IMPORTANT

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KEEP IN MIND

The translation was performed by Google Translate, but it hasn't been corrected yet

We are currently working

on the final version.

INSTITUTE OF VETERINARY SCIENCES

Mentouri Brothers University CONSTANTINE 1

Special Pharmacology

Chapter 1: Antibiotics

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Glossaire	Glossary
Acides nucléiques	Nucleic acids
Antibiotique	Antibiotic
Antibioprophylaxie	Antibiotic prophylaxis
Antibiorésistance	Antibiotic resistance
Bactériostatique	Bacteriostatic
Bactéricides	Bactericidal
Chat	Cat
CMB	CMB
CMI	MIC
Cobaye	Guinea pig
Conjonctivite	Conjunctivitis
Défense	Defence
Dindon	Turkey tusk
Famille	Family
Germe	Germ
Gram	Gram
Hote	Host
Hamster	Hamster
Mammite	Mastitis
Membrane cytoplasmique	Cytoplasmic membrane
Méningite	Meningitis
Mode d'action	Mode of action
Néphrotoxicité	Nephrotoxicity
Paroi bactérienne	Bacterial cell wall
Pigeon	Pigeon
Pneumonie	Pneumonia
Protéines	Proteins
Spectre	Spectrum
Synthèse	Synthesis

Goals

At the end of this course, the student will be able to:

- Understand the different classes of antibiotics.
- Identify the mechanism of action of each class.
- Be able to identify the molecules within each class.
- Understand the possible combinations of these molecules.
- Understand the guidelines for using antibiotics.

1) Historical background

Several scientists, such as **Pasteur** and **Joubert** in **1877,** and **Vuillemin** in **1889,** observed that certain Microorganisms inhibited others, while others fought specific diseases.

Microbiologist **Alexander Fleming** in **1929,** on one of his cultures of *Staphylococcus aureus,* contaminated by a mold: *Penicillium notatum,* it was observed that the bacteria no longer grew in the the area where the mold was growing. Fleming suspected that it was secreting a substance inhibitor which he named Penicillin. He later proved that Penicillin was not harmful to the man and suggested using it as an antibiotic.

In **1939, Florey** and **Chain** purified penicillin G and, with **Abraham** and **Heatley,** demonstrated its virtues as a medicine.

Waksman S. sifted through thousands of microorganisms. With **Schatz** and **Bugie,** he discovered the **"Streptomycin"** in **1944** in cultures of the bacterium Streptomyces griseus.

In **1948, Ehrlich** isolated **"Chloramphenicol"** from Streptomyces and **Duggar isolated** Tetracycline.

Streptomyces proved to be a valuable bacterium: it is the origin of many other antibiotics. such as erythromycin **(1952),** amphotericin B **(1956),** vancomycin **(1956),** kanamycin **(1957),** Lincomycin **(1962).** In **1963,** Gentamicin was extracted from a mold. From then on, researchers around the world relentlessly sought to find new antibiotics and to create semi-synthetic varieties (such as Chloramphenicol) from existing strains, or to chemical synthesis (such as Sulfonamides, Quinolones) with the aim of greater efficiency.

2) Definition of an antibiotic

Antibiotics are naturally occurring substances produced by microorganisms. (microscopic fungi and bacteria), or chemical synthesis, which, at very low concentrations have the power to inhibit the growth, or even destroy, of bacteria or other microorganisms without poisoning the host (eukaryotic cells).

The term antibiotic derives from that of antibiosis (from the Greek anti "against" and bios "life"), it designates a molecule that destroys or blocks the growth of bacteria.

In the first case, we speak **of a bactericidal antibiotic ,** and in the second case, **an antibiotic. bacteriostatic.** The same antibiotic can be bacteriostatic at low doses and bactericidal at higher doses. higher.

