GLOSSARY: INFECTIONS AND ANTIBIOTICS

ANTIBIOTIC GROUPS (SELECTION)

Antibiotics can be classified on the basis of different criteria such as their efficacy, chemical structure or mode of action. Selected groups of antibiotics and the microorganisms they affect are shown in the table below:

<table>
<thead>
<tr>
<th>Group</th>
<th>Typical spectrum of activity</th>
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<tbody>
<tr>
<td>Penicillin G</td>
<td>• Streptococci incl. pneumococci</td>
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<tr>
<td></td>
<td>• Gonococci, meningococci, etc.</td>
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<tr>
<td>Aminopenicillins</td>
<td>• Streptococci incl. pneumococci</td>
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<td></td>
<td>• Enterococci and a few Gram-negative pathogens that do not produce beta-lactamase</td>
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<td></td>
<td>• Not effective against staphylococci and anaerobes that produce beta-lactamase</td>
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<tr>
<td>Aminopenicillins in combination with beta-lactamase inhibitors</td>
<td>• Streptococci incl. pneumococci</td>
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<td></td>
<td>• Gram-positive bacteria that produce beta-lactamase incl. meticillin-sensitive staphylococci</td>
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<td></td>
<td>• Enterococci</td>
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<td></td>
<td>• Gram-negative enterobacteria that produce beta-lactamase incl. E. coli or Klebsiella (but not ESBL)</td>
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<tr>
<td>Aminopenicillins in combination with beta-lactamase inhibitors</td>
<td>• Gram-positive bacteria including enterococci</td>
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<tr>
<td></td>
<td>• Some Gram-negative pathogens that produce beta-lactamase (not ESBL)</td>
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<td></td>
<td>• Pseudomonads</td>
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<tr>
<td>Isoxazolyl penicillins</td>
<td>• Gram-positive pathogens that produce beta-lactamase (staphylococci penicillins)</td>
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<td>Older macrolides</td>
<td>• Atypical pneumonia pathogens (Chlamydia, Mycoplasma, Legionella spp)</td>
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<tr>
<td></td>
<td>• Streptococci incl. pneumococci</td>
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<tr>
<td></td>
<td>• Inadequate effect against Haemophilus influenzae</td>
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ANTIBIOTIC PROPHYLAXIS

Unlike antibiotic therapy in which antibiotics are used to control existing infections, medications used for antibiotic prophylaxis are administered before, during or immediately after a medical procedure to prevent an infection developing. The choice of suitable antibiotic is made empirically based on past experiences of which pathogens are likely to be present and taking into account the local epidemiology of resistance. This affects predominantly orthodontic/orthopaedic, trauma or dental procedures and/or at-risk patients with a weakened immune system. Antibiotic prophylaxis can involve either systemic or local administration of antibiotics with a combination of both types of administration also possible. With local administration, there may be very high antibiotic concentrations present in the affected area while the systemic load remains low (Fig. 1). Combining systemic and local administration of antibiotics for infection prophylaxis is a well-established procedure, particularly in orthopaedics and trauma surgery.

ANTIBIOTIC RESISTANCE

Bacteria can be resistant to one or more antibiotics, that is, they develop resistance to the particular antibiotics. This resistance results from random mutations that confer a
survival advantage on the affected bacterium when there is an appropriate selection pressure. Resistance then spreads rapidly. If the corresponding resistance genes are also located on plasmids (ring-shaped DNA structures), antibiotic resistance can also spread very rapidly between different species through an exchange of these plasmids. This is particularly the case when the different bacterial species are found in the same environment, e.g., the soil, the intestines, waste water, biofilms, etc.

There are different types of antibiotic resistance, e.g., primary resistance (an antibiotic lacks efficacy for certain bacteria) and secondary resistance (loss of efficacy of an antibiotic in a non-primarily resistant bacterium due to a mutation or an exchange of genetic material with others). Multidrug resistance is the absence of susceptibility of a bacterium to several antibiotics from different classes.

Antibiotic resistance is a problem with grave consequences. It is therefore important to reduce the inappropriate use of antibiotics.

ANTI-INFECTIVES

The umbrella term “anti-infective” refers to medications used to treat infectious diseases. Depending on the type of pathogen, these are classified as antibiotics (against bacteria), antifungics (against fungi), antihelmentics (against worms), antiprotozoal drugs (against protozoa such as the pathogens that cause malaria, dysentery, etc.) and virostatics (against viruses).

BACTERIA

Bacteria are microscopic single-celled organisms without a nucleus that are found in almost every environment. They reproduce rapidly by cell division. They are primarily differentiated on the basis of their shape (spherical, rod or spiral shaped) but are now also classified by their genetics. Of the countless species of bacteria, it is presumed that only a fraction are known and have been researched.

