Antibiotics

An antibiotic (from the Greek anti: "against," and bios: "life") is a natural or synthetic substance that kills bacteria or blocks their growth. In the first case, it is called a bactericidal antibiotic, and in the second, a bacteriostatic antibiotic. When the substance is used externally to kill bacteria by contact, it is not called an antibiotic but an antiseptic.
An antibiotic can be both bactericidal and bacteriostatic, depending on its dosage.
Many existing antibiotics are made up of natural molecules produced by microorganisms: fungi or other bacteria. These microorganisms produce them to eliminate competing bacteria with which they compete in their environment. However, only a small number of natural antibiotics are usable in human therapy, due to issues of bioavailability in the body or adverse effects. Many molecules on the market today are synthetic molecules, derived from natural antibiotics or not, particularly to overcome resistance problems.
Antibiotics act specifically on bacteria, blocking an essential step in their development: cell wall synthesis, DNA, protein synthesis, or energy production, etc. This blockage occurs when the antibiotic binds to its target, a molecule in the bacterium that participates in one of these essential metabolic processes. This interaction between the antibiotic and its target is highly selective, specific to bacteria, and these compounds are generally not active against fungi or viruses. Other molecules exist that are active against these other types of infectious agents; these are called antifungals or antivirals, and are distinct from antibiotics.
The widespread introduction of antibiotics after World War II was one of the most significant therapeutic advances of the 20th century. Antibiotic treatments have increased life expectancy by more than ten years, more than any other medical treatment.[2] However, the widespread, even excessive, use of certain antibiotics, including for preventive, curative, or dietary supplement purposes in animal feed, fish farming, veterinary and human medicine, and as pesticides for plant treatment (against fire blight, for example), has introduced selective pressure that has led to the development of antibiotic-resistant microorganism populations and a general decline in therapeutic efficacy. In hospitals, this leads to an increased risk of nosocomial infections due to a lack of appropriate treatment against certain particularly resistant germs.

General Information

Definition

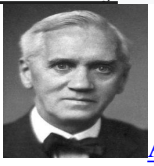
In simplified terms, an antibiotic is, in the medical field, "an organic chemical substance of natural or synthetic origin that inhibits or kills pathogenic bacteria at low concentrations and possesses selective toxicity." Selective toxicity means that it is specific to bacteria and that the antibiotic molecule does not affect the infected host, at least at the doses used for treatment.

More generally, for microbiologists and chemists, an antibiotic is an antibacterial substance.

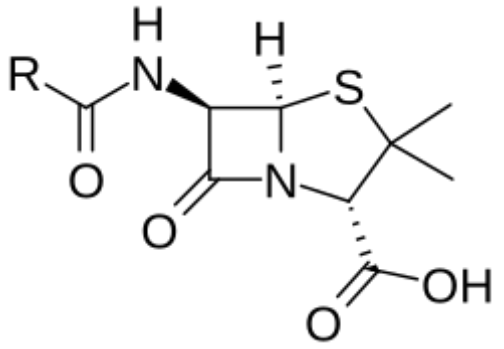
There have been variations in this definition that differ in the presence or absence of the concepts of selective toxicity, microbial origin, and limiting the target to bacteria only.

Antiseptics are not antibiotics. Their function is to kill as many germs as possible (bacteria, fungi, viruses). Their mode of action is not specific; they are used only topically in external application, and if misused (for example, if too concentrated), they can cause lesions and/or delay healing.
Antibiotics are generally not effective against viruses. A product that fights viruses is called an antiviral. However, ongoing studies tend to demonstrate some effectiveness of certain antibiotics in specific cases, such as the effect of teicoplanin on Ebola virus disease.

Discovery


Alexander Fleming, découvreur de la pénicilline en 1928.