Table 1 shows the antibacterial effect of some antibiotics:

Table 1: Antibacterial effects of antibiotics

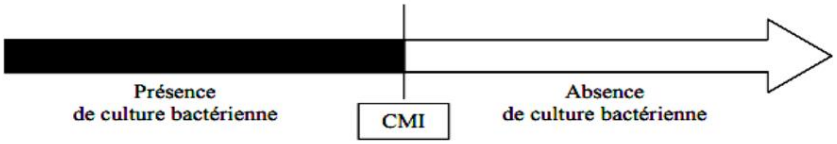
Classes of antibiotics with action	
Bacteriostatic, bactericidal	
ÿ-lactam macrolides Sulfamids Tetracyclines Nitrofurans Phenicoles	Quinolones Aminoglycosides Nitroimidazoles Glycopeptides Polymyxins Synergistines Fusidic acid

The distinction between the two types of action can be made by comparing the MIC (Concentration) *in vitro* Minimum Inhibitory Concentration) and the MBC (Minimum Bactericidal Concentration).

Definition of the CMI

The MIC is the lowest concentration of antibiotic capable of causing complete inhibition of the growth of a given bacterium, noticeable to the naked eye, after a given incubation period

The CMI can be represented as follows:



Definition of CMB

It corresponds to the lowest concentration of antibiotic capable of reducing a 99.99% of a bacterial population, in other words capable of producing a survival rate of less than or equal to 0.01% of the initial colony (one bacterium per 10000 seeded).

** The MIC and MBC are close for bactericidal antibiotics and far apart for bacteriostatic antibiotics.

Clinical implication: A bacteriostatic antibiotic cannot by itself eradicate an infection; by preventing bacterial proliferation, it merely facilitates the destruction of germs by the host's defenses.
In cases of severe infection and/or with a large inoculum, and in animals with deficient immune defenses, especially in older animals, it is classically recommended to prescribe a bactericidal antibiotic rather than a bacteriostatic one.

3) Spectrum of activity of an antibiotic

In veterinary medicine, 50 antibiotics have received their marketing authorization; they are divided into **11 families:**

Beta-lactams (subfamilies: Penicillins and Cephalosporins), Aminoglycosides, Phenicols, **Tetracyclines, Macrolides & related drugs,** Polypeptides, **Sulfonamides, Quinolones,** Nitroimidazoles, Nitrofuran derivatives, Benzyl-Pyrimidine nucleus derivatives.

The spectrum of activity (or action) for a given antibiotic is defined as the list of species microbial strains, the majority of which are found to be susceptible.

When the spectrum of activity is limited to a certain number of bacterial species, it is said to be **"narrow".** , while an antibiotic that is active against many bacteria is said **to be "broad spectrum".**

Finally, a bacterium that is insensitive to an antibiotic is defined as being resistant.

A broad-spectrum antibiotic acts on a large number of bacteria (on Gram-positive bacilli and cocci). and gram-) (e.g., Tetracycline, Phenicols). (Table 2)

A narrow spectrum antibiotic only acts on gram+ or gram- bacilli and cocci (e.g. Penicillin G, Macrolides).

Table 2: Spectrum of activity of some antibiotics according to the nature of the bacterial cell wall

Family	Antibiotic	Gram +	Gram -
ÿ-lactams	Penis G	+	-
	Oxacillin	+	-
	Ampicillin	+	+
Aminosides	Gentamicin	+	+
	Tobramycin	+	+
Phenicoles	Chloramphenicol	+	+
Tetracyclines	Doxycycline	+	+
Macrolides	Erythromycin	+	-
Glycopeptides	Vancomycin	+	-
Quinolones	Nalidixic acid	-	+
Others	Fustidic acid	+	-

4) How antibiotics work

Unlike antiseptics and disinfectants, antibiotics generally act in a way that **very specific to certain structures of the bacterial cell.**

This high specificity of action explains why antibiotics are active at very low concentrations, on the order of µg.ml-1, on bacteria; they generally act specifically by blocking an essential step in their development: the synthesis of their cell wall, DNA, and proteins. energy production…etc. (figure.1).

This blockage occurs when the antibiotic binds to its target: a molecule of the bacteria that participates in one of these essential metabolic processes. This interaction between the antibiotic and its The target is very selective, specific to bacteria.

