# Macrolides

Macrolides are bacteriostatic antibiotics, which also have a bactericidal effect on some strains. It is a medium-spectrum antibiotic.

## Structure and mechanism of action

The structure is based on a macrocyclic lactone ring. Macrolides are basic substances, but their basicity is not strong enough to limit their absorption from the GIT. They are mostly used in the form of salts.

The mechanism of action is inhibition of proteosynthesis by reversible binding to the 50S subunit of the ribosome.

Because the chemical structure and mechanism of action are different from beta-lactams, macrolides can be used as an alternative antibiotic for hypersensitivity or resistance.

## Antimicrobial spectrum

Macrolides are particularly effective against G + bacteria (similar to penicillins).

It also acts on G− microorganisms (Corynebacterium diphtheriae, Bordetella pertussis, Campylobacter jejuni, Helicobacter pylori, Haemophilus influenzae, Neisseria catarrhalis) and anaerobic pathogens in addition to Bacteroides fragilis.

Furthermore, spirochetes (Borrelia burgdorferi, Leptospira, Treponema pallidum) and intracellular parasites (Mycoplasma, Legionella pneumophila, Chlamydia pneumoniae, Chlamydia trachomatis, Toxoplasma gondii).

## Pharmacokinetics and pharmacodynamics

They are rapidly absorbed from the digestive tract, and absorption is reduced by food. They penetrate well into tissues and body fluids. They do not cross the blood-brain barrier. They also penetrate well into the intracellular environment, where they concentrate. The effectiveness of macrolides can then be evaluated according to the ratio of intracellular and extracellular concentration. In smokers, there is a higher accumulation of macrolides inside the cells due to the increased activation of lysosomes. They penetrate the placenta and the fetus.

They are eliminated in the bile and, to a lesser extent, in the urine. Monitoring of macrolides in the blood or possible dose reduction is only necessary for very severe renal impairment. Macrolides should not be used in patients with hepatic impairment.

The effectiveness of macrolides correlates with the value of the area under the curve over time (0-24 hours) and the minimum inhibitory concentration (AUC / MIC). Lower values may cause the antibiotic to be less effective and thus increase the risk of developing resistance. The efficiency decreases with decreasing pH.

## Resistance

Resistance is cross-linked between macrolides and may be caused by:

- methylation of rRNA, thereby reducing the affinity of macrolides for the 50S subunit of the ribosome;
- efflux (active transport from the cell);
- enzyme.

## Side effects and interactions

Some macrolides (eg erythromycin) increase intestinal motility, which manifests itself in GIT problems - diarrhea, anorexia, nausea and vomiting. In addition, acute cholestatic hepatitis may occur, manifested primarily by fever, jaundice and hepatic impairment. We classify this reaction as hypersensitive. Macrolides can affect the repolarization phase of the heart, which results in a prolongation of the QT interval. This leads to ventricular tachyarrhythmias such as torsades de pointes, up to cardiac arrest. Patients with cerebrovascular or coronary disorders, or patients on potassium channel blocker therapy (amiodarone) are particularly at risk.

The most common interaction is irreversible inhibition of cytochrome P450. A significant decrease in the function of this enzyme occurs when it interacts with theophylline. Other drugs that interact with CP450 are antivirals (protease inhibitors - saquinavir, indinavir, ritonavir and non-nucleoside reverse transcriptase inhibitors - zidovudine), and immunosuppressants (cyclosporine, tacrolimus), which leads to increased plasma concentrations of macrolides (e.g. Digoxin, some antihistamines (terfenadine, astemizole, loratadine), statins, fibrates and dihydropyridines may potentiate QT prolongation. Antiepileptics such as carbamazepine may significantly reduce clearance and thus increase the plasma concentration of macrolides in the body. Prothrombin time should be monitored when interacting with warfarin.

## Indication

The effect of macrolides is slow, so they are not indicated in the treatment of life-threatening and serious infections. They are used for less serious infections, especially where beta-lactam antibiotics cannot be used. Another indication is suspected mycoplasma, legionella, chlamydial infections and infections caused by other

atypical microorganisms. They are also used in ENT infections, skin and soft tissue infections, in the treatment of Lyme disease.

Clarithromycin is used as part of Helicobacter pylori eradication with amoxicillin or metronidazole and a proton pump inhibitor. We also use them for protozoal infections such as toxoplasmosis, lambliosis, intestinal amebiasis and cryptosporidiosis. The new macrolides can be used in the treatment of tuberculosis. Topical application of erythromycin is used in the treatment of acne vulgaris.

## Macrolides with a 14-membered lactone ring

The classic representatives include erythromycin. State Office for Drug Control: erythromycin is currently only available in topical form for the treatment of acne vulgaris. A major complication is the growing resistance to this antibiotic. Another representative is, for example, roxithromycin. Tissue concentration exceeds plasma concentration. It can be used during pregnancy and in children. Clarithromycin National Office for Drug Control: Clarithromycin is well absorbed from the gastrointestinal tract and is rapidly metabolised. It is used to treat Mycobacterium leprae infection and in combination to treat Helicobacter pylori. Not suitable for pregnancy.

## Ketolides

Semisynthetic antibiotics derived from a 14-membered lactone ring. The representative is telithromycin. State Office for Drug Control: telithromycin. It is given orally, absorbed quickly and almost without residue, absorption is not affected by food. It penetrates well into tissues, even alveolar macrophages.

## Macrolides with a 15-membered lactone ring

## Azalides

The representative is azithromycin. State Office for Drug Control: azithromycin. It acts on the same microbial spectrum as erythromycin. It is more effective against Haemophilus influenzae, Neisseria gonorrhoeae, Campylobacter and atypical mycobacteria. Due to its specific pharmacokinetics, it is often referred to as an intelligent antibiotic. Its serum concentration is very low, while in the area of inflammation and tissues the level is high, it is concentrated in phagocytic cells and lysosomes. In addition, it has an extremely long half-life ($T_{½}$ = 2-4 days) [1], which allows to shorten its administration time. Another advantage is that it does not have the same risks as erythromycin. It is more stable against acidic pH, it is not dependent on food intake. It is excreted by the kidneys, so when the kidneys have reduced function, it accumulates in the body.

## Macrolides with a 16-membered lactone ring

The most common representatives include spiramycin. State Office for Drug Control: spiramycin, which is the drug of choice for the treatment or prophylaxis of primary toxoplasmosis in pregnancy and congenital toxoplasmosis in the newborn. It is used in combination with pyrimethamine and sulfadiazine. In the first trimester, we use only separate spiramycin. It can also be used to treat asthmatics treated with theophylline

## Links

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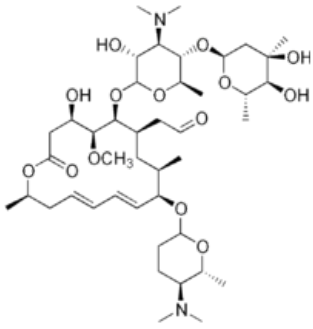

Spiramycine

## Source

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## References


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