The first antibiotic identified was penicillin. While Ernest Duchesne discovered the curative properties of Penicillium glaucum as early as the late 19th century, the discovery of penicillin is attributed to Sir Alexander Fleming, who noticed in 1928 that some of his bacterial cultures in forgotten dishes had been contaminated by the experiments of his lab neighbor studying the fungus Penicillium notatum, and that this fungus inhibited their reproduction. However, the importance of this discovery, its implications, and its medical uses were only understood and developed after its rediscovery, particularly between the two World Wars, following the work of Howard Walter Florey, Ernst Chain, and Norman Heatley in 1939.



Structure de la pénicilline.

Bactericidality and Bacteriostasis

Based on their effect on bacteria, antibiotics are divided into two categories: bactericidal antibiotics, which kill bacteria (e.g., β-lactams, aminoglycosides), and bacteriostatic antibiotics, which inhibit bacterial growth without directly killing them (e.g., macrolides, tetracyclines). In this case, bacterial elimination relies on the host's immune defenses.

Studies of antibacterial activity have distinguished time-dependent bactericidal antibiotics (β-lactams, glycopeptides) from concentration-dependent ones (aminoglycosides, fluoroquinolones). For the former, efficacy depends on the duration of exposure to a concentration higher than the minimum inhibitory concentration of the antibiotic, while for the latter, it depends on the maximum antibiotic concentration to which the bacteria are exposed. The choice between using bactericidal or bacteriostatic antibiotics depends on the clinical context: in cases of severe infections, such as endocarditis or meningitis, for example, bactericidal antibiotics are preferred.

01. Inhibition of bacterial cell wall synthesis by targeting peptidoglycan

β-Lactams

β-Lactams constitute the largest family of antibiotics, both in terms of the number of available molecules and their applications. The discovery of penicillin G, followed in 1945 by that of cephalosporins from Acremonium chrysogenum (formerly Cephalosporium acremonium), paved the way for the development of numerous other semi-synthetic or synthetic β-lactams. These antibiotics share a common structural characteristic: a β-lactam ring, a four-membered nitrogenous heterocycle, essential for their antibacterial activity. Their classification is based on the nature of the nucleus fused to the β-lactam ring:

• Penicillins (penam nucleus) include several subclasses: penicillin G, penicillin A (amoxicillin), penicillin M (oxacillin), carboxypenicillins (ticarcillin), and ureidopenicillins (piperacillin).

• Cephalosporins (cepheme nucleus) are classified from the 1st to the 5th generation and also include cephamycins (cefoxitin) and oxacephemes (moxalactam).

• Carbapenems (penem nucleus) are distinguished by the replacement of the sulfur atom with a carbon atom, giving them a very broad spectrum of activity and good stability against β-lactamases.

• Monobactams (monocyclic), with aztreonam as the sole representative, contain an unfused β-lactam ring with specific activity against Gram-negative bacilli.

• Siderophore cephalosporins (cefiderocol) are next-generation cephalosporins coupled to a siderophore, allowing them to utilize bacterial iron transport systems to enter cells. This strategy enhances their efficacy against multidrug-resistant Gram-negative bacilli, including carbapenemase-producing bacilli.

Beta-lactams have a broad spectrum of activity, varying according to subclass and generation. Overall, depending on the specific molecule, they are active against the majority of Gram-positive bacteria (streptococci, staphylococci) and many Gram-negative bacteria (Neisseria meningitidis, enterobacteria, or Pseudomonas aeruginosa). They are indicated for the majority of infections: ENT, respiratory, urinary tract, intra-abdominal, sepsis, meningitis, and endocarditis. Their good tolerability and pharmacokinetic profile make them a first-line treatment in many situations.