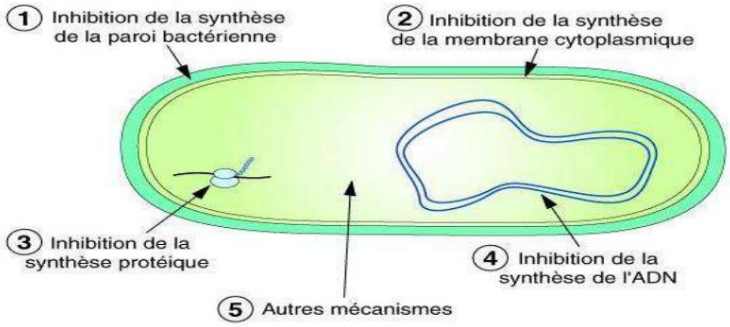


Figure 1: Mode of action of antibiotics

4.1. Antibiotics inhibiting bacterial cell wall synthesis

This is the mode of action of beta-lactams (subfamilies: Penicillins and Cephalosporins).

The action of these antibiotics is mediated by their beta-lactam ring. Indeed, this ring possesses a very strong affinity for the catalytic site of PBPs (Penicillin-Binding Proteins), enzymes essential for the synthesis and remodeling of peptidoglycan (Murein) in the bacterium.

PLPs are transpeptidases, enzymes involved in the stabilization of peptidoglycan in forming inter-peptidoglycan bonds. Peptidoglycan is the main constituent of the cell wall of all bacterial species and an inhibition of its synthesis leads to the death of the bacterium by shock osmotic. Therefore, peptidoglycan inhibitors possess bactericidal activity.

Noticed:

Bacteria have acquired the ability to produce **beta-lactamases** (enzymes that hydrolyze beta-lactams: penicillinases or cephalosporinases, depending on whether they preferentially destroy penicillins or cephalosporins) over millions of years. These enzymes, closely related to PBPs, are produced in the environment by certain bacterial colonies or fungi to regulate bacterial cell wall metabolism, but primarily to protect against the production of beta-lactams (this is antibiotic resistance).

4.2. Antibiotics that inhibit the cytoplasmic membrane

Due to the similarity between the membranes of bacterial cells and eukaryotic cells, the Antibiotics active on the membrane are toxic, and only a limited number of molecules have been found therapeutic use.

Polymyxins: Polymyxin B and Polymyxin E (colistin), are composed of a polypeptide cyclic and a fatty acid. Through their hydrophobic ends, these antibiotics penetrate the interior of the membrane and become incorporated into the lipid layer while the hydrophilic end remains oriented towards the outside. This results in a disorganization of the membrane structure, which causes the death of the cell.

4.3. Antibiotics that inhibit protein synthesis

These are the most numerous compounds. Antibiotics act by inhibiting or disrupting certain steps in biosynthesis essential to bacterial life by attaching to ribosomes, subunits

30S (e.g., **Aminoglycosides, Tetracycline)** or 50S (e.g., **Macrolides and Phenolics),** which disrupts the Protein synthesis.

4.4. Antibiotics active on the metabolism of nucleic acids and their precursors

Antibiotics are distinguished as being active on the one hand on RNA synthesis and on the other hand on synthesis DNA or its precursors:

Rifamycin works by blocking RNA polymerase

Quinolones inhibit bacterial DNA synthesis by binding to the complex "DNA gyrase" by preventing bacterial DNA replication and transcription

Sulfonamides act on the synthesis of folic acid, a cofactor in the synthesis of Purine and pyrimidine bases to be incorporated into nucleic acids. Their specificity of action This stems from the fact that eukaryotes do not synthesize folic acid.

Diaminopyridines inhibit the reduction of folic acid by taking advantage of the difference sensitivity of bacterial dihydrofolate reductase compared with the enzyme of eukaryotic cells.

Nitrofuran derivatives act by disrupting DNA replication

Nitroimidazoles act by inhibiting nucleic acid synthesis, leading to death rapid growth of the bacteria.

4.5. Antibiotics that inhibit metabolic pathways

In prokaryotes, metabolism proceeds through very diverse pathways, because they have acquired a capacity adaptation to life in nutrient-rich environments and survival conditions very different from eukaryotes. Despite this fact, the number of antibiotic molecules acting at this level and usable in clinical practice is very limited.

4.6. Anti-anaerobic antibiotics

Some bacteria are capable of living anaerobically by using redox pathways. independent of oxygen, and can reach significantly lower redox potential levels than in eukaryotes. This allows the specific metabolic activation of certain molecules, such as Nitroimidazoles, and give them a particular effect on these organisms (and other parasites) anaerobes).

