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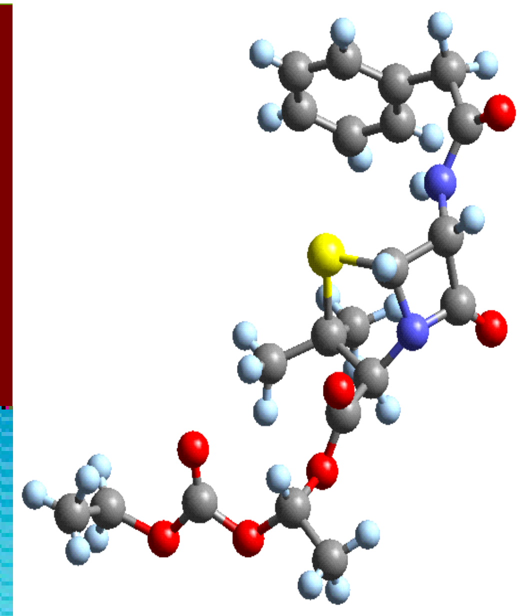

Antibiotics

Cursuri Romeo T. Cristina ®

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Antimicrobial therapy

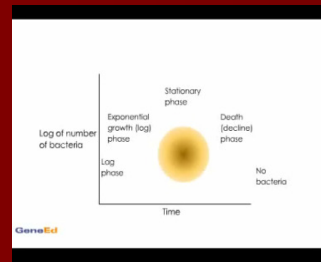
Principles

The aim of an efficient therapy is, first of all, to obtain efficient drug concentration levels at the infection place, while avoiding toxic concentrations from plasma and organs.

Any therapeutic decision should be made taking into account the "the therapeutic triangle":

- ► drug
- ► pathogen agent
- ► patient

Antibiotics



- Are biologically active metabolites produced by microscopic germs, as a means to fight with their competitors (bacteria, in general, but not only them).
- The antimicrobial term : any natural compound, synthetic or semi-synthetic that can stop microbial and fungal growth.
- The first step when initiating a therapy is to choose the best antibiotic that is suitable to heal the animal.

History

- *The bacterial antagonism* was noticed by Pasteur, who observed that the growth of a culture of *Bacillus anthracis* is stopped in the presence of Bacillus piocianic (pseudomonas).
- In 1885, Victor Babeş, studied the bacterial antagonism and proposed the term *antibiosis* in therapy.
- The „antibiotic” term was introduced by Vuiellamin.

- The first antibiotic discovered: penicillin (Fleming 1921)
- In therapy, after 1941, Chaine and Florey isolated the pure form (crystallized G penicillin)
- 1944 appeared streptomycin, discovered by Waksmann.
- chloramphenicol in 1947,
- chlortetracycline in 1948,
- semi-synthetic penicillins in1958,
- cephalosporin in 1960,
- fluoroquinolones in 1980

According to the action spectrum, antibiotics can be:

- antimicrobial,
- antifungal,
- antiprotozoal,
- antiviral and
- antitumoral.

http://www.thingsyoungerthanmccain.com/penicillin

Studying antibiotic efficiency

The most important tests are:

a. The biological assays:

- Allows= precise and sensitive determination of antibiotics
- Diffusion method= an usual technique for β-lactams
- Detectable limits= order ng./ml. (10-9g/ml).
- Agar plates seeded with a selected bacterial strain over which are placed various dilutions of the test antibiotic.
- The plates at 37°C, after reading is done, based on the area of lysis caused by the test antibiotic, often relative to a standard antibiotics.

b. Physico-chemical assays

- The usual methods for testing antibiotics are: spectrophotometry, fluorometry and, recently, high-performance liquid chromatography (HPLC).
- These assays = less sensitive, compared to the biological tests = are dependent on the methods of preparation and purification of samples.
- Of these HPLC = the most versatile and has perspectives of usage.

c. *In vitro* tests

- It is desirable to determine the susceptibility of a strain isolated from diseased animals in oder to select the correct therapeutic demeanor.

Disc method (DM)

- Rather qualitative test = is based on the application of antibiotic impregnated paper discs placed on inoculated Petri plates.
- The disadvantage = the need to isolate pure cultures for tests = the postponement with 24-36 h. of the results.
- Under field conditions , time = too long, so, it is takes to much time when dealing with an animal in need of an optimal treatment.
- Resolving (commonly chosen by practitioners) = starting broad-spectrum antibiotic treatment, without waiting for the results.

Minimum Inhibitory Concentration (MIC)

- Gives quantitative measure of a bacterial population to an antibiotic.
- Considered the most common standard method of analysis of the effectiveness of an antibiotic.
- MIC = by increasing the concentration of microorganisms in successive concentrations of antibiotic.
- The lowest concentration that will stop the growth of bacteria will be considered MIC.
- The figure obtained will not be considered absolute because it is affected by many variables (e.g. the number of organisms inoculated at the beginning of the test (which should be approximately 105 bacteria/ml).

Minimum Bactericidal Concentration (MBC)

- Used in high concentrations,that will then be added to a new range of antibiotics.
- After incubation, the tubes are reseeded in adequate medium and compared with a subculture of control tubes before incubation, obtaining three variants:
- similar growth with control tubes= bacteriostatic action
- disparate growth = incomplete bactericidal action
- sterile medium (no growth) = bactericidal action,

lowest concentration that will give this result will be considered MBC for the studied antibiotic, for a specific bacterial populations.

Minimum antibiotic concentration (MAC)

- *In vivo* antibiotics =therapeutic activity with lower concentration than MIC, therefore, interpretations like serum concentrations, cannot be taken *ad literam* to express an antibiotics effieciency.
- MAC = the concentration of the antibiotic that will reduce the growth of an organism in vitro by a factor of 10 (i.e. 1 log.).
- The MAC value should be = a quarter or one-tenth of the value of MIC, depending on the antibiotic and the organism.
- The existence of beneficial effects at low concentrations explains why relatively low doses, subtherapeutical, can be unexpectedly clinically effective.

Antibiotic

classification according to action groups

Courses Prof. Romeo T. Cristina

β-Lactams

–extraction, semisynthetics and cephalosporin penicillin

Aminoglycosides

rings- top: streptomycin

Macrolides

- top: erythromycin

Cyclic polypeptides

- top: B polymyxin

Tetracycline

- top: tetracycline

Chloramphenicol

- top: chloramphenicol

Sinergistine

Various antibiotics

- Antibiotics that cannot be assigned to structural and chemical standpoint.

β -Lactams

- *narrow spectrum:* G+ cocci, bacilli and G+ G- cocci.
- *not active against the G- bacteria.*
- actions: on actinomycetes and spirochetes.
- semi synthetic penicillins (ampicillin, amoxicillin) can act also on G-bacteria.

Aminoglycosides

- *compensatory spectrum towards β-lactams,*
- active also on G- and G+ bacteria,
- for this reason are associated with β -lactams.
- more active on the acid-alcohol-resistant bacillus (bacilul Koch).

Macrolides

- active on: G+ cocci and bacilli
- less active over: G- cocci and G- bacteria
- furthermore: actinomyces, mycoplasma, protozoa, spirochetes.

Sinergistine

- over G+ and G- cocci, G+ bacilli
- *are not active* over G- bacilli
- acts on actinomycetes, mycoplasma and some protozoa.

Cyclic polypeptides

- some of them: polymyxin B, colistin = good activity on Gram-bacteria and actinomycetes.
- others : bacitracin, tyrothricin on G+ bacteria.

