

Bacterial Infections: Gram-Positive Cocci

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



Staphylococci

Without any exception, the group of staphylococci involves 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. In the following, their genus is referred to with the letter 'S'. Staphylococci are facultative anaerobic.

Staphylococcus aureus

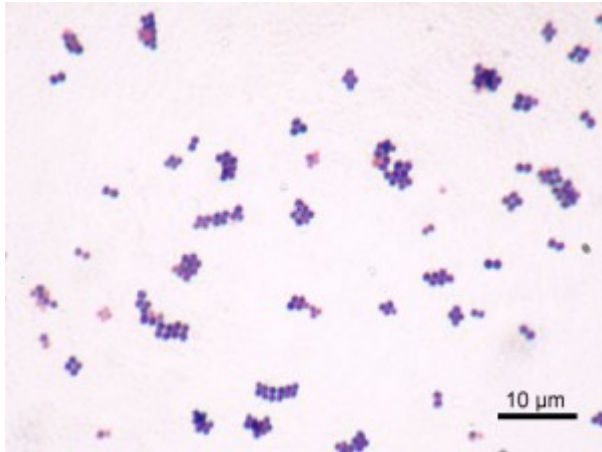


Image: "Staphylococcus aureus" by Y Tambe. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Morphology and culture

When being examined via a microscope, *S. aureus* appears in Gram staining as blue grape-like clusters of spherical bacteria. A culture can be grown on blood agar plates. There it appears as yellowish pigmented colonies which partially show areas of hemolysis around them.

Virulence factors

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

Diagnostics

S. aureus is part of the catalase-positive respectively clumping-factor-positive staphylococci. This can be proven in a test for the clumping factor. The clumping factor is a protein which 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 as liquid with an all-over turbidity.

Clinical picture

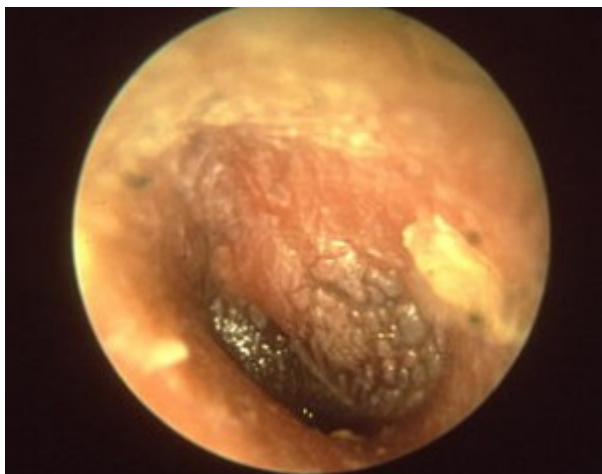


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S. aureus causes many disease patterns. Among those are infections of the skin and soft tissue, e.g., boils, wound infections, sinusitis, otitis media, infections of the eyelid, diabetic foot ulcers, osteomyelitis, impetigo contagiosa and infections that are associated to foreign bodies.

In addition to this, systemic diseases, such as sepsis, pneumonia and endocarditis, can occur. Toxic diseases, such as foodborne infections, the staphylococcal scalded skin syndrome (SSSS) and the toxic shock syndrome (TSS), can also be caused by *S. aureus*.

Treatment

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

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

Staphylococcus epidermidis

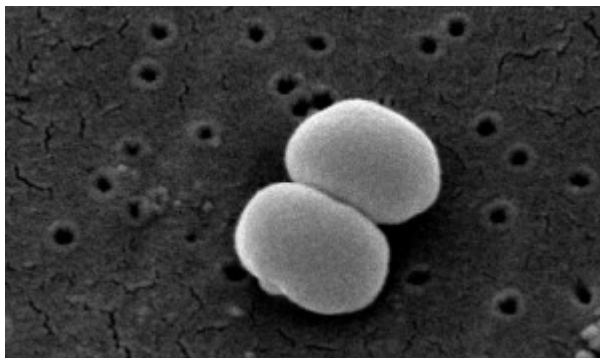


Image: "Staphylococcus Epidermidis" by CDC. License: Public Domain

Morphology and culture

In Gram staining, the cocci of *S. epidermidis* show a blue color and arrange in grape-like clusters. The culture shows small colonies which are whitish or yellowish pigmented. Usually, there is no sign of hemolysis.