There are many modes of action. It is important to know them because they allow you to understanding the mechanisms of natural and acquired bacterial resistance.

5) Classification of antibiotics

Antibiotics can be classified according to:

Their origin (natural, artificial…)
Their chemical structure (amino acid derivatives, heterosides, polycyclic)
Their spectrum of activity (bactericidal, bacteriostatic)
Their mode of action (on the cell wall, protein synthesis, DNA synthesis).

We will adopt the classification according to the mode of action.

5.1. Antibiotics acting on the cell wall: beta-lactam family

Generalities

Beta-lactams are bactericidal molecules that all share the characteristic of possessing a beta-lactam nucleus in their chemical structure.

This is a large family of antibiotics most commonly used in antibiotic prophylaxis and in Antibiotic therapy is composed of several subclasses, including derivatives of penicillin and cephalosporins.

These molecules exert their antibiotic effect on germs with a cell wall rich in peptidoglycan and are ineffective against organisms lacking a cell wall (Mycoplasmas).

5.1.1. Penicillins

Classification

Penicillins are acidic molecules; they are classified according to their spectrum of action:

1. Narrow-spectrum penicillins **susceptible** to beta-lactamases 2. Narrow-spectrum penicillins **resistant** to beta-lactamases 3. **Broad-spectrum penicillins susceptible** to beta-lactamases 4. Broad-spectrum penicillins **susceptible to beta-lactamases with extended spectra**
5. Broad-spectrum penicillins **protected against beta-lactamases** (potentiated penicillins).

1) Narrow-spectrum penicillins sensitive to beta-lactamases

Penicillins of this class are active against many Gram-positive bacteria (Streptococci, *Neisseria meningitidis)* but against a limited number of non-Beta-producing Gram-negative bacteria lactamases. They are sensitive to hydrolysis by staphylococcal penicillinases secreted by the Gram (-) bacteria.

This group includes:

1) Penicillin G "Benzylpenicillins"
• Immediate effect: sodium salt and potassium salt, e.g., Penicillin G-sodium. • Delayed effect: benzathine salt: Benzylpenicillin + Benzathine: Extencilline (ND)
• Semi-delayed effect: procaine salt: Procaine penicillin: Procilline (ND)
2) Penicillin V: Phenoxymethylpenicillin: Oracilline (ND)
3) Phenethacillin: Bronchocillin (ND)

Pharmacological properties and indications:

Penicillin G: Benzylpenicillin

- **Pharmacokinetics**

Penicillin G is not absorbed orally. In fact, it is rapidly degraded by hydrolysis in the acidic stomach before even reaching the general circulation, hence a Very low oral bioavailability (< 30%). Therefore, penicillin G is not suitable for administration by the oral route.

Penicillin G is completely absorbed via the parenteral route. Absorption varies depending on the... chemical form (alkaline salt or organic salt).

Aqueous solutions of **alkali salts** of penicillin G (example: sodium benzylpenicillin), very Water-soluble, they diffuse easily, allowing for rapid absorption of the antibiotic. Indeed, Maximum plasma concentrations are reached 30 minutes after administration. thus conferring immediate action.

Organic salts (procaine and benzathine salts) release penicillin G slowly and exert a prolonged effect over time. This is referred to as a semi-delay or delayed effect.

The semi-delayed action of procaine salt lasts for approximately 12 hours. And most importantly, it eliminates the action painful penicillin injections at the injection site. This allows for longer intervals between injections. immediate-effect sodium salt.

Benzathine salt (benzathine benzylpenicillin) releases penicillin G in an even more slow. This release continues 2 to 3 weeks after systemic administration.

However, blood concentrations rarely reach minimum inhibitory concentrations. (MIC). This salt is used in veterinary medicine only topically for the prevention against certain bacterial diseases. It is sometimes associated with procaine salt.

In practice, a combination of alkaline salt and organic salt is used (combination of Sodium benzylpenicillate and procaine. Combination of benzathine benzylpenicillate and procaine), thus enabling effective penicillinemia to be achieved from the first hour and maintained at least for 24 hours.