Tetracyclines

- *wide spectrum:* active over G+ şi G- cocci, rickettsiae, spirochetes, mycoplasmas, actinomycetes and some protozoa.
- acts: on large viruses

An antibiotic's course of action

- *germistatic*
- *germicide*
- *bacteriolytic*

The action depends on the antibiotic concentration

Classification of the substances with antibiotic activity that are mainly used in VM

Bactericidal	Bacteriostatic
Penicillin	Tetracycline
Cephalosporin	Erythromycin
Aminoglycosides	Sulfonamides
Rifampicin	Novobiocine
Quinolones	Chloramphenicol

Presentation of bacterial genera and their appurtenances (after Brander, 1991)

Genus	Coloration	Species	Disease caused
Actinobacillus	Gram Positive	*Lignieresi*	Actinobacillosis
Actinomyces		*Bovis*	Actinomicosis
Bacillus		*Anthracis*	Antrax
Clostridium		*Tetani*	Tetanus
Corynebacterium		*Pyogenes*	Abscesses, mastitis
Erysipelotrix		*Rhusiopathiae*	Erysipelas (pigs)
Listeria		*Monocytogenes*	Listeriosis (sheep)
Micobacterium		*Tuberculosis*	Tuberculosis
Peptostreptococcus		*Indolicus*	Abscesses, mastitis
Staphylococcus		*Aureus*	Abscesses, mastitis
Steptococus		*Uberis*	Mastitis
Bacterioides	Gram Negative	*Fragilis*	Anaerobic abscesses
Bordetella		*Bronchiseptica*	Kennel cough
Brucella		*Abortus*	Brucellosis
Campilobacter		*Jejuni*	Diarrhea (canine)
Escheria		*Coli*	Diarrhea
Fusibacterium		*Necrophorus*	Diarrhea (canine)
Haemophilus		*Suis*	Arthritis, meningitis
Klebsiella		*Aerogenes*	Mastitis
Moraxella		*Bovis*	Hemorrhagic ophthalmia
Pasteurella		*Haemolytica*	Shipping fever
Proteus		*Mirabilis*	Diarrhea
Pseudomonas		*Aerugenosa*	Otits
Rickettsia		*Bovina*	Tick fever
Salmonella		*Typhimurium*	Salmonellosis
Treponema		*Hyodisenteriae*	Dysentery (pigs)

Kinetics of common antibiotics in veterinary medicine
(after Brander, 1991)

Antibiotic	Acid/ Base	% Plasma coupling	Half-life	% Unmodified excretion	Administration path
Penicillins					
Ampicillin	A+B	25	1 – 1,5	90	p.o., i.m., i.v.
Amoxicillin	A+B	18	1,5	90	p.o., i.m., i.v.
Benzyl penicillin	ACID	50	0,5 – 1	60 – 90	i.m., i.v.
Carbenicillin	ACID	47	1 – 2	90	i.m., i.v.
Cloxacillin	ACID	95	0,5 – 1	30 – 40	p.o., i.m., i.v.
Cephalosporin					
Cephalodin	ACID	56	0,5 – 1	60 – 90	i.m., i.v.
Cephaloridine	ACID	5	1 – 2	70	i.m., i.v.
Rifampicin	ACID	85	2 – 3	15	p.o.
Macrolides					
Erythromycin	BASE	20	1,5	15	p.o., i.m.
Lincosamides	BASE	90	5	15	p.o., i.m.
Tetracyclines					
Tetracycline	BASE	50	10	60	p.o., i.m.
Oxytetracycline	BASE	30	10	70	p.o., i.m.
Aminoglycosides					
Gentamicin	BASE	25	2,5	90	i.m., i.v.
Streptomycin	BASE	30	2,4	80	p.o., i.m., i.v.

Classification
According to the antibacterial activity

Type of antibacterial activity	Substance
I. Inhibition of cell wall synthesis	Penicillins, Cephalosporins, Vancomycin, Bacitracin
II. Damage of the bacterial membrane permeability	Polymyxin, Colistin, Nystatin, B Amphotericin
III. Inhibition of protein synthesis	Chloramphenicol, Tetracycline, Aminoglycosides, Lincomycin, Erythromycin
IV. Inhibition of nucleic acid synthesis	Quinolones, Sulfonamides, Rifampicin Trimethoprim

The provisions relating to antibiotics of each country requires judicious choice of antibiotic associations, in the light of the new provisions relating to residues, the concept of *polyfarmacy* in the case of antibiotics, is a difficult issue.

The effective antibiotic combination must follow the following rules:

Bactericidal + Bactericidal = Synergy

(eg. carbenicillin + gentamicin, penicillin + streptomycin)

Bacteriostatic + Bacteriostatic = additive effects

(eg. erythromycin + tetracycline)

Bacteriostatic + Bactericide = Antagonism = *Does not apply!*

β-Lactams

- considerate *bactericidal,*
- activity: in the logarithmic phase of multiplication
- bacteriostatic: in low concentrations or
- bacteriolytic: in high concentrations.

Aminoglycosides

- *bactericidal* antibiotics,
- this is why they are not associated β-Lactams

Tetracycline and Chloramphenicol

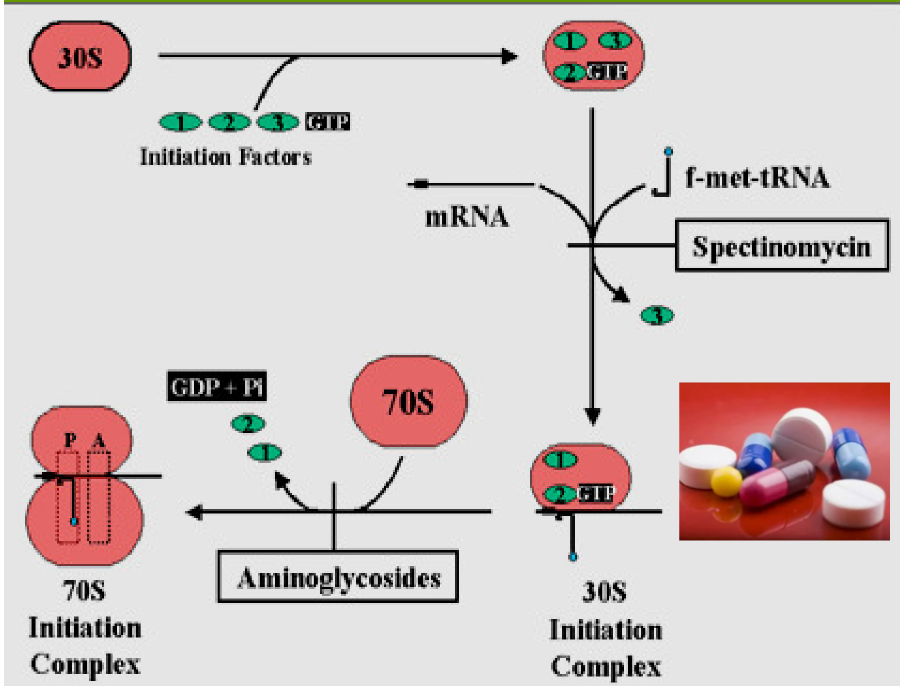
- *bacteriostatic* antibiotics,
- *it is not allowed their association with bactericidal antibiotics!*

In some antibiotics (spiramycin and pristinamycin)

- *The bacterial pause phenomenon* has been described

Types of action:

- Level = bacterial wall
- Level = cell membrane
- On = protein synthesis,
- Interferes = nucleic acid metabolism