Glycopeptides and Lipoglycopeptides

Glycopeptides are natural antibiotics produced by actinobacteria of the genus Amycolatopsis. Second-generation lipoglycopeptides, such as dalbavancin, have semi-synthetic modifications that enhance their affinity for bacterial membranes, their bactericidal activity, and prolong their plasma half-life. Glycopeptides and lipoglycopeptides selectively inhibit peptidoglycan synthesis, leading to progressive weakening of the cell wall and bacterial lysis secondary to osmotic imbalances. Vancomycin's activity is bactericidal but slow and time-dependent, while lipoglycopeptides exhibit enhanced bactericidal activity due to their structural modifications []. Glycopeptides and lipoglycopeptides are active only against Gram-positive bacteria because of their large size and structure, which prevent them from crossing the outer membrane of Gram-negative bacteria. Their spectrum includes the majority of Gram-positive bacteria: staphylococci (particularly methicillin-resistant Staphylococcus aureus, including methicillin-resistant Staphylococcus aureus – MRSA), streptococci, and enterococci. They are administered parenterally and are indicated for severe Gram-positive infections (endocarditis, bacteremia, pneumonia, skin or bone and joint infections), particularly when β-lactams cannot be used. The use of vancomycin is also limited due to its nephrotoxicity. Lipoglycopeptides with a long half-life allow for less frequent administration, which is useful for outpatient treatment.

Fosfomycin

Fosfomycin, discovered in 1969, is a low molecular weight, water-soluble antibiotic, an analog of phosphoenolpyruvate, and is naturally produced by several species of Streptomyces[]. Fosfomycin inhibits the synthesis of peptidoglycan precursors at the first stage of this process[].

Fosfomycin is active against Gram-positive bacteria (staphylococci) and many Gram-negative bacteria (enterobacteria, Pseudomonas aeruginosa), including multidrug-resistant strains. It is primarily prescribed orally, in combination with trometamol, for the treatment of uncomplicated lower urinary tract infections in women. It can also be used parenterally for severe infections caused by multidrug-resistant bacteria, in combination with other antibiotics[]. Due to its high sodium content, parenteral administration of fosfomycin can lead to sodium overload, limiting its use in some patients[].

02. Action on the Cell Membrane

The existence of an intact plasma membrane is necessary for bacterial survival. Its role is twofold: firstly, it sequesters metabolites and ions needed within the cytoplasm; secondly, it maintains a proton gradient between the inside and outside of the cell, generated by the respiratory chain and the Krebs cycle, which allows for the storage of cellular energy. This proton gradient feeds ATP synthase, which produces ATP. Any disruption of the membrane's impermeability breaks down these barriers, chemiosmotic energy is dissipated, and the cytoplasmic contents leak into the extracellular environment. A number of antibiotic molecules act on the cell membrane, either by acting as detergents that disrupt lipids, or by creating a pore (a hole) in the membrane that allows the leakage of cellular components. As a reminder, gramicidin is a peptide that inserts itself into the membrane by forming a cylindrical pore allowing the escape of cations, but which no longer seems to be used.

Polymyxins (B, E/colistin)

Polymyxins are natural cyclic polypeptides, discovered in 1947, produced by Paenibacillus polymyxa. They are cationic molecules whose mechanism of action relies on an electrostatic interaction with the negatively charged lipopolysaccharides of the outer membrane of Gram-negative bacteria, thereby disrupting the membrane's permeability. This disruption facilitates their penetration and access to the

cytoplasmic membrane, with which they interact, causing the formation of pores. This results in the leakage of intracellular components, including ions and small molecules essential for bacterial metabolism, leading to cell death. Active only against Gram-negative bacteria, polymyxins target Enterobacteriaceae, P. aeruginosa, and Acinetobacter baumannii. Only polymyxin B and polymyxin E (or colistin) are used in clinical practice. Polymyxin B is primarily used topically (eye drops, ear drops), while colistin is administered parenterally in severe infections. Due to its nephrotoxicity and neurotoxicity, colistin is now reserved for situations where therapeutic options are limited.