Virulence factors

For healthy people, there is no risk of infection through *S. epidermidis*. It is part of the commensal human skin flora.

Diagnostics

Contrary to *S. aureus*, the *S. epidermidis* does not have a coagulase and is therefore found among coagulase-negative staphylococci. Hence, there is an all-over turbidity to be seen in a test for clumping factor. To distinguish *S. epidermidis* from other species of staphylococci, one can perform a sensitivity test to desferrioxamine.

Clinical picture

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

Treatment

S. epidermidis shows resistance to numerous antibiotics. Most prominently, this includes penicillin and methicillin. Preparing an antibiogram is therefore always required. A combination of vancomycin + aminoglycoside + rifampin can be a reasonable treatment.

Staphylococcus saprophyticus

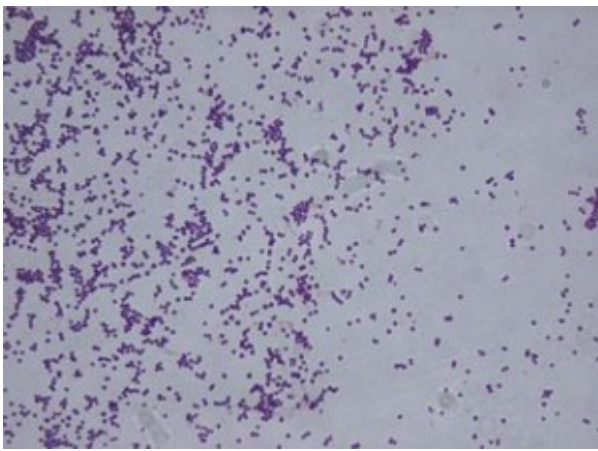


Image: "Staphylococcus Saprophyticus" by Riraq25. License: [CC BY-SA 3.0](#)

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 whitish or yellowish without hemolysis. It does not form spores.

Virulence factors

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

Diagnostics

S. saprophyticus is a coagulase-negative staphylococcus with a negative result when tested for the clumping factor. In order to distinguish it from other coagulase-negative staphylococci in lab diagnostics, 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 a 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 a lot of common antibiotics. It is, however, in most cases, sensitive to cotrimoxazole, which is therefore frequently used as treatment.

Streptococci

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

The following table shows a classification of the most important pathogens of the group of streptococci, which is abbreviated 'S.' below:

Hemolysis pattern	Lancefield antigen	Name
β (= large, yellowish zone of hemolysis)	A antigen	<i>S. pyogenes</i>
	B antigen	<i>S. agalactiae</i>
α (= green hemolysis)	No antigen	Viridans streptococci, pneumococci
γ (= no hemolysis)	D antigen	Enterococci

Group A: Streptococcus pyogenes



Image: "Streptococcus Pyogenes" by CDC. License: Public Domain

Morphology and culture

A look through the microscope shows blue cocci which are sized 1 μm and arranged in chains. The 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* possesses an enzyme called streptokinase which is able to digest fibrin and thus helps the bacteria to spread through tissue. Hyaluronidases support this process, too.

Diagnostics

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

Clinical picture

An 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, phlegmons and a necrotizing fasciitis.

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

Treatment

Means of choice for the treatment of an *S. pyogenes* are penicillin G or V. Cephalosporins of the first to third generation, 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 streptococcus with beta-hemolysis. Due to having the B antigen in its cell wall, it is part of the Group B streptococci.