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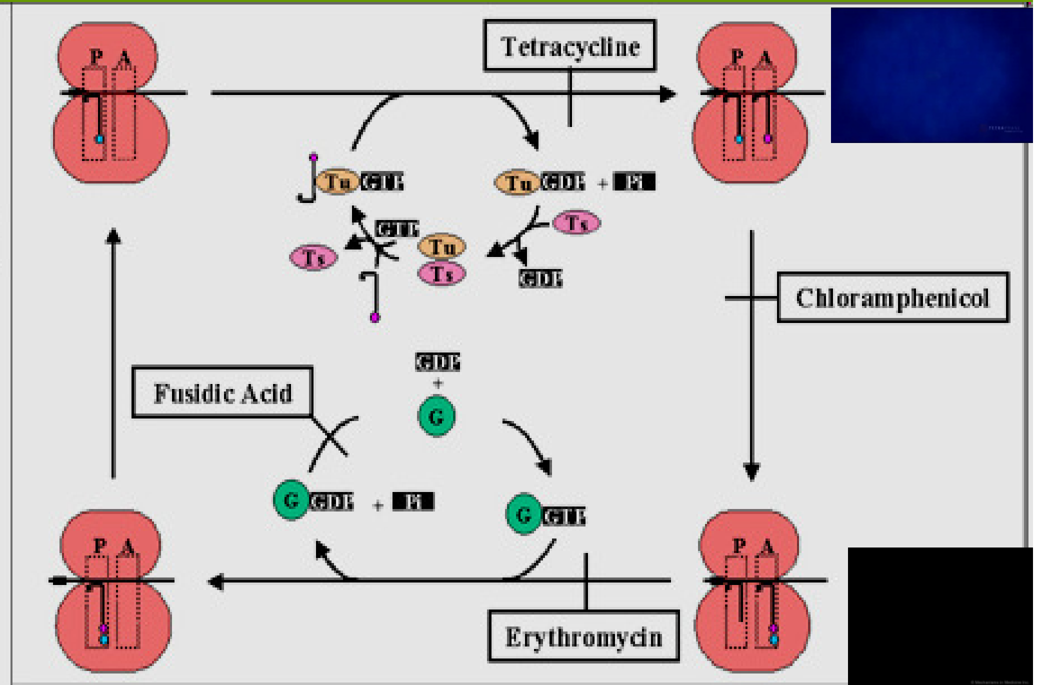

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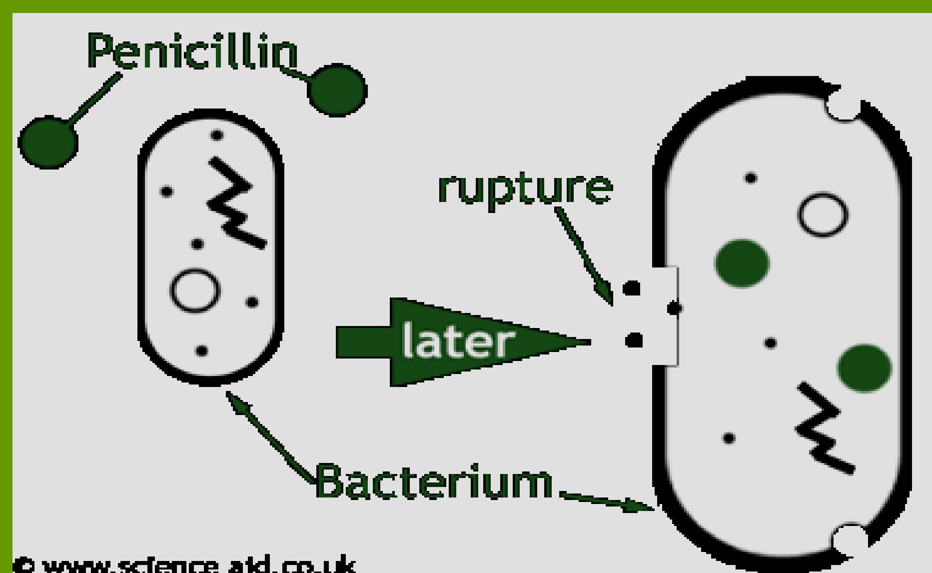

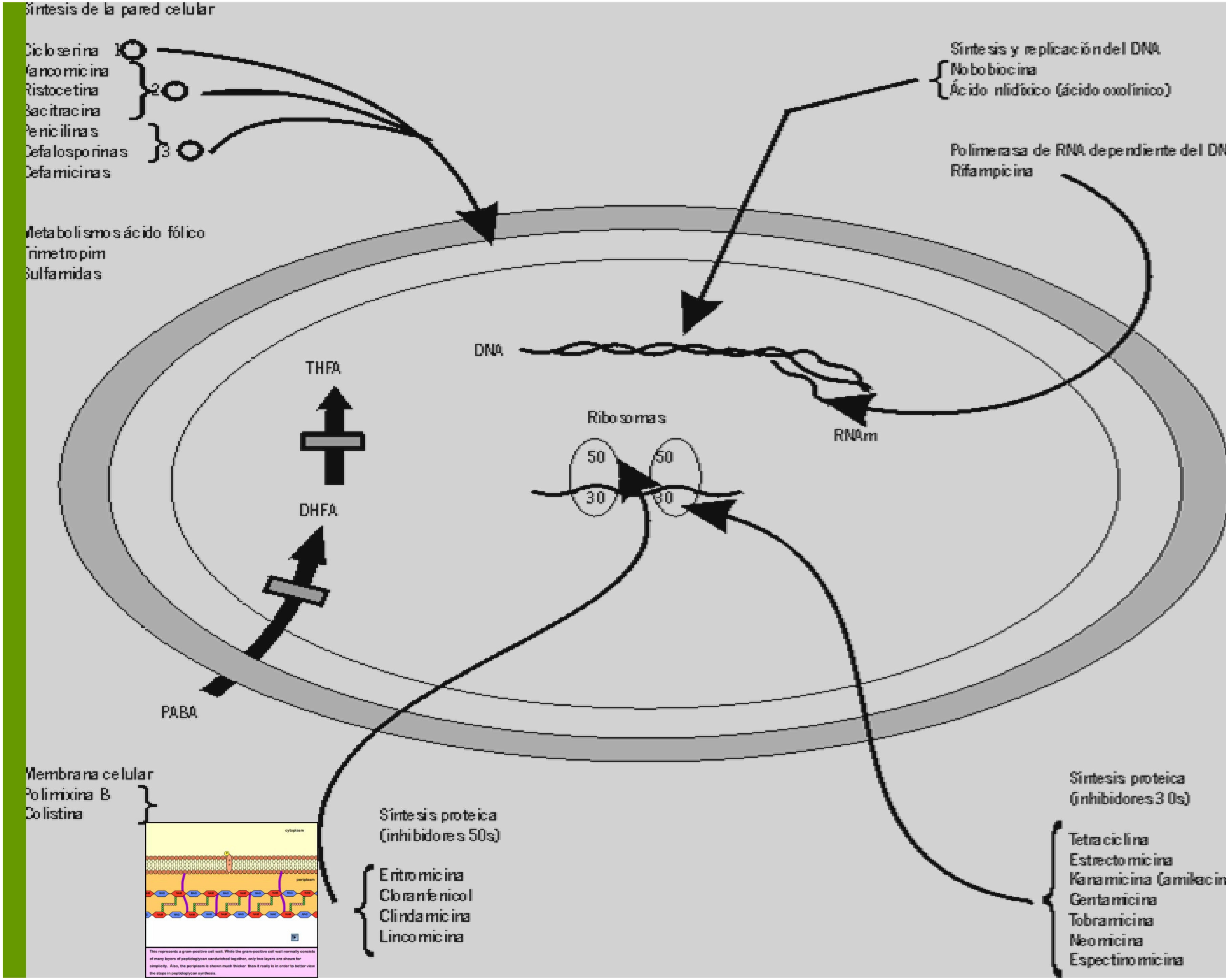

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On the cell membrane:

- Penicillins, polymyxins, colistin, novobiocin, streptomycin, neomycin, kanamycin, gramicidin, tirocidina, amphotericin, nystatin ...