Lipopeptides (daptomycin)

Daptomycin is a relatively recent antibiotic (2003) belonging to the cyclic lipopeptide family, naturally produced by Streptomyces roseosporus. Its bactericidal mechanism of action relies on a calcium-dependent interaction with the bacterial cytoplasmic membrane, resulting in a loss of the electrochemical gradient, leading to inhibition of essential cellular functions and ultimately bacterial death. Daptomycin has a spectrum of activity limited to Gram-positive bacteria. Administered parenterally, it is indicated for many severe infections, particularly those caused by methicillin-resistant Staphylococci, including methicillin-resistant Staphylococcus aureus, such as endocarditis. It frequently replaces vancomycin, which is nephrotoxic. In contrast, daptomycin, which is inactivated by pulmonary surfactant, is not used to treat pneumonia.

03. Inhibition of Nucleic Acid Synthesis

The synthesis of nucleic acids, DNA and RNA, is absolutely vital for cells; without it, cell division and protein synthesis are impossible. A number of compounds can directly or indirectly block these nucleic acid biosynthesis pathways and consequently possess antibiotic activity.

Quinolones and Fluoroquinolones

Quinolones constitute a class of synthetic antibiotics, the first compound of which, nalidixic acid, was discovered in 1962 as a byproduct of chloroquine synthesis. Active only against Gram-negative bacilli and having poor tissue penetration, its use has remained limited to urinary tract infections [].

The introduction of a fluorine atom at position 6 of the quinoline ring led to fluoroquinolones, the first of which was norfloxacin in the 1980s. This modification improved pharmacokinetic properties and broadened the antibacterial spectrum, giving rise to second-generation fluoroquinolones, such as ciprofloxacin and ofloxacin, whose good tissue penetration allowed for the expansion of indications beyond urinary tract infections. Third-generation fluoroquinolones (levofloxacin, the levorotatory enantiomer of ofloxacin), and then fourth-generation fluoroquinolones (moxifloxacin, delafloxacin) have a broader spectrum of activity against Gram-positive bacteria, Mycobacterium tuberculosis, and certain anaerobic bacteria.

Rifampicin

Rifampicin is a semi-synthetic antibiotic derived from rifamycins, natural metabolites produced by Amycolatopsis rifamycinica (formerly Streptomyces mediterranei), discovered in 1957 [].
Its mechanism of action is based on the inhibition of transcription. Rifampicin binds specifically to the β subunit of RNA polymerase at the nascent RNA exit channel. This binding forms a stable rifampicin-enzyme complex that blocks the progression of the transcriptional complex. The cessation of transcription mechanically leads to the inhibition of protein synthesis, thus giving rifampicin rapid bactericidal activity [].
The spectrum of rifampicin is primarily directed against Gram-positive bacteria, due to its limited penetration into Gram-negative bacteria. Its good tissue and intracellular distribution allows its use in deep infections, particularly osteoarticular infections, as well as against intracellular pathogens such as Brucella and Legionella. Highly active against Mycobacterium tuberculosis, it is a cornerstone of antituberculosis treatment. Administered orally or parenterally, it must always be used in combination therapy due to the high risk of resistance selection in monotherapy.

Imidazoles

Metronidazole, an antibiotic in the imidazole family, is a synthetic molecule derived from 2-nitroimidazole (or azomycin), initially isolated from Streptomyces eurocidicus. It is a prodrug that

requires enzymatic action to exert its bactericidal activity. This action occurs under strictly anaerobic conditions. It generates unstable cytotoxic derivatives, which cause DNA breaks, a mechanism considered to be the main effect of metronidazole. Metronidazole has a targeted antibacterial spectrum, active against strict anaerobic bacteria, including the genera Bacteroides and Clostridium, as well as certain microaerophilic bacteria such as Helicobacter pylori. It is a first-line treatment for anaerobic bacterial infections.

4. Inhibition of Protein Synthesis

Protein synthesis is an essential process in living cells. The central player in this process, in which messenger RNA is translated into protein, is the ribosome, the cellular organelle responsible for this step. The details of the translation mechanism and the ribosomes of bacteria are significantly different from those of eukaryotes. A large number of antibiotic molecules exploit these differences and are capable of selectively blocking protein translation in bacteria, but not in humans or animals.