The great majority of all bacteria species are harmless to humans and we even live in symbiosis with some species: We need intestinal bacteria for our digestion and we also have many harmless bacteria living on our skin and mucous membranes that protect us against invasion by pathogenic species.

Only a few bacteria species cause diseases in the human body when they enter the body and start to replicate. This opportunity presents itself particularly in immunocompromised people and as a result of major medical procedures. What is critical for preventing a bacterial infection is first preventing contamination. This means that stringent hygiene measures on hospital wards and also in the operating room that comply with the sterilisation and disinfection guidelines are of major importance.

Bacterial infections are primarily treated with antibiotics but sometimes the focus of the inflammation also has to be removed surgically. Some bacteria have developed immunity to certain antibiotics (resistance) over time. The spread of antibiotic resistance can be attributed to a special feature of bacteria: Most of their genetic material is present as a large chromosome but they also have short, ring-shaped genetic structures known as plasmids. A special characteristic of these plasmids is that they can be exchanged among completely different species. Antibiotic resistance genes are located primarily on plasmids and can therefore spread rapidly.
TREATMENT OF INFECTIONS CAUSED BY RESISTANT PATHOGENS

Even for the treatment of simple bacterial infections, the type of treatment, that is, the choice of appropriate antibiotic, must be carefully determined based on the germ present. Every case requires an exact diagnosis of the underlying germ. When treating infections caused by resistant germs, most antibiotics have a limited effect or are not effective at all. Reserve antibiotics should generally then be used. These should only be used for particularly severe infections and/or if the infectious bacteria have developed resistance to other antibiotics. Reserve antibiotics are in no way more effective than standard antibiotics. They often have considerable side effects.

BIOFILMS

Biofilms develop when microorganisms settle on surfaces. There they form communities in which the bacteria are surrounded by a matrix made up of water and biopolymers (polysaccharides, proteins, lipids and nucleic acids) that is formed by the microorganisms. This process can take weeks or even years and occurs in several stages. Biofilms offer microorganisms protection from desiccation and toxic substances and enable them to survive periods without nutrients. In more than 60% of all bacterial infectious diseases, the pathogens protect themselves by forming biofilms because the mucous-like matrix formed by the bacteria is very difficult for immune cells and active substances to penetrate. Bacteria in biofilms also greatly slow down their metabolism and their growth rate. Antibiotics are only effective against metabolically active, rapidly growing bacteria, however. Depending on the level of activity, cells can also constantly detach from the biofilm. This can lead to chronic or recurrent infections, for example. Effective control is usually only possible at an early stage of biofilm development. Due to their reduced metabolic activity, pathogens that are present in biofilms are also difficult to culture using conventional methods and have therefore only been poorly investigated. The metal or polymer surfaces of implants and medical devices that are left in the body for longer periods (catheters, artificial heart valves, shunts, etc.) provide particularly favourable conditions for the formation of biofilms. About half of all nosocomial infections are the result of surgical implants.
DIAGNOSIS
A diagnosis summarises and evaluates the information provided by diagnostics about the symptoms of a disease and identifies and classifies the disease. The diagnosis forms the basis of subsequent medical treatment (therapy).

DIAGNOSTICS
Diagnostics is the umbrella term covering all measures that lead to identification (diagnosis) of a disease. It includes physical and, if applicable, instrumental examinations, laboratory analyses of body tissues and secretions, imaging procedures and many more.

ONE-STAGE/TWO-STAGE (REVISION)
One-stage and two-stage treatment concepts are used nowadays to treat prosthesis infections. In the one-stage concept, during one operation the infected prosthesis is replaced by a revision prosthesis after radical surgical excision of the infected or even necrotic tissue. In the two-stage concept, the two surgeries are carried out separated by an interval of several weeks. In the first procedure the infected prosthesis is first removed, the infected tissue excised and then, after a bridging period of several weeks, the new prosthesis is implanted. During the bridging period patients are generally provided with a spacer made of bone cement that releases high levels of antibiotic directly into the infected joint cavity over about four weeks. The spacer acts as a placeholder to prevent shortening of the muscles and tendons around the affected joint and allows the patient limited mobility and partial loads. It is removed after the new prosthesis is inserted.

ESBL-PRODUCING GRAM-NEGATIVE BACTERIA
ESBL stands for extended-spectrum beta-lactamase. Beta-lactamases are enzymes that open up beta-lactam rings and are therefore able to inactivate an important group of antibiotics, the beta-lactam antibiotics (e.g., cephalosporins). These antibiotics disrupt the structure of the bacterial cell wall.