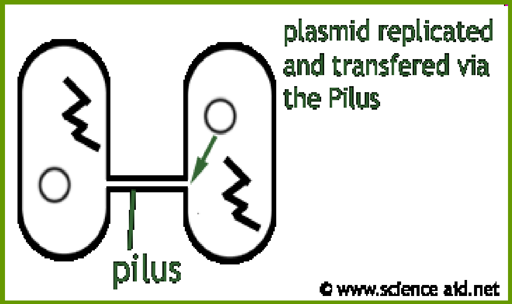
On protein synthesis:

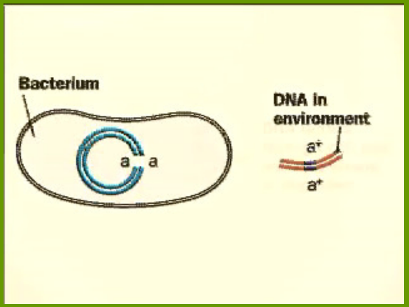
- chloramphenicol, streptomycin, neomycin, kanamycin, erythromycin, tylosin, oleandomycin, lincomycin ...

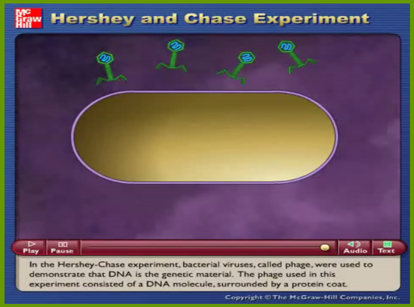
Interferes with the nucleic acid metabolism:

- griseofulvin, actinomycin ...

Antibioresistance







- natural
- artificial

Natural antibiotic resistance:

Leads to the clarification of the antibacterial spectrum.

Earned antibiotic resistance:

appears (faster or slower) to all antibiotics.

Is due to misuse, unreasonable use of antibiotics.

Once installed it can be:

- ***final*** **(permanent)**
- ***reversible***

The resistance

- Is limited to the one antibiotic = uncrossed.
- Can extend to other antibiotics = crossed antibioresistance
- Can also occur through changes in the genotype.
- Antibiotic therapy should be performed with an attack dose and continued with a maintenance dose.
- Treatment must be carried until the bacteriological cure, that is 24-48 h after the clinical recovery.
- It is forbidden to associate β-Lactams with the groups of tetracycline or chloramphenicol.

Secondary and toxic phenomenons

There can exist secondary phenomena, *direct or indirect,* produced during antbiotherapy.

Aminoglicosides

- **has toxic actions on the pair of cranial nerves VII**
- ***nephrotoxic,* degenerative processes during renal excretion.**

Streptomycin

Affects the vestibular branch, with balance disorders

Dihydrostreptomycin alters the cochlear branch: deafness or decreased hearing acuity.

Penicillin

in high doses is toxic for the CNS.

Tetracyclines, **especially** **chlortetracycline:**

- hepatotoxic, degenerative phenomena on hepatocytes

Chloramphenicol

- in high doses or long treatments; degenerative phenomena on hematopoietic organs (bone marrow).

Penicillin and şi β-Lactams

- *Sensitization* = an indirect phenomenon *:* bacteriolytic phenomenon to penicillin = *bacterial endotoxin release by cell lysis* - Jarisch-Harscheimeyer

After massive and lasting treatments p.o.:

- superinfections with fungi (especially Candida albicans).

β- Lactams

Penicillin

was the first antibiotic introduced (1928, Fleming)

Extraction from cultures of Penicillium species:

- *nodatum,*
- *crustosum,*
- *crysogenum*

An international unit (I.U. = U.I.):

the amount of active substance that stops a diameter of 24 mm standard strain development (Oxford) of S. aureus.

1 I.U. = *0,6 gamma of standard penicillin*

In Romania: 1 mg penicillin = 1500 - 1600 I.U.

Kinetics

► is not administered p.o., only as i.m., s.c. or i.v. injections

Most frequently: profound *i.m.*

The time of action is short: 4-6 h. at crystalline penicillin G : 4-6/day

Exists *retard penicillins (deposit):*

► esters of penicillin G,

► procaine penicillin and

► benzathine penicillin = are slowly absorbed at the site of administration

- Great *diffusion* in tissues and organs.
- Good penetration trough lungs, diffuses in tissues and organs.
- *Renal concentration* where it is totally eliminated.
- *Diffuses in: placenta,* reaching 50% in the fetal liquid.
- Hard diffusion in C.S.F.
- *Eliminating*: renal and mammary, if it is found in milk, it is banned from usage.
- It is also eliminated through: saliva, bile, but also through eggs.

Therapeutical indications

- infections: hyperacute and acute with sensitive germs
- infections: pulmonary, omphalophlebitis, phlegmons, abscess, mammary, renal
- Infectious diseases: anthrax, emphysematous coal, actinomycosis, tetanus, strangles, gaseous, gangrene, contagious respiratory catarrh, erysipelas, enzootic pneumonia in pigs
- septicaemic condition
- streptococcal polyarthritis
- mastitis, intramammary and
- on general path.

Esters of Penicillin G
(deposit penicillin)

It is used in association with: crystallized penicillin G (Efitard), from: 100000 U.I., crystalline penicillin G and 300.000 U.I., procaine penicillin (Tripedin, Propamicin).

- *Benzathine penicillin, ester of the Penicillin G with dibenzyl-ethylene-diamine radical= penicillin, chronic type* (*Moldamin*)
- *The antibiotic base: the quantity of a pure antibiotic, without taking into account its actual salt.*
- *Procaine penicillin,* ester of benzyl penicillin G

Asocilin:

- penicillin, streptomycin sulfate and aluminum stearate.

Tardomyocel:

- benzathine penicillin, dihydrostreptomycin sulfate.

Marbadal

- the association between marfanil and badional plus seed oil.
- vials, and it is used in the treatment of endometritis.

In: external conditions and as prophylactic in artificial inseminations.

Semisynthetic penicillins

Obtained by introduction of precursors into cultures of Penicillium.

The precursors ► are taken over by microorganisms and bound to the *6-aminopenicilanic acid.*

Penicillin V (phenoxymethyl penicillin)

From: P. crisogenum at which is added the phenoxymethyl precursor

The elimination: renal, gastrointestinal and biliary.

Penicillin V: is generally used in small animals.

Pheneticillin (Broxil)

p.o. high blood level, without special advantages,

is not resistant to penicillinase

Propicillin (Ultrapen)

p.o. high blood level,

resistant to penicillinase, hardly activated by it.

Methicillin (Celbamine)

obtained by grafting dimethoxyphenyl radicals. Unstable in acidic medium, resistant to penicillinase and extremely active at staphylococcus.

Oxacillin

- semisynthetic penicillin gastric fluid resistant
- p.o. administration

Cloxacillin (Orbenine)

- acid-resistant and penicillinase-resistant penicillins
- p.o. or parenteral administration

Nafticillin

- gastric fluid and penicillinase resistant
- the qualities are similar to cloxacillin.

Ampicillin

- Spectrum: wide
- obtained: by grafting the aminobenzyl radical.
- The maximum action: on G- bacillus.
- Administration: oral or parenteral.

Pivampicillin

- Absorption: good digestive
- Resistance: at gastric fluid
- Blood level: high.

Borampicillin

- **Action:** caused by its solubility,
- **Absorption:** very good (2-3 times higher than ampicillin)

Amoxicillin

- semisynthetic penicillin.
- **Administration:** p.o. or parenteral.

Amoximast

- in mammary infusions.

Ticarcillin

- semisynthetic, different names: ticillin.
- administration- i.m., i.v.
- wide spectrum (aerobic, anaerobic G+ and G-).
- great absorption at the genital and intestine levels.
- over: resistant germs at Amoxicillin and unpotencialised Ticarcillin (e.g. Klebsiella, Pseudomonas, S. aureus)

Piperacillin

- wide spectrum. It is well absorbed p.o.
- active, unchanged in the urine.
- i.v, i.m. administration.

Carbecillin

- incompletely absorbed po,
- rapidly hydrolysed by certain enzymes.

