterococci**

Enterococci mostly occur in the human gastrointestinal tract. They do, however, colonize animals and the environment. The most common are *Enterococcus faecalis* (80–90%) and *Enterococcus faecium* (5–15%). Natural resistance to cephalosporins is an important characteristic of this species!

**Enterococcus faecalis and Enterococcus faecium**

**Morphology and culture**

When viewed through a microscope, *E. faecalis* and *E. faecium* occur as gram-positive cocci, arranged in chains. They can also build pairs. Enterococci are catalase-negative and do not demonstrate hemolysis on blood agar. Their cell walls contain Lancefield antigen D.

**Virulence factors**
*E. faecalis* has several virulence factors that help the bacterium to invade and destroy tissue. These include gelatinases, hyaluronidases, proteases, adhesins, and cytolysin A.

**Diagnosis**

*E. faecalis* can be grown on a culture medium, e.g. blood agar, in order to verify its occurrence. It shows resistance in an optochin susceptibility test.

**Clinical picture**

Enterococci are the 2nd most common cause of urinary tract infections and the 3rd most common cause of native valve endocarditis (endocarditis lenta). They can also be responsible for septicemia, peritonitis, and wound infections, especially in nosocomial infections or after cephalosporin therapy. Due to their natural resistance, treatment with cephalosporins exerts a selection pressure. However, in many cases, colonization with enterococci is innocuous.

**Treatment**

Due to their penicillin-binding-protein PBP5, enterococci are resistant to cephalosporins ('enterococci gap' of cephalosporins). Cotrimoxazole and penicillin G are ineffective as well.

Aminopenicillins and vancomycin are suitable treatment modalities. However, resistance to those antibiotics (vancomycin-resistant enterococci, VRE) can occur, in which case linezolid can be used. It is also possible to encounter multi-resistant species, which can hardly be treated with antibiotics.

**Alpha-hemolytic streptococci**

This group includes viridans streptococci and pneumococci. Their form of alpha-hemolysis is sometimes also called green hemolysis since it shows a green color on blood agar. They are not assignable to a Lancefield antigen.

- *Streptococcus pneumoniae*

**Morphology and culture**

Through a microscope, *S. pneumoniae* appears as blue diplococci or short chains in gram staining. A green zone of hemolysis is notable on blood agar.

**Virulence factors**
The most important virulence factor of *S. pneumoniae* is its capsule. It has additional factors like pneumolysin, an IgA specific endopeptidase, neuraminidases, and hyaluronidases.

**Note:** About 50% of all people have pneumococci without adverse effects.

**Diagnosis**

On culture, alpha-hemolysis in combination with gram-positive diplococci when viewed through a microscope is indicative of *S. pneumoniae*. In addition, one can recognize a slight sinking in the middle of a cell. Since pneumococci are sensitive to optochin. Optochin susceptibility tests can help to distinguish them from *viridans streptococci*.

**Clinical picture**

The clinical picture depends on elements like the patient’s age or underlying disease. Typical pneumococcal diseases include bronchopneumonia and lobar pneumonia, as well as meningitis, otitis media, sinusitis, and septicemia when the patient is severely infected.

**Treatment**

To prevent infection, 13- and 23-valent vaccines exist. The standing committee on vaccination (STIKO) generally recommends vaccination beginning in the 2nd month of life, and which has to be repeated 3 times. Penicillin G and V or ampicillin are treatments of choice for *S. pneumoniae*. Ceftriaxone or vancomycin also are suitable.

*Streptococcus viridans*

![Image](image.png)  
*Image:* Streptococcus viridans. By CDC, License: Public Domain

The term ‘*S. viridans*’ is misleading since it includes several species of streptococci with green hemolysis. The fact that subgroups can be differentiated makes the term viridans streptococci more suitable. Some species are part of the commensal flora of the pharynx, others of the vaginal flora or gastrointestinal tract.

**Morphology and culture (Streptococcus viridans)**

When viewed through a microscope, gram staining shows blue cocci arranged in chains. Culture shows green zones of hemolysis around the colonies which makes them alpha-hemolytic streptococci. Viridans streptococci do not have any Lancefield antigen in their cell walls.
**Virulence factors**

*Viridans streptococci* have the ability to synthesize extracellular polysaccharides. In doing so, they provide a habitat for other bacteria and contribute to the development of caries.

**Diagnosis**

Viridans streptococci can be identified on blood agar. Here, they show the characteristic green zone of hemolysis. Unlike pneumococci that also demonstrate green hemolysis, they show resistance in an optochin susceptibility test.

**Clinical picture**

Next to their role in the development of caries, *viridans streptococci* are the second most common cause of native valve endocarditis. If bacteria enter the bloodstream, e.g., after a tooth extraction, they can cause subacute endocarditis lenta. They are also associated with the development of appendicitis.

**Treatment**

Apart from penicillin G or V and aminopenicillins, cephalosporins or combinations with vancomycin, gentamicin, or clindamycin can be used to treat an infection.

**References**


In Acton, Q. A. (2012). *Advances in gram-positive cocci research and application*.


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