Penicillin G is distributed primarily extracellularly. Its plasma half-life is short (1 to 2 hours).

Penicillin G is eliminated primarily via the kidneys, with 80% being eliminated unchanged. by active tubular secretion. This explains its use in therapy, particularly in the treatment of urinary tract infections.

- **Indications**

Penicillin G is used as monotherapy for:

ENT infections (streptococcal tonsillitis)

Pneumococcal or anaerobic pneumonia

meningococcal or pneumococcal meningitis

and urinary tract infections.

- **Adverse or toxic effects**

In the treated animal, certain adverse effects can be observed:

- An imbalance of the cecal flora and allergic reactions

1) The administration of penicillin G by intramuscular or subcutaneous route leads to the

Guinea pigs and **hamsters** experience an imbalance in their cecal flora (Gram-positive flora), which is the cause of a

Dysenteriform enterocolitis fatal within a few days in these species (Contraindicated).

2) Allergic reactions are rare in animals. They are known in cattle, equines and

In dogs, however, allergic reactions are common and can be severe.

These allergic reactions manifest as hives, itching, and anaphylactic shock with collapse.

cardiovascular and acute pulmonary edema.

This allergy is due to the inactivation (metabolization) of penicillins by the body.

Note: Horses are particularly sensitive to procaine, which is present in the composition of certain

penicillin-based preparations (penicillin-procaine).

**The presence of traces of penicillin G in milk leads to adverse effects in the industries

Fermented dairy products (yogurt, cheese, etc.). Penicillin residues may be present.

Food products of animal origin pose a certain danger to the consumer.

the risk of a hypersensitivity reaction occurring in a previously sensitized individual is

theoretically possible.

The dose that triggers the allergy = 15 IU Penicillin G.

Penicillin V

A molecule stable in an acidic gastric environment, used orally. Its bioavailability is 50 to

60% of the administered dose. Its elimination is urinary.

Penicillins of groups G and V have a narrow spectrum. They are primarily active on

Gram-positive bacteria, in particular, affect cocci (streptococci) and Gram-positive bacilli. The majority

Gram-negative bacteria are naturally resistant, with the exception of *Pasteurella multocida* and

Fusobacterium necrophorum by secretion of ÿ lactamases.

Phenethacillin:

-Antibiotics with a particular affinity for bronchopulmonary tissue (indicated in conditions)

respiratory).

- Found at high levels in milk in active form (indicated in mastitis).

2) Narrow-spectrum penicillins resistant to ÿ-lactamases

The molecules in this group that are stable in acidic media are:

1) M-type penicillins: Methicillin (Peni-staph: ND) and **Nafcillin** (parenteral preparations), **Isoxazolyl penicillin: e.g. ,** Oxacillin: BRISTOPEN (ND) and Cloxacillin: ORBENINE
2) Flucloxacillin

Group M penicillins are less active against Gram-positive bacteria. Their spectrum is limited to staphylococci producing ÿ-lactamases.

All penicillins in this group generally have two advantages over penicillin G: they are active orally and resistant to staphylococcal beta-lactamases. This explains their of particular interest in the treatment of deep cutaneous staphylococcal infections in dogs, The treatment is necessarily long (3 weeks to 1 month minimum), hence the importance of administration oral and at high doses (40mg/kg).

Group M penicillins (Oxacillin and Cloxacillin) are also indicated in the treatment local streptococcal and staphylococcal mastitis in dairy cows, in infections with susceptible staphylococci, particularly in respiratory, renal, urogenital, and bone infections, joint and endocarditis.

3) Broad-spectrum penicillins sensitive to beta-lactamases

Penicillins of this class generally have three advantages over penicillin G: they are active When taken orally, they exhibit a broad spectrum of activity, being active against both bacteria and Gram (+) and Gram (-), finally they resist the ÿ-lactamases secreted by Gram(-) bacteria.

This group includes:

Aminopenicillins: penicillin A •
Ampicillin: Peni A, Totapen (ND..) •
Amoxicillin (or Hetacillin): Amoxil, Clamoxyl (ND..)

These two antibiotics are used successfully in small clinics for carnivores and in pediatrics. They possess a significant enterohepatic circulation (biliary elimination), which explains their persistence. quite long in the body and consequently, their digestive toxicity has been demonstrated in some rodents.