Cephalosporins

Penicillamine structure: contains β-lactam ring.

Classes: extraction*, semi-synthetic and synthetic.*

The natural ones (Cefalosporina C) are extracted from *Cephalosporium acremonium.*

More resistant to β-lactamases produced by staphylococcus, towards against lactamases produced by gram negative bacteria are known these cases:

a. total resistance to all lactamases,

b. resistant to one or more lactamases,

c. there is no resistance.

Pharmacokinetics

Are absorbed orally (generation I) and parenterally.

Diffusion: great in tissues and organs

Good penetration: in parenchyma, pleura, pericardium, synovialis.

Difficult penetration : trough eyes and CSF.

The last generation: penetrates the H.E. barrier.

Acts: 8-12 h., with an administration of 2-3 times/day

Mode of action: bactericidal

Mechanism of action: similar to penicillins

Three groups of cephalosporin a.u.v.:

- ☞ 1st generation
- ☞ 2nd generation
- ☞ 3rd generation

1st generation:

- Cefadroxil,
- Cefazolin,
- Cefalexin,
- Cefaclor (p.o.),
- Cefalotin,
- Cefapirin,
- Cefacetril,
- Cefrodin.

Great action: *G+ bacteria, G+ cocci and*

Average action: *G- cocci, but more intensive over Stafilococcus,.*

Restricted activity over Gram – bacteria.

2nd generation:

Representatives :

- Cefamandole,
- Cefanocid,
- Ceforanide,
- Cefotetan,
- Cefoxidin,
- Ceftiofur,
- Cefuroxin.

Action: G+ bacteria

Active: G - : *E. coli, Proteus, Klebsiella, Pasteurella, Salmonella*

Very active against: **indole-positive species:** *Proteus, Haemophillus*

Resistance: *Citrobacter, Enterobacter and P. aeruginosa*

3rd generation

Representatives:

- Cefoperazon,
- Cefotaxin,
- Ceftozidin,
- Ceftozoxin,
- Ceftrixon,
- Moxalactam.

Spectrum:

The widest, the family representatives are active against P. aeruginosa.

A weaker action against G+,

Acts strongly against G- ,

Active against: Pseudomonas, B. fragilis and B. bronhiseptica.

Side effects

Low toxicity, considered non-toxic.

The high doses (especially in human medicine) gives:

Effects: *nephrotoxic and hepatotoxic.*

In animals:

irritation at the injection site (case of Cephalotin)

Recommended in the treatment of:

- respiratory infections,
- excretory system infections,
- osteomyelitis
- mastitis

Ceftiofur

i.m administration in: cattle, sheep, swine and poultry

Acts bactericidal

***Mechanism:* inhibition of bacterial cell wall synthesis.**

***Spectrum of action:* wide**

Effective on most germs.

It is not active against mycoplasma.

Very good tolerance.

Representatives:

Vetimast (cafacetril), Kefa-Mastin retard (cephalexin + dihydrostreptomycin) Pathozone (cefoperazone), EXCENEL (ceftiofur)

Pyassan capsules (cephalexin) Naxcel injection (ceftiofur).

Aminoglycosides

- Head of the group: streptomycin. They are also called glycosaccharides
- Isolated from: *Streptomices*, especially *Str. griseus*
- White crystalline powder, odorless, bitter taste.
- The action is expressed in: *U.I.* or *ponderal*.
- 1 U.I.: the amount of pure active substance = inhibits the growth of a standard strain of E. coli in a ml of culture medium.
- 1 U.I. = 1 microgram of streptomycin base;
- abroad 1000 U.I.=1 mg , In Romania: 1 mg=700 U.I.

Antibacterial spectrum

Complementary to penicillin!

- active on : G+ and G- cocci, G- bacteria.
- weak on G+ and acid-alcohol-resistant (*B. Koch, M. tuberculosis, M. leprae*).

Mode of action: bactericidal

in the multiplication and resting phase of the bacteria.

Action

distorts the process of protein synthesis, combines with RNA from ribosome and disrupts the microbial synthesis.

The penicillin-resistant staphylococci and streptococci, streptococcus equi, fowl cholera, salmonellosis, leptospirosis, mycoplasmosis, in septic complications of diseases, pneumonia, septicemia, urinary tract infection.

Effects: neurotoxic and nephrotoxic.

Do not administer: *i.v.* only exceptionally in very slow perfusions.

Intrarahidian is administered in slow dose and in dilute solutions

Administered in aerosols, in the respiratory diseases.

Neomycin (Negamycin)

Isolated from: *Str. fradiae (Waksmann)* is a mixture: neomycin A, B and C.

White powder, odorless, soluble in water.

Bactericidal or bacteriostatic, depending on dose.

Active: G+

Very active: G- intestinal

Synergistically with: streptomycin, erythromycin, and bacitracin

Major Indications: gastroenteritis in young animals.

External: as powder and ointment of 0,5 – 4 - 5%.

Dynacin

Preparation based on neomycin, excellent in enteritis

It can be used: i.u., by introducing 10-20 cpr. at once.

Very efficient: associated with furazolidone, nitrofuran...

Nestrepin

Based on: neomycin and dihydrostreptomycin

Used in: mastitis in cows.

Fluocinolone N

Contains: fluocinolone and neomycin sulphate.

As: ointment, spray in skin disorders.

Quadrex

Contains: neomycin base, vitamins A, B, D_3, E and glucose

In pigs: in water until weaning

Kanamycin (Resistomycin)

From: *Str. kanamicetus* isolated by Japanese.

White powder, crystalline (sulphate or hydrochloride salt)

Acts: similar to streptomycin comprising mostly G-, mycobacterium, and acts also on G+.

In: local, suppurative, genital and digestive conditions, *p.o.*

Framycetin

from: *Streptomyces lamandulae,*

Spectrum: wider, similar to Kanamycin.

Acts: bactericidal and slightly bacteriostatic.

Administration: parenteral (sulphate salt)

Is: *nephrotoxic* and *neurotoxic*

Paromomycin

from: *Str. paromomyceticus*.

Acts: strongly on G- and amoebas.

Is: *nephrotoxic*

Administration: p.o. in enteritis.

In 120-150 mg operculated capsules.

Gentamicin

From: *Mycromonospira purpurea* with two fractions: C_1 and C_2.

Used: sulphate salt, white powder, amorphous, stable, resistant to changes in pH.

Acts: bactericidal and bacteriostatic,

In: multiplying logarithmic phase and and latency phase.

Diffusion: in tissues, high concentrations in the urine.

Indicated in: acute and chronic urinary tract infections, sepsis, gastrointestinal infections

Effects: neurotoxic and nephrotoxic.

Rifampicin (A, B, C, D)

Extract: from *Streptomyces mediteranei*,
Action: bactericidal or bacteriostatic
Spectrum: wide, resistant to digestive juices.
Acts: on G+.
Administration: p.o., but also i.m. and i.v.
Diffuses: great in tissues.
Elimination: gallbladder, feces, urine.
It is not toxic to the eighth pair of cranial N.
Intervenes in: general enteric infections.
Antagonist: penicillin and tetracyclines.

Aminosidine

From: *Str. crestomyceticus* (A sulphate)
Action: bactericidal, bacteriostatic
Spectrum: wide
Toxic effects: similar to streptomycin, but slightly intense.

Gabbrocol

Suspension: 8-hydroxyquinoline and aminosidine sulphate.

Spectinomycin

Wide spectrum: G-, mycoplasma, staphylococci, streptococci.

In: urinary and genito-urinary infections, postpartum

From: *Streptomyces flavopersicus*.

Organic base, soluble in water in the base or salt form.

Spectinomycin

bacteriostatic, inhibits protein synthesis.

Spectam a.u.v solution used in the prevention of enteritis.

Apramycin

From: *Streptomyces tenebrarius*.