In fact, approximately half of the antibiotics used therapeutically (with marketing authorization) target the bacterial ribosome. These antibiotics are divided into several classes, differing in chemical nature and mode of action. Most interact with ribosomal RNA. Finally, some antibiotics block translation by inhibiting the action of translation factors associated with the ribosome.

Aminoglycosides

Streptomycin, the first member of this family, was isolated in 1944 from Streptomyces griseus. The main molecules used clinically include gentamicin, tobramycin, amikacin, netilmicin, and, more recently, plazomycin. These compounds differ in their spectrum of activity, pharmacokinetic properties, and sensitivity to inactivating enzymes.

Aminoglycosides exert their activity by binding to the 16S rRNA of the 30S subunit of the bacterial ribosome, prematurely interrupting translation and inhibiting overall protein synthesis.

Tetracyclines

Tetracyclines, whose parent molecule is tetracycline, was isolated in 1940 from Streptomyces aureofaciens. Semi-synthetic modifications were subsequently made to broaden their spectrum and improve their pharmacokinetic properties. Among the main molecules are doxycycline, minocycline, and more recently, tigecycline (glycylcycline) and eravacycline (fluorocycline).

Macrolides, Lincosamides, and Streptogramins

Macrolides, lincosamides, and streptogramins are grouped by a common mechanism of action, targeting the 50S subunit of the bacterial ribosome. Erythromycin, a historic molecule discovered in 1952 and initially isolated from Streptomyces erythraeus, was followed by more stable semi-synthetic derivatives, such as clarithromycin, azithromycin, and josamycin.

Lincosamides, of which clindamycin is the main representative, are derived from lincomycin, produced by Streptomyces lincolnensis.

Oxazolidinones

The oxazolidinones, the leading example of which is linezolid, constitute the latest class of fully synthetic antibiotics, discovered in the late 1970s but commercialized in 2000. More recently, tedizolid has been developed with reduced toxicity.

Oxazolidinones inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit at an early stage of translation, interrupting messenger RNA reading and protein synthesis [].

Phenicols

Chloramphenicol and thiamphenicol, antibiotics in the phenicol family, inhibit protein synthesis by binding to the 50S ribosomal subunit at the peptidyltransferase site. Despite their broad spectrum, they are rarely used due to their toxicity and are reserved for certain infections, such as meningitis in resource-limited settings [41].

Fusidic acid

Fusidic acid, a steroid antibiotic derived from Fusidium coccineum, acts by binding to elongation factor G and blocking ribosome translocation. Primarily active against staphylococci, it is used for the topical or systemic treatment of skin infections. However, it should not be used as monotherapy for systemic infections due to the high risk of resistance development.

5. Disruption of Bacterial Metabolism

Another important class of antibiotics interferes with the production of essential metabolites, blocking the synthesis of various essential cell components: lipids, amino acids, and nucleotides.
One particularly important pathway that is frequently targeted is that of folate (vitamin B9) synthesis. Its derivatives, notably dihydrofolate and tetrahydrofolate, are involved in group transfer reactions to a single carbon atom (methyl, formyl) and, in particular, in methylation reactions. These reactions are essential for the synthesis of thymine and, consequently, DNA. These folate-dependent carbon transfers also play a central role in the metabolism of certain amino acids: methionine, glycine, and serine, and therefore indirectly in protein synthesis.