Group A penicillins are indicated for infections caused by Gram-positive bacteria. and Gram-negative bacteria, particularly in the general treatment of septicemia and digestive infections, Respiratory and urinary (colibacillosis) and cutaneous (with association with clavulanic acid) infections. They are also indicated in the local treatment of mastitis due to Gram+ and Gram- bacteria.

Amoxicillin, which is well absorbed through the digestive tract with or without food, is the most prescribed antibiotic in this group.

Note: -
Some delayed-release formulations such as long-acting Amoxicillin allow for administrations to be spaced every 36 to 48 hours; they have the disadvantage of not always being well tolerated at the injection site - Group A and M penicillins are
used prophylactically in industrial calf and poultry farming for the prevention of certain bacterial diseases caused by susceptible organisms.

Attention!
Penicillins A are strictly contraindicated in rabbits and, more generally, in...
lagomorphs, as well as guinea pigs and hamsters, due to a risk of fatal dysenteriform enterocolitis.

4) Broad-spectrum penicillins sensitive to beta-lactamases with extended spectra:

Examples of this class include:

1. **Carboxypenicillins:** Carbenicillin, Ticarcillin 2.
Ureidopenicillins: Azlocillin, Mezlocillin.
3. **Piperacillin penicillins:** Piperacillin

The spectrum of action of these derivatives, Ticarcillin, Mezlocillin and Piperacillin, extends to several Gram-negative bacilli: *Pseudomonas aeruginosa (pyocyanic), Proteus, Enterobacter.* They are presented only in injectable form via intravenous route and are used in hospital settings.

These compounds are reserved for human medicine.

5) Broad-spectrum penicillins protected against beta-lactamases (potentiated penicillins)

Examples of this new chemotherapeutic approach include Amoxicillin or the Ticarcillin combined with clavulanic acid, ampicillin combined with Sulbactum, and the Piperacillin combined with Tazobactam.

1) Amoxicillin or ticarcillin + clavulanic acid: • Amoxicillin + clavulanic acid (AUGMENTIN®, SYNULOX ND) • Ticarcillin + clavulanic acid (CLAVENTIN ND)
2) Ampicillin + Sulbactum
3) Piperacillin + Tazobactum (Tazocillin ND): very rarely used

Clavulanic acid, sulbactum, and tazobactum are ÿ-lactamase inhibitors.
staphylococcals. These molecules, with a structure similar to ÿ-lactams, bind irreversibly to the catalytic site of the enzyme "ÿ-lactamase", preventing its subsequent action on the antibiotic (ÿ-lactam) co-administered. This combination, however, remains the cause of a number of failures.
therapeutics in the treatment of deep cutaneous staphylococcal infections in dogs.

5.1.2. Cephalosporins

This subclass of beta-lactam is obtained from cultures of *Cephalosporium acremonium* in 1948.

Pharmacological properties:

These are acidic substances with bactericidal antibiotic activity.

broad spectrum (Gram (+) and (-)) with lower intensity of action than penicillins.

Antibiotics are used in penicillin-resistant infections and in allergic individuals.

provide excellent antibiotic coverage.

Note:
Cephalosporins should be considered second-line antibiotics in veterinary medicine. They should only be used in specific cases after more conventional antibiotic therapy has failed.

Classification and main indications

Cephalosporins are classified into 4 generations according to their chronology of appearance in therapeutic activity corresponding to a specific antibacterial activity:

First generation (especially Gram-positive): •
Cephalexin (Rilexine ND) •
Cefapirine (Cefatar ND) • Cefazolin
(Cefovet ND)

Second generation (spectrum extended to include Gram-negative bacteria):
• Cefalonium (Cepravin ND) •
Cefuroxime

Third generation (spectrum further broadened towards Gram-negative bacteria): • Ceftiofur (Exenel
ND) • Cefoperazone (Pathozone ND)

Fourth generation (Gram- and Gram-positive): •
Cefquinome (Cobactan ND)

Cephalexin, Ceftiofur, and Cefquinome are indicated for the treatment of septicemia,
General infections: respiratory, urinary, bone, skin (cutaneous staphylococcal infections),
joint.