Acts: bactericid on G+, G-, mycoplasma.

Used in: enteritis in calves and piglets.

The macrolides

Large molecule, comprises large lactone rings linked to each other by dimethylated oses?. (=Oze)

Antibiotics with: narrow spectrum of action.

Erythromycin

From: Streptomyces eritrema.

Active on: G+, G+ şi G- cocci.

Action: bacteriolytic or bactericidal, depending on dose.

Indications: in respiratory conditions. genitourinary infections , enteritis.

Erythromycin lactobionate (salt with lactobionic acid)

dissolves in distilled water or 20-33% glucose solution.

It is not dissolved in physiological saline, because precipitates.

In: *anthrax, strangles ,foals septicemia, mastitis, suppurative conditions*

Erythromycin thiocyanate (Gallimycin)

Two forms: injectable solution for mammals and birds.

Tylocin (Tylazin)

Homologue erythromycin isolated from *Streptomyces spp.*

White powder, insoluble in water.

Recommendations: Avian mycoplasmosis, diseases with PPLO germs.

Spiramycin (Rovamycin)

From: *Streptomyces abmofaciens*.

Slightly soluble in water, with acids it forms salts.

Resistant to: digestive fluids, is bacteriostatic.

Active on: anaerobes, rickettsiae and spirochetes.

Does not: *cross* the *H.E. and H.O*. barriers

Concentrates: in bile,

Metabolism and elimination trough: bile, feces, urine.

Carbomycin (Magnamycin)

From *Streptomyces halstadti*, with 842 Å MW).

Microcrystalline powder, yellowish, slightly soluble.

Action: similar to penicillin.

Spectrum: wide action on G+.

Acts: bactericidal and bacteriostatic

Concentrates in: liver, gallbladder, kidney, eliminating through this paths.

Stafilomicin (Stafilocilin)

From: *Streptomyces virginae*.

Light yellow powder, bitter, resistant to gastric fluids.

Action: bacteriostatic; Strong against staphylococcus.

Eliminated through: urine

Oleandomycin

From: cultures of *Streptomyces antibioticus.*

Spectrum: similar to erythromycin.

on G+ (cocci, pneumococci, staphylococci, streptococci).

Elimination: massive through bile and less (5-120%) via urine.

Action: *in I.U. The International standard= 880 U.I./mg.*

Sigmamycin

Composition: one part oleandomycin and two parts tetracycline.

On: G+, G- germs.

In: bronchitis, pneumonia, bronchopneumonia, genitourinary and external infections, infectious diseases.

Taociclin

From: one part oleandomycin, triacetyloleandomycin + two parts tetracycline.

Lincomycin (Lincocin)

From: cultures of *Streptomyces linconcusis.*

Very active against: B.anthracis.

G- bacteria= is not sensitive to Lincomycin.

p.o. administration in operculated capsules.

Clindamycin

Action: similar to Lincomycin

Used: in the treatment of mastitis.

Cyclic polypeptides

Antibiotics of bacterial origin,

Consisting of: amino acids and a fatty acid.

Extremely toxic, only for local usage.

The head of the series is:

Polymyxin

Extracted from cultures of: *Bacillus polimixa*.

There are five known polymyxins: *A, B, C, D* şi *E.*

Polymyxin B = bacteriostatic or bactericidal action, regardless of the development stage of the bacteria.

Active on: G-, E. coli, enterobacteriacee, Pseudomonas, Shigella, etc

Bacitracin

From: cultures of *Bacilus subtilis* or *Bacillus licheniformis*

A mix of four polypeptides: A, B, C and F.

For veterinary use: Bacitracin A is more used.

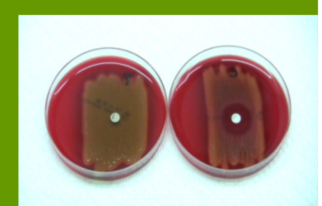
Action: bacteriostatic (bactericidal) G+ and G- cocci, G+ bacteria.

Thyrothricin

From culture of: *Bacillus brevis.*

Action: bactericidal= tension modifications in the cell membrane

It is quite toxic parenterally.



Colimycin (Colistin)

From cultures of: *Aerobacter colistireus.*

In: genitourinary and digestive infections with G-

Tetracycline group

Broad-spectrum antibiotics, even very large.

Structure form: four linearly fused rings.

Extracted from cultures of: *Streptomyces spp*.

Form: small crystals, yellow, insoluble in water but soluble in the form of salts.

Broad antibacterial spectrum : G+ şi G- cocci, G+ şi G- bacteria, actinomycetes, rickettsia, spirilla, large viruses and protozoa.

Mode of action: bacteriostatic.

Can't be associated with: bactericidal antibiotics (ex. β-Lactams).

Action: interferes with protein synthesis.

By: chelating metals that are necessary for the development and multiplication of bacteria.

Different distribution: high concentration in : liver, kidney, lung and spleen.

Excretion: slow renal excretion

Toxic phenomenon: different, depending on the type of tetracyclines.

p.o. administration= fungal stomatitis, erythema, blisters on buccinator mucosa.

Hepatic disorders: especially when using chlortetracycline

Accumulates in: bones , teeth, affecting the bone system = fragility.

Solvocilin (Pyrrolidine-Methyl-Tetracycline)

Injectable tetracycline widely used in veterinary medicine.

Doxycycline (Vibramycin)

derivative with similar properties, but with a longer action: 24h

It is a: semisynthetic antibiotic

It is the most active form of tetracyclines.

Galisan = tablets used to treat coccidiosis.

The tablets contain tetracycline base and Furadicil.

Is associated with Vitamin K3 in a 1% solution in drinking water.

Dizenter = 1p tetracycline, saprosan 3p, 6p dimetridazole in the excipient.

In the treatment of: dysentery and enteritis.

Clortetrasol

Mixture: tetracycline, chloramphenicol, prednisolone acetate and lidocaine.

In: bronchopneumonia, pleurisy, sepsis in newborns, infectious diseases, arthritis, mastitis.

Terapentane T

Mixture: aureocilin, furazolidone, oxychinolein, astringent and Gallic bismuth (gastric dressing) = gastroenteritis in calves: 1-2 times/day

Trierra

Mixture: oxytetracycline, bacitracin zinc, furazolidone, enzymes, vitamins and growth factors.

As: antimicrobial and anti-stress factor

Broad spectrum of activity, most often, introduced in the feed.

Mibazon

Contains: basic tetracycline, neomycin sulfate, tetracycline sulfate, prednisolone, excipients.

Chloramphenicol group

http://pil39.en.ec21.com/Products--1055230.html
http://www.world-trades.com/selling/617/621/veterinary-3.html

Chloramphenicol

Spectrum: wide, from: cultures of *Streptomyces venezuelensis*.

Chloramphenicol= small molecule► 2 forms: levorotatory & *racemic*.

Action: bacteriostatic, (cannot be associated with β-Lactams)

Cross: the haematoencephalic *barrier*

Diffuses: well through the placental *barrier*

Elimination: metabolized by the kidney, bile and feces.

Levorotatory form = in infections with G+, G- cocci, G+, G-bacillus.

Racemic Chloramphenicol is poorly absorbed, used only in birds and chickens with typhoid and pullorum infection.

Various antibiotics

Pristinamycin

From: *Streptomyces antibioticus*.

Belongs to the group of Synergistines

Elimination: renal.

Administration: local or external.

In: powders, solutions, ointments, inhalable solutions.

Tiamulin

http://www.farmavet.ro/ro/produse/view/tiamulin-10

semisynthetic antibiotic derivative of Pleuromutilin – produced by *Pleurotus nautilus.*

Active: mycoplasma, treponema, leptospira, G+ şi G- germs

Main indication:

swine dysentery with B hyodysenteriae

In: enzootic pneumonia in pigs, mycoplasma arthritis, swine enteric and pulmonary infections.