Virulence factors

Primarily, *S. agalactiae* causes infections in animals. Concerning humans, it is particularly dangerous during pregnancy and childbirth. As virulence factors, it features 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 B antigen with the help of antibody-coated particles.

Clinical picture

S. agalactiae is well-known for its connection to septicemia in newborns. It is believed that colonization of the female vagina by B streptococci could 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 first few hours to days, and a “late onset” infection, which manifests several days to weeks after the birth. The lethality rate of an early onset infection in premature infants is at 50%, that of a late onset infection at 25%.

Treatment

If there is prenatal proof for an infection with B streptococci, 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

Among Group C streptococci, one can find for example *S. anginosus*, a bacterium that 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 during studies and is hence not further considered here.

Group D: Enterococci

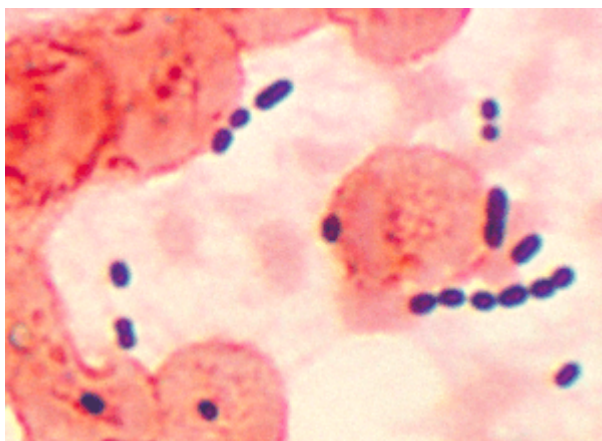


Image: “Enterokokken” by CDC. License: Public Domain

Enterococci mostly occur in the human gastrointestinal tract. They do, however, colonize animals and the environment too. Most common are the species *enterococcus faecalis* (80 - 90%) and *enterococcus faecium* (5 - 15%). The name enterococcus is referred to as ‘E.’ below. A 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 perform hemolysis when grown on blood agar. Their cell walls contain the Lancefield antigen D.

Virulence factors

Several virulence factors are known for *E. faecalis* which help the bacterium to invade

and destroy tissue. This includes gelatinases, hyaluronidases, proteases, adhesins and cytolysin A.

Diagnosics

It is sufficient to grow *E. faecalis* 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 second most cause for urinary tract infections, and the third most cause of native-valve endocarditis (in the form of endocarditis lenta). They can also be responsible for septicemia, peritonitis and wound infections, especially in the course of nosocomial infections or after treatment with cephalosporins. Due to their natural resistance, the 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.

Suitable as a treatment are aminopenicillin antibiotics or vancomycin. However, a developed resistance toward 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*

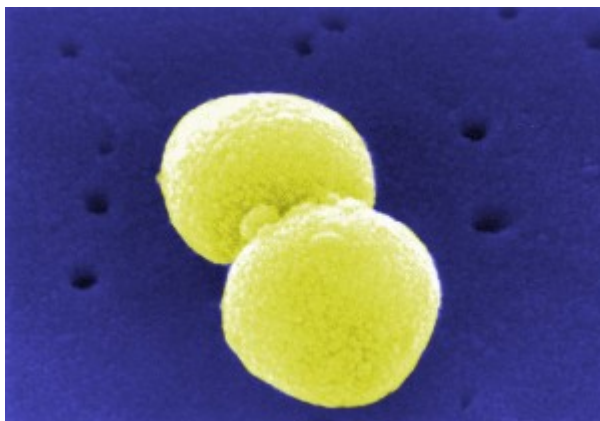


Image: "Streptococcus Pneumoniae" by Dr. Richard Facklam.
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Morphology and culture

Through a microscope, one can see *S. pneumoniae* as blue diplococci or short chains in Gram staining. A green zone of hemolysis attracts the viewer's attention when looking at

a culture on blood agar.

Virulence factors

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

It is important to know that about 50% of all people are populated with pneumococci without them causing diseases.