ESBL become problematic if the ability to produce this enzyme is transferred to Gram-negative rod-shaped members of the Enterobacteriaceae family. These bacteria (e.g., E. coli, Klebsiella spp and Proteus spp) live in the intestines of healthy people but are also ingested from the environment and are important for the functioning of the intestinal flora. If they obtain the ability to form ESBL from the environment, this is not dangerous in and of itself. It becomes a problem when the ESBL bacteria – in mechanically ventilated or immunocompromised patients, for instance – replicate in the mucous membrane of the large intestine or the urinary or respiratory tract and cause pathological symptoms. This can lead to infections of the urinary tract that are difficult to treat, lung inflammations that heal poorly or wound healing disorders in which wounds suppurate and emit a strong odour of putrefaction.

ESBL-producing bacteria are resistant to an entire range of antibiotics and often only certain reserve antibiotics remain as a treatment option, primarily carbapenems with the antibiotic colistin often being the last option.

IMPLANT-ASSOCIATED INFECTION/PERIPROSTHETIC INFECTION
After implantation of a prosthesis, infections can develop that are often difficult to diagnose. Acute early infections that develop soon after surgery are differentiated from delayed infections that generally have a chronic course as well as late infections that usually have an acute course. A periprosthetic infection (PPI, also known as a prosthetic joint infection) generally manifests as persistent or increasing joint pain and early prosthesis loosening.

Early infections that occur up to three months after surgery usually develop as wound infections with acute local and systemic signs of infection. Delayed infections that can occur up to 24 months after surgery are also usually contracted intraoperatively and are caused by slow-growing bacteria. Late infections can develop at any point, even several years after implantation of the prosthesis. In these cases, the infection develops as a result of the spread of bacteria from a remote infection site, that is, via the blood circulation as a rule (haematogenous).

The following rule of thumb applies to chronic infections: The later they develop, the more difficult they are to diagnose and treat because the classic signs of inflammation and significantly elevated laboratory values are generally absent. The bacteria also form tenacious biofilms. A combination of various methods is needed for diagnostics including aspiration of joint fluid (puncture), biopsies of tissue samples
from different sites as well as sonication (ultrasound cleaning) of the removed prosthesis to detach the biofilm. In addition to radical surgical excision of the infected and necrotic tissue, the treatment of a prosthetic joint infection includes the systemic and local administration of antibiotics, ideally with combination preparations. Before therapy, a biofilm-specific antibiogram should be prepared. Identifying pathogens and any antibiotic resistance or susceptibility is a major challenge in clinical microbiology, particularly for slow-growing pathogens.

was carried out using the representative antibiotic methicillin. Until the 1990s, MRSA strains were found almost exclusively in hospitals and became a problem in recent years primarily because they also developed resistance to other antibiotics as well (multiresistant germs). The glycopeptide antibiotics such as vancomycin are used to control MRSA strains. For about 20 years, MRSA strains have also been found outside hospitals, making it necessary to differentiate between hospital-acquired (HA) and community-acquired (CA) MRSA. There is also livestock-associated (LA) MRSA that is the result of using antibiotics in animal husbandry.

MRSE (METHICILIN-RESISTANT STAPHYLOCOCCUS EPIDERMIS)
Similar to MRSA, there are also antibiotic-resistant strains of the skin bacteria Staphylococcus epidermis. S. epidermis and other staphylococci form part of the completely normal skin and mucosal flora of humans and do not cause any diseases. The antibiotic-resistant S. epidermis strains (MRSE) are also no danger to healthy people. If, however, they infect people with a weakened immune system – via implanted foreign bodies such as catheters, prostheses, artificial joints, pacemakers, heart valves and so on – treatment becomes difficult because antibiotics have no or little effect.