It is used under the name: *Dynamutilin*

Forms of usage: *Dynamutilin granules and Dynamutilin 200 injection.*

Contains: tiamulin fumarate hidrogenate 45% and granulated lactose.

In: pigs and poultry : respiratory infections, enzootic pneumonia etc.

In birds: curative and preventive in Avian mycoplasmosis treatment,

In: mycoplasma produced by *Mycoplasma synoviae* and *Mycoplasma meleagridis*, in chickens and turkeys.

Incompatible with: Monensin and ionophores: Salinomycin or Narogin and even Dimetridazole = *toxic mixtures.*

Antifungal therapy

Therapeutic principles

Fungal infections can be classified in:

a. systemic infections

b. superficial infections

General mode of action:

topical and systemic = on microscopic fungi,

Action: fungicidal or fungistatic

Mecanism: blocking of the enzymes involved in carbohydrate metabolism.

Antimycotics are classified in antimycotics with:

- topical action
- systemic action
- mixed activity

Topical antifungals

Colored chemotherapeutics group

- *phenol*
- *hexachlorophene*
- *benzalkonium chloride*
- *fuchsine and*
- *resorcinol* = bactericidal and significant fungicidal activity.

In: contact dermatitis, commonly used in various combinations

Cutis therapy: phenol-fuchsin and resorcinol solution (Castellani sol.)

Organic acids

Acids with long chain lipids: undecylenic, caprylic, salicylic and benzoic

Effects: fungistatic, solutions or ointments 2-10% = topical

Comercial: Zincudan ointment 10% (undecylenic acid+ undecylenic zinc + salicylanilide), Mycosid pulv. (Na-p-chlor-benzoic).

Tolnaftate

Efficient activity: *Epidermophyton, Trichophyton, Microsporium*

It has no effect on: *Candida.*

Usual concentrations: 1%.

Benzuldazic acid

sodium salt (Defungit) = solution 0.5% for the treatment of dermatophytes

Imidazoles

Contain: imidazole rings

Spectrum: antifungal, antiprotozoal, antibacterial, antiparasitic

Mode of action:

Block: ergosterol synthesis and due to the enzymatic inhibition,

Determine: amplifies the amount of peroxides in the cell.

The most popular preparations are from topics category:

Clotrimazole, Econazole, Miconazole, Ketoconazole, Thiabendazol.

Clotrimazole

Action= similar to other imidazole compounds

Efficient = exclusively local on: Aspergylus (first choice in fungal keratitis, solution or ointment 1%, x 3/3 h.), *Epidermophyton, Microsporium, Trichophyton, C. albicans.*

Rarely produces: irritation, itching, erythema and edema.

Commercial: *Canesten* (ointment, tablets, solution).

Miconazole

Similar activity with Ketoconazole.

In associated preparations: Canoderm, Surolan, OE therapy, dermatophytosis.

Natamycin

cyclic polyene that has the cell membrane as site of action.

Candicidin

Acts: fungistatic. It is insoluble.

External: ointment 1% or vaginal ovules, especially in candidosis.

Saramicetin

Acts: fungistatic. It is insoluble.

In: subcutaneous fungal infections.

Tricomicin

Acts: fungistatic, hard to be absorbed

Local: in the treatment of candidosis, but also active: in trichomoniasis.

Variotin

fungistatic and fungicidal used locally in trichophytosis.

Systemic antifungals

Griseofulvin

From: cultures of Penicillium grisofulgum, among the first used in the oral administration

in the treatment of trichophytosis *in animals, in epidermophytosis infestations with: Epidermophyton, Trichophyton, Microsporum.*

Griseofulvin has no effect on bacteria and on Candida.

It seems that in cats with an advanced state of pregnancy = teratogen.

Pimaricin

From: cultures of *Streptomyces natarensis*.

Acts: fungistatic and fungicid.

Insoluble in water and is not absorbed.

Used: external, in local applications (ointment 2%).

On: *Candida albicans* (which produces stomatitis, vaginitis). Efficient: skin dermatophytosis and appendages local therapy.

Commercial: Pimafucin drops, tablets, cremes.

Polyenes

Stamycin (Nystatin)

- antifungal antibiotic extracted from cultures of Streptomyces nursei, it's a polyene macrolide antibiotic.

Is dosed in I.U. = The minimum amount which inhibits a culture of Saccharomyces cerevisiae in one ml of broth.

1 mg standard substance = 2000 I.U.

Spectrum of action

On: Candida and Tricophyton.

Action: it occupies the places of stearolic coupling on the fungal cell membrane = alterations of fungal membrane permeability and ion depletion.

Absorbs: very hard in the digestive tract.

Efficacy: visceral mycoses = *moderate*

not recommended = toxicity, parenteral administration

Commercial: Nystatin tablets.

Amphotericin (B and C)

From: cultures of *Streptomyces nodosus* (also polyene).

Acts: on generalized mycoses: candidosis, histoplasmosis, cryptococcosis, blastomycosis, coccidiomycosis.) on which other systemic antifungals are not effective.

Has the fastest action of the systemic antifungals

Capable of: therapeutic associations, that decrease its nephrotoxicity (most frequently with ketoconazole).

Commercial: Fungizone inj.

Imidazoles

Mod of action:

Interferes with ergosterol synthesis and coupling of phospholipids in the fungal cell membrane = rupturing and loss of cellular content

Most efficient in:

candidiasis, criptococcidiosis, aspergillosis, coccidioidomycosis in big and companion animal = good results.

Distribution: good, great diffusion in tissues and organs

Ketoconazole: well metabolized in the liver,

Inactivated metabolites = eliminated through bile.

Triazoles

Group of five azo structures possessing:

- 3 atoms of nitrogen in the triazole nucleus,
- coupled to aromatic rings = Excellent antifungal activity.

Considered the latest generation of systemic antifungals!

Acts on many species of fungi: Aspergylus, Candida, Cryptococcus, Coccidioides, Histoplasma…

Presents a low toxicity.

The most known representative is:

Itraconazole

Lipophilic compound,

Administered p.o.: is well absorbed,

Couples: highly to plasma protein,

Does not: penetrate the barrier H. E.

Fluconazole

Couples: weakly to plasma proteins,

Penetrates: well humors.

Metabolization: în măsură foarte...?

Mycetin

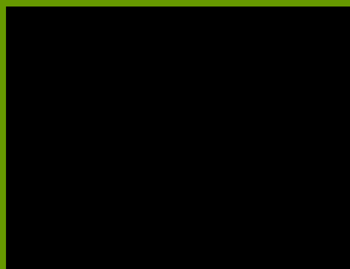
Chemical structure: similar to chloramphenicol.

Action: fungicidal

Keratolytic properties: indicated in dermatomycosis.