Diagnostics

The diagnosis is already obvious if the culture shows alpha-hemolysis in combination with gram-positive diplococci when viewed through a microscope. In addition, one can recognize a slight sinking in the middle of a cell. Since pneumococci are sensitive toward optochin, an optochin susceptibility test can help to distinguish them from *viridans streptococci*.

Clinical picture

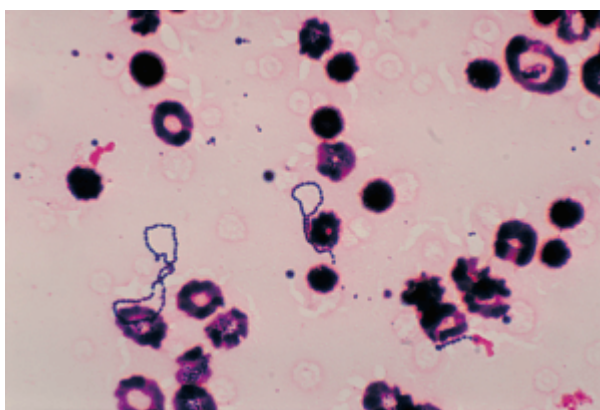
The clinical picture depends on elements like the patient's age or underlying disease. Typical pneumococci-caused diseases include bronchopneumonia and lobular pneumoniae, as well as meningitis, otitis media, sinusitis and septicemia when the patient is severely infected.

Treatment

In order to prevent an infection, 13- and 23-valent vaccines exist. The Standing Committee on Vaccination (STIKO) generally recommends a vaccination beginning with the second month of life that has to be repeated three times.

The means of choice for treatment are penicillin G and V or ampicillin. Ceftriaxone or vancomycin are suitable too.

- *Streptococcus viridans*



[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, other of the vaginal flora or the gastrointestinal tract.

Morphology and culture

When viewed through a microscope, the Gram staining shows blue cocci arranged in chains. The culture shows green zones of hemolysis around the colonies which assigns them to the alpha-hemolytic streptococci respectively to those who show green hemolysis. The viridans streptococci do not have any Lancefield antigen linked to 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.

Diagnostics

Viridans streptococci can be proven by growing them on blood agar. Here, they show the characteristic green zone of hemolysis. Contrary to pneumococci, which perform a green hemolysis as well, they show resistance in an optochin susceptibility test.

Clinical picture

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

Treatment

Well-suited for a treatment are, besides penicillin G or V and aminopenicillins, cephalosporins or combinations with vancomycin, gentamicin or clindamycin.

Review Questions

You can find the correct answers below the list of references.

1. A young woman comes to the doctor's office with an infection of the urinary tract. Which treatment is most likely indicated?

- A. She is treated with penicillin.
- B. She is treated with cotrimoxazole.
- C. She is treated with cephalosporins.
- D. She is treated with vancomycin.
- E. She is treated with gentamicin.

2. A boy suffers from otitis media. Which bacteria are most likely responsible?

- 1. *Pneumococci*
- 2. *S. aureus*
- 3. *S. agalactiae*
- 4. *Viridans streptococci*

- A. 1 and 2 are correct.
- B. Only 4 is correct.
- C. Only 2 is correct.
- D. Only 1 is correct.
- E. 1 and 4 are correct.

3. A prosthetic valve endocarditis is most likely caused by...

- A. ...*S. aureus*.
- B. ...*Enterococci*.
- C. ...*S. epidermidis*.
- D. ...*S. pyogenes*.
- E. ...*Viridans streptococci*.

References

Gorbach, S. L., Bartlett, J. G., & Blacklow, N. R. (2004). *Infectious diseases*. Philadelphia: Lippincott Williams & Wilkins.

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

Shimeld, L. A., & Rodgers, A. T. (1999). *Essentials of diagnostic microbiology*. Albany, NY: Delmar Publishers.

Correct answers: 1B, 2A, 3C

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Notes