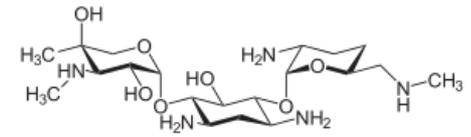


# Aminoglycosides

Aminoglycosides are **bactericidal antibiotics**, mainly used in hospitals.

## Mechanism of action

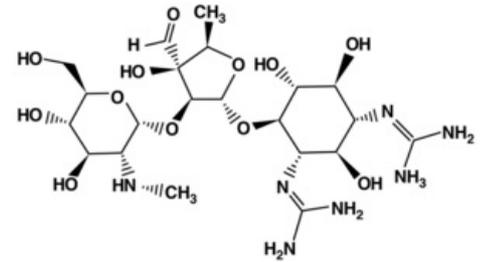
They inhibit protein synthesis by irreversible binding to the 30S subunit of the ribosome.



Structure of gentamicin

## Antimicrobial spectrum

Aminoglycosides are **mainly effective against infections caused by Gram-negatives** (*Escherichia*, *Klebsiella*, *Enterobacter*, *Serratia*, *Citrobacter*, *Pseudomonas*, *Acinetobacter*, *Salmonella*, *Shigella*) and Gram-positives (*Staphylococcus aureus*, including  $\beta$ -lactamase-producing strains, *Staphylococcus epidermidis*). Less sensitive to resistant are *streptococci* and *enterococci*. Anaerobes are naturally resistant.



Structure of streptomycin

## Pharmacokinetics

Aminoglycosides are not absorbed per os and act locally in the GIT. They are used **parenterally (mostly i.v.)**. They are also well absorbed after **i.m. administration**. They penetrate **poorly into body fluids and tissues**. They are **not metabolised and are excreted by glomerular filtration**. Elimination is markedly reduced in renal impairment (in patients with renal insufficiency and failure; in children in the first week of life, especially premature infants due to renal immaturity; in old age when glomerular filtration decreases due to reduced renal blood flow). In these cases, aminoglycosides may accumulate and cause toxic damage. In the renal tubules, they enter cells by active transport and penetrate into lysosomes, where they cause intracellular shedding of autolytic lysosomal enzymes and subsequent cell autolysis and necrosis.

## Pharmacodynamics

**The effect of aminoglycosides is dependent on plasma concentration.** They are hydrophilic, so they do not penetrate biological membranes easily. They are subject to active O<sub>2</sub>-dependent transport across the inner part of the membrane (therefore they do not act on anaerobes). They induce a rapid killing phase (6 h), followed by a bacteriostasis phase (even when antibiotic concentrations are low), when bacterial regrowth does not occur. This phase is also called the "**post-antibiotic effect**" (**PAE**). Its magnitude is determined by the size of the c<sub>max</sub>, and the type of bacteria. It is amplified by the presence of leukocytes. Combination with  $\beta$ -lactams facilitates penetration by passive diffusion.

## Side effects and toxicity

Aminoglycosides are potentially **ototoxic**. Ototoxicity may be acute (after high dose) from reversible blockade of calcium current in hair cells, which can be corrected by calcium administration because of the competitive antagonism between the antibiotic and calcium. Chronic ototoxicity is attributed to the time of exposure (AUC) and is up to 50% irreversible, unpredictable, sudden and intense after **5-7 days** of treatment. Adverse effects include neurotoxicity. Aminoglycosides are also nephrotoxic due to their effect on the renal tubules. The damage tends to be reversible. It is important to note that they are one of the few antibiotics whose effect and toxicity correlate closely with plasma concentrations (better than dose). Yet the difference between the concentrations underlying antibiotic and toxic effects is small (they have a narrow therapeutic window). Therapeutic drug monitoring (TDM) is performed.

## Benefits of aminoglycosides

- **Bactericidal**
- **postantibiotic effect**
- **low price**

## Indications

Treatment with aminoglycoside antibiotics is indicated for more **serious infections: septic conditions, CNS infections, respiratory tract infections (pneumonia), intra-abdominal and hepatobiliary infections, endocarditis, complicated urinary tract infections** with sensitive agents included in the antibiotic spectrum. In monotherapy they are used only in urinary tract infections, otherwise in combination mostly with  $\beta$ -lactams. In *enterococcal* endocarditis in combination with ampicillin.