Therapeutics

Of the thousands of known antibiotics, only slightly more than a hundred are effective and usable for medical applications and are therefore part of the modern pharmacopoeia. The others are too toxic, too unstable, or have insufficient bioavailability in humans. The antibiotics currently in use are most often molecules derived from natural products, whose structure has been slightly modified to improve their therapeutic properties or circumvent resistance problems. Others are no longer used because pathogenic bacteria have become resistant to them; this is the case, for example, with streptomycin, which was once used to treat tuberculosis.
Nearly half of the antibiotics used therapeutically target the bacterial ribosome, and about a quarter of them are beta-lactams, which target bacterial cell wall synthesis. Looking at prescriptions, we see that beta-lactams (penicillins and cephalosporins) are the most frequently used antibiotics, particularly by general practitioners. In France, they represent almost two-thirds of the defined daily doses used, ahead of macrolides (~15%)].

Activity Parameters

Analysis of the activity of a given antibiotic on a bacterium has led to the definition of several qualitative and quantitative parameters. The first of these is the spectrum of activity, which defines the list of bacterial species against which an antibiotic is effective. The spectrum is specific to each antibiotic and can change over time due to the emergence of new resistances in different bacterial species. The other major concept in antibiotic therapy is that of the minimum inhibitory concentration, or MIC. In practice, the MIC is defined as the minimum concentration of antibiotic required to completely inhibit (bacteriostasis) bacterial growth after 18 to 24 hours of exposure at 37°C. This can be further broken down into several variations:

Side Effects

Several mechanisms can explain the adverse effects associated with taking antibiotics, including:
• Immunotoxicity: the drug then acts as a sensitizing agent. The main classes of antibiotics involved are beta-lactams and sulfonamides. According to the Gell and Coombs classification, reactions are categorized as follows:
• Type 1 reactions causing anaphylactic phenomena (asthma, anaphylactic shock). Penicillins can induce anaphylactic reactions with a prevalence of 0.01% [ref. 1968, but widely cited in the literature]
• Type 2 reactions (cytopenia, hemolytic anemia, etc.),
• Type 3 reactions (immuno-allergic vasculitis, etc.),
• Type 4 reactions (delayed hypersensitivity).

• Anaphylactoid reactions: Too rapid an infusion of vancomycin can lead to Red Man Syndrome, linked to a histamine release phenomenon.
• Metabolic disorders:
• Fusidic acid or rifampicin can cause hyperbilirubinemia.
• Amphotericin B increases the risk of hypokalemia.

• Drug interactions (enzyme induction and inhibition):
• Some antibiotics are enzyme inhibitors. This is the case for macrolides, certain tetracyclines such as doxycycline, metronidazole, and certain azole antifungals (fluconazole, itraconazole, ketoconazole, miconazole). They can then lead to an overdose of vitamin K antagonists (VKAs), theophylline, ergot derivatives (ergotism, necrosis of the extremities), and an increased risk of hypoglycemia (with azoles).

• Some antibiotics are enzyme inducers. This is the case for rifampicin and rifabutin. They can then decrease the levels of estrogen-progestin contraceptives and increase the hepatotoxicity of isoniazid.
• Phototoxicity of fluoroquinolones, tetracyclines, or voriconazole.

Antibiotic resistance

When a bacterial population is exposed to an antibiotic in its environment, it undergoes selective pressure, favoring cells best able to resist the effects of these molecules. Gradually, the emergence of genetic modifications allowing for a higher level of resistance is thus selected. The action of antibiotics on bacteria induces an accelerated Darwinian evolutionary process that can be observed on a human timescale. The first antibiotics were introduced in the late 1930s; and today, resistance to these first-generation compounds—penicillin and streptomycin—has become so widespread among bacteria that their use for therapeutic purposes has ceased. The following table shows the dates of introduction of the major families of antibiotics into the therapeutic arsenal and the dates of appearance of the first resistances on clinical strains[].

Antibiotique	Année d'introduction	Apparition des premières résistances
Sulfamides	1936	1940
Pénicilline G	1943	1946
Streptomycine	1943	1959
Chloramphénicol	1947	1959
Tétracycline	1948	1953
Erythromycine	1952	1952
Ampicilline	1961	1973
Ciprofloxacine[80]	1987	2006