MULTIRESISTANT PATHOGENS
Multiresistant pathogens are bacteria that are resistant to several or even all available antibiotics. Infections with these pathogens can therefore be treated only with difficulty or not at all. Nosocomial infections are increasingly caused by resistant or multiresistant pathogens. The increased and uncontrolled or incorrect use of antibiotics in humans and animals has led to an increase in the number of multiresistant bacteria. Multiresistant pathogens do not generally cause more frequent infections nor are such infections more aggressive. The danger is that if an infection develops, they are difficult to treat because most medications are ineffective. In addition to MRSA, certain Klebsiella spp, enterococci and pseudomonads are also multiresistant pathogens.
NOSOCOMIAL INFECTION
A nosocomial infection (colloquially referred to as a “hospital infection”) is an infection that develops during or shortly after hospitalisation or an outpatient treatment. The most important nosocomial pathogens include bacteria, fungi and viruses. Hospitals and medical practices that handle many infected patients cannot be kept 100% microbe-free, despite the most stringent efforts, and many bacteria are also highly resistant and also colonise everyday objects and medical devices. This means that, in addition to other patients and clinical personnel, common sources of infection include objects such as door handles and wash basins as well as tubes, catheters, ventilation equipment, etc. Contact infection is just as likely as airborne transfer. What is critical in reducing nosocomial infections is good hygiene, that is, careful disinfection or sterilisation.
For healthy people with an intact immune system (nursing staff, doctors, visitors), these hospital microorganisms generally do not present any risk. There is a higher risk for patients if devices or implants are inserted into the body. Immunocompromised patients are particularly at risk. Postoperative wound infections are some of the most common nosocomial infections.

RESERVE ANTIBIOTICS
Reserve antibiotics are antibiotics that are only supposed to be used for infections that are particularly severe and/or the infectious bacteria have developed resistance to other antibiotics. As far as possible, they should not be used for infections with a simple course to avoid the development of resistance.
Reserve antibiotics are no more effective than other antibiotics but because of their relatively rare and controlled use, fewer bacteria have developed resistance to them. They often cause considerably more side effects than conventional antibiotics.
Vancomycin is, for example, the reserve antibiotic against Staphylococcus aureus.

Fig. 4: Staphylococcus aureus in the biofilm on a catheter surface
SCREENING
In the broadest sense, screening uses systematic test methods to identify individual elements with certain properties from among a large number of elements (e.g. patients, hospital pathogens, etc.). In the case of hospital pathogens and antibiotic resistance, for example, in a hospital all newly admitted patients are systematically tested for the presence of certain resistant germs (admission screening). It can help to limit the spread of certain germs but is not a panacea because it is laborious and expensive, only identifies certain bacteria and cannot detect the development of new strains.

STANDARD ANTIBIOTICS
The standard antibiotics are about a dozen preparations that have been used for years or decades to control microbial infections. Relevant lists from the WHO or individual countries and regions differ. The standard antibiotics include aminoglycoside antibiotics, cephalosporins, gyrase inhibitors, macrolide antibiotics, penicillins, sulfonamides, tetracyclines, trimethoprim and tuberculostatic drugs. They are used to control practically all bacterial infections and are therefore important across all medical disciplines.

VANCOMYCIN-RESISTANT ENTEROCOCCI (VRE)
Enterococci – usually referring specifically to the intestinal bacterium Enterococcus faecium – are common pathogens that cause nosocomial infections, particularly in patients in intensive care units. At-risk patients are usually very ill, older patients with a weakened immune system. Enterococci are often multiresistant. Vancomycin-resistant enterococci, the VRE bacteria, are particularly problematic. Because they are resistant to vancomycin, one of the reserve antibiotics, they are a feared nosocomial microorganism. They have often also developed resistance to a number of other antibiotics which leaves very few treatment options available.

AVOIDING RESISTANCE
The unnecessary or incorrect use of antibiotics accelerates the development and spread of resistant bacteria. Every time antibiotics are taken, the pathogens and the intestinal flora are exposed to a selection pressure, that is, the development and spread of resistance is favoured. For this reason, antibiotics should not be used speculatively. Bacterial infections should be treated with an adequately high dose of antibiotics over the shortest possible period. The antibiotic therapy used should target the actual pathogen present (antibiogram). Furthermore, it must be clarified as a matter of course whether the infection is actually bacterial in origin before prescribing an antibiotic.

If a course of antibiotics is not completed, this favours the survival of slightly resistant germs and further adaptation to the antibiotic. What is important, therefore, is an exact diagnosis, a prescription-only requirement (this is not the case in many countries) and taking the antibiotic precisely in accordance with the doctor’s instructions. There is still a great deal of educational work required in human medicine, however. According to a 2013 Cochrane Library survey of 89 studies from 19 countries, up to 50% of antibiotic use is inappropriate, leading to increased antibiotic resistance, lengthened hospital stays for patients and subsequently increased costs to patient, hospitals and commissioners (Davey P et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD003543. doi:10.1002/14651858.CD003543.pub3. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003543.pub3/epdf)

In the US, in 2010 to 2011, there was an estimated annual antibiotic prescription rate per 1000 population of 506, but only an estimated 353 antibiotic prescriptions were actually appropriate, demonstrating the need for establishing a goal for outpatient antibiotic stewardship (Fleming-Dutra KE et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011. JAMA. 2016;315(17):1864–1873. doi:10.1001/jama.2016.4151)