# Representatives of antibiotics

- basic aminoglycosides of older type (with defined indication): **streptomycin, neomycin, kanamycin**
- highly effective newer ones with lower toxicity: **gentamicin, tobramycin, amikacin, netilmicin**

## Streptomycin

It is the drug of choice for **brucellosis, tularemia, nodular fever**, used as an **antituberculosis**. In combination with penicillin, it is used to treat endocarditis caused by viridial *streptococci* or *enterococci*.

## Gentamicin

The basic broad-spectrum antibiotic of this group. It should not be given to pregnant women, newborns and premature infants. Adverse effects include nephrotoxicity (albuminuria, proteinuria), ototoxicity (dizziness, vertigo), curareform effects (neostigmine is an antagonist), skin manifestations, increased liver tests, changes in blood pressure and others.

## Amikacin

It is used to treat infections that are caused by gentamicin-resistant microbes.

## Links

### Related articles

- Antibiotics

### Sources

- MARTÍNKOVÁ, J., S. MIČUDA a J. CERMANOVÁ. *Antibiotika* [online]. [cit. 2010-07-25]. <<https://www.lfhk.cuni.cz/farmakol/predn/bak/kapitoly/atb-bak.doc/>>.
- LINCOVÁ, Dagmar a Hassan FARGHALI, et al. *Základní a aplikovaná farmakologie*. 2. vydání. Praha : Galén, 2007. ISBN 978-80-7262-373-0.

## Antibiotics and chemotherapeutics

<b>baktericidal</b>	<b>aminoglycosides</b>	amikacin, gentamycin, isepamycin, neomycin, netilmicin, spectinomycin, streptomycin, tobramycin		
	<b>antituberkulotics</b>	izoniazid, cykloserin, ethambutol, ethionamid, kapreomycin, pyrazinamid, viomycin		
	<b>beta-lactam</b>	cephalosporins	I.generation	cafazolin, cefadroxil, cefalexin, cefalotin, cefapirin
			II.generation	cefuroxim, cefamandol, cefpodoxim, proxetil, cefprozil monohydrate, cefuroxim-axetil
			III.generation	cefotaxim, cefetamet pivoxil, cefixim, cefoperazon, cefsulodin, ceftazidim, ceftibuten, ceftriaxon, co-cefoperazon
			IV.generation	cefepim, cefpirom
			V.generation	ceftarolin
		carbapenems	imipenem, doripenem, ertapenem, merapenem	
		monobaktams	aztreonam	
		penicillins	narrow-spectrum penicillins	penicillin G, penicillin V, cloxacilin, dicloxacilin, oxacilin, flucloxacilin
	broad-spectrum penicillins		amoxicilin, ampicilin, ticarcilin, piperacilin	
	beta-lactam inhibitors		co-amoxicilin, co-ticarcilin, sulbaktam, tazobaktam	
	<b>glycopeptides</b>	teikoplanin, vankomycin		
	<b>quinolones</b>	I.generation	nalidixic acid, oxolinic acid	
		II.generation	ciprofloxacin, norfloxacin, pipemidic acid, rosoxacin	
III.generation		sparfloxacin, enoxacin, fleroxacin, lomefloxacin, ofloxacin, pefloxacin		
IV.generation		moxifloxacin		
<b>nitroimidazoles</b>	metronidazol, ornidazol			
<b>nitrofurans</b>	furazolidon, nifuratel, nifuroxazid, nitrofurantoin,			
<b>polypeptide antibiotics</b>	bacitracin, colistin, gramicidin, polymyxin B			
<b>rifamycins</b>	rifampicin, rifabutin, rifaximin, rifamycin			
<b>bakteriostatic</b>	<b>amphenicol</b>	azidamfenikol, chloramfenikol, florfenikol, thiamfenikol		
	<b>glycylcyclines</b>	tigecyclin		
	<b>lincosamides</b>	klindamycin, linkomycin		
	<b>macrolides</b>	I.generation	erytromycin, josamycin, oleandomycin, spiramycin	
		II.generation	azithromycin, clarithromycin, roxithromycin	
	<b>oxazolidinones</b>	linezolid		
	<b>pyrimidines</b>	co-trimoxazol, pyrimetamin, trimetoprim		
	<b>streptogramins</b>	streptogramin A, B		
	<b>sulphonamides</b>	sulfamothoxazol, sulfasalazin, sulfathiazol, sulfisoxazol		
	<b>sulfones</b>	dapson		
<b>tetracyclines</b>	doxycyklin			