Orientative therapeutical indications of the main antifungal (Summary)

The type of disease	Type of administration	
	Local	Systemic
Systemic mycoses	---	Ketoconazole Amphotericine B
Dermatomycosis	Natamycin Miconazole Povidone iodine Benzoic acid	Griseofulvin Ketoconazole
Fungal keratitis	Clotrimazole Natamycin Miconazole	---
Fungal mastitis	Nystatin Clotrimazole Natamycin	---
Fungal otitis	Miconazole Nystatin Natamycin Thiabendazole	---



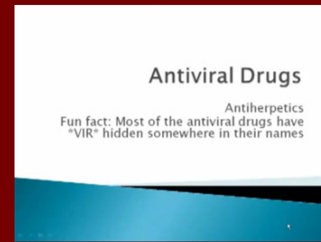
Representatives of the antifungal group

(Synthesis Cristina, 2011)

Group	Representatives	Routes of administration
Allylamine and other non azole inhibitors of ergosterol biosynthesis	Amorolfine	Topical
	Butenafine	Topical
	Naftifine	Topical
	Terbinatine	P.O. Topical
Antimetabolites	Flucytosine	PO, IV –removed from the market
Azoles	Fluconazole	PO, IV
	Itraconazole	PO, IV
	Ketoconazole	PO, Topical
	Posaconazole	PO
	Ravuconazole	in development
	Voriconazole	PO, IV
	Clotrimazole	Topical
	Econazole	Topical
	Miconazole	Topical
	Oxiconazole	Topical
	Sulconazole	Topical
	Terconazole	Topical
	Tioconazole	Topical

Chitin synthase inhibitors	Nikomycin Z	Parenteral–in dezvoltare
Inhibitors of glucan synthesis	Caspofungin	IV
	Micafungin	IV
	Anidulafungin	IV
Polyene	Amphotericin B (AmB)	IV, Topic
	AmB - lipid complex	IV
	AmB - colloidal complex	IV
	AmB -lysosomal complex	IV
	AmB - oral suspension	PO
	Nystatin - lysosomal complex	IV – in development
Topics	Nystatin	Topical
	Pimaricin	Ophthalmic
Other systemic representatives	Griseofulvin	PO
Other topic representatives	Ciclopiroxolamine	Topical
	Haloprogin	Topical
	Tolnaftate	Topical
	Undecylenate	Topical

Antiviral antibiotics



Antibiotics that:

- ***block the protein synthesis enzymes and degrades DNA***

Intervenes in:

- ***RNA synthesis or***
- ***stimulates the elaboration of interferon by appropriate cells***

Helenin

- **Produced by: *Penicillium funiculosum.***
- **Structure: nucleoside with antiviral activity.**

Cytin

- **From: cultures of fungi that are parasites for tea leaves.**
- **Macromolecular substance= stimulates the antiviral activity,**
- **Results: in sarcomatosis**

Antiprotozoal antibiotics

Puromycin

- **Interferes:** enzymes which ensures purine metabolism
- **Inhibits:** nucleic acid synthesis.

Phytoncides and zooncides

Elaborated by: *superior plants and metazoans (multicellular animals and multicellular plants)*

Action: *germicidal and were named* :

- phytoncides (from plants) and

- zooncides (from animals).

Contact:
allicin.2009@gmail.com

Allicin

Extracted: from garlic and onion.

Isolated= crystalline substance soluble in water.

Substance: volatile or sublime.

Action: G+ şi G- germs, viruses and acido-resistents

Tomatine

Isolated: from tomatoes, soluble in water and alcohol.

Activity: inhibits G+ bacteria and fungi.

Dicumarine

From: red clover and melilot.

Active: against G+ germs.

Is: insoluble in water, soluble in organic solvents.

Zooncides

Obtained from animal tissues and secretions

Lysozime

Isolated: by Fleming, 1922

In: almost in all animal tissues, especially secretions.

Spermine

From: animal sperm.

Active: especially on G+.

Ecmoline

From: fish roe.

Active: on G+ and G-

Nonspecific therapy stimulation

- In animal and plant tissues = nutritive exchanges.
- Under the influence of some unfavorable factors: low temperature, UV-rays, etc, in these tissues = substances with undefined chemical structure.
- These structures= role in defense against the mentioned factors , being known as: biogenic stimuli(biostimulins).

Use:

- Tissues that are transplanted s.c.,
- Extracts or
- Suspensions from selected tissues, being triturated.

If biostimulines are introduced in an animal organism:

- improve physiological functions,
- intensify the immunological defense processes and produce
- extension of the pharmacodynamic effect of drugs when simultaneously administered.
- It is observed especially on diseased animals, in practice, using tissues collected aseptically and stored at 2-3°C, for: 10 days (necessary time for the formation of biostimulines)

Liver tissue suspension

- **In:** endometritis, hypoplasia, utero-ovarian hypofunction.
- **Administration:** s.c., repeated to one week.

Spleen tissue extract

- **In:** pneumopathies, sulfonamido-antibiotic therapy.
- Administered s.c. It is also a good stimulator.

Placenta extract.

- **In:** eye disorders, eczema, urticaria, dystrophies.
- **Administered:** s.c. or i.m. There are standard forms (2ml ampoules.)

Total extract eye (TEE)

- From: bovine eyes = used as ocular trophic.
- Form: 1ml ampoules containing ocular tissue.

Aloe extract

- From: *Aloe ferox* in the presence of water.
- Amplifies the defense function,
- Exceptional role in: tissue regeneration.

Biostimulators

in compound feed = 10-100, maximum 200ppm.

Commercials:

Nitrovin (Payzone) = 40 ppm;

Carbadox = 50 ppm, preventing colibacillosis = in piglets

Arsalinic acid= 80-90 ppm, gastroenteritis in piglets;

Piglet Pro-gen contains: aminoarsenate sodium.

Antibiotics with biostimulation role.

Aurex, Tylan, Tetraxim.

When using serotherapy it may occur also favorable action on chronic inflammatory processes (skin, joints, muscles) = until now it has not been found an explanation.

- Because they produce favorable effects by using some protein substances, method = *nonspecific protein therapy*
- Favorable effects were observed when administrating metals or metalloids in a colloidal state: colargol, protargol after injection = surprising changes.

- For this reason, it is used in this case the term: ***nonspecific stimulant therapy*** ***or*** ***of non-specific shock.***
- It seems that they involve amendments that refer to the ***body's reaction*** towards foreign substances that needs to be eliminated.
- **Nonspecific therapy:** in infectious, allergic diseases alergice associated with specific medication or inflammatory processes of the skin and joints, *that once reacutised* will heal more easily.
- ***Not indicated in acute inflammation*** **(eg. pneumonia)!**

Iodosept (Yatren)

- Ampoules: 5ml or 10ml 3%.
- Activity: antiseptic, amoebicid and nonspecific stimulator.
- In: pneumonia, actinobacillosis, adjuvant in surgical and infectious diseases, alone or in association with casein (*Yatren casein*).
- Administered: s.c. or i.m. daily or at 2-3 days, or per month.
- In: actinomycosis and botryomycosis, perifocal injections at AM.

Iodinated collagen

- Injectable solution with: iodosept, sodium bicarbonate, sodium citrate, and collagen.
- In the form of: 50 and 100 ml. vials
- Nonspecific stimulant: pneumopathies, i.m. and sc daily.
- Mechanism of action: E.R. system activation and increasing general body strength.

Polidine

- From: *heat-killed bacteria in physiological saline,* with the addition of phenol and bile.
- Role: *increases the body's* reactivity.
- Stimulates the antibodies production

Omnadin

- Foreign version of Polidin, composed of non-pathogenic bacterial proteins, salts, billary lipids.
- Administered: injectable s.c. and i.m.
- the best adjuvant in the sulfonamide and antibiotherapy
- Does not produce brutal rebound of chronic inflammations,
- Stimulates the body's resistance.

Gammaglobulin

- **Ampoules:** 2 ml injectable solutions,
- **Contains:** 15-20% human immune serum globulin.
- **Protection:** noticed in infectious diseases, administered i.m.

Serotherapy

- Normal horse serum, or any other serum (e.g. anti-erysipelothrix-rhusiopathiae serum) is administered at an interval of 2 days
- This enhances the coagulability of the blood, therefore it is recommended in haemorrhagic enteritis.

Galactotherapy

- S.C. injection of kimmed and sterilized milk by boiling.
- Initial: small doses, then gradually increased, administered once every 2-4 days.
- Very good results in otitis and eye affections.

Autohaemotherapy

- Involves: own venous blood which can be citrated.
- Administrations: s.c., progressive doses at AM, beginning with 10 ml and further from 2 to 2 days with 10 ml extra, up to 50 ml.
- In: the treatment of allergic dermatitis in dog and
- In: big animals (horse): malanders and synovitis.

Thank you for your attention!