The most commonly used molecule in veterinary medicine for domestic carnivores is the
Cephalexin.

Cephalexin, Cefazolin, Cefoperazone, Cefalonium, and Cefquinome are indicated for the
local treatment of mastitis caused by Gram+ and Gram- susceptible bacteria.

Pharmacokinetics

The gastrointestinal absorption of most cephalosporins is poor; therefore, the parenteral route is preferred.
is often preferred. With the exception of Cephalexin, which has rapid gastrointestinal absorption and
complete.

Cephalosporins are widely distributed throughout the body. They are distributed at the tissue level.
richly vascularized (lungs, liver, etc.). Therefore, they can be used in
numerous diseases. However, they do not cross the blood-brain barrier.

Cephalosporins undergo little biotransformation. Their elimination is primarily renal.

5.2. Antibiotics acting at the cell membrane level: Polypeptides (polymyxins)

General characteristics and main molecules

Polymyxins are narrow-spectrum bactericidal antibiotics; they interact strongly with the phospholipids of the bacterial cell membrane and radically disrupt its permeability and its function.

However, they are currently experiencing a resurgence of interest for the treatment of infections. nosocomial infections with multi-resistant germs, because they remain active against strains having developed resistance mechanisms to conventional classes of antibiotics.

Main molecules:

• Polymyxin E (Colistin) •
Polymyxin B (for topical use only)

These molecules are generally poorly tolerated, both in humans and animals and reserved for local use (cutaneous, ophthalmic or ENT: caution with perforated eardrum).

5.3. Antibiotics acting on protein synthesis

5.3.1. Aminoglycoside or Amino-glucoside Family

General characteristics

Aminoglycosides possess bactericidal antibiotic activity.

The main strength of their spectrum of action lies in their action against Gram (-) bacteria and most Aerobic bacteria.

They require oxygen to pass through the bacterial cell wall => ineffective on anaerobes.

Aminoglycosides form a good combination with ÿ-lactams (e.g., ÿ-lactam + aminoglycoside (Dihydrostreptomycin or Kanamycin), it is synergistic and bactericidal: the ÿ-Lactam alters the bacterial cell wall, allowing the aminoglycoside to penetrate and then lyse. of the bacteria.

Pharmacokinetics:

These are basic, chemically stable, highly water-soluble molecules that cross very They damage biological membranes and are not absorbed orally (use by parenteral IM).

Rapid and extensive diffusion in biological fluids and tissues, low diffusion in CSF except in cases of meningitis.

They are not bioprocessed. Their elimination is primarily renal (half-life: 2 hours, in the absence of renal insufficiency) in active form.

Side effects:

Nephrotoxicity except for GENTAMYCIN: to be avoided in patients with renal insufficiency.

Ototoxicity, especially in cases of prolonged treatment and at high doses.

Neuromuscular blockage, allergy.

Main molecules

Streptomycin (numerous formulations, natural origin)
Dihydrostreptomycin (numerous specialties)
Gentamicin (Forticine*, natural origin)
Kanamycin (Kanacillin *)
Neomycin (numerous specialties)
Spectinomycin (Spectam *)
Apramycin (Apramycin *, Apralan *)
Framycetine (Bieskadog*)

1) Streptomycin

Used in infections caused by Staphylococci, Streptococci, Mycoplasmas, and Mycobacteria

Widely used in the treatment of streptococcal mastitis

Intrauterine administration for the treatment of endometritis is common

Not recommended for certain species: Cat (kidney toxicity) - Turkey - Pigeon

2) Dihydrostreptomycin – DHS

It is a simple derivative of Streptomycin, used particularly in beekeeping against Bacillus and Streptococcus.

3) Gentamicin

This aminoglycoside is the best tolerated by the kidneys despite the active elimination of the molecule: exploited in urinary tract infections in all species.

In livestock it is used during infections with Gram+, mycoplasmas, *Pseudomonas.*

Like Neomycin and Polymyxin, Gentamicin is a weak basic antibiotic and

Being water-soluble and unable to cross the membrane barrier, it therefore remains concentrated at application site (ocular, auricular, etc.) where their activity can be expressed without loss by resorption (local action on pathogenic flora and superinfections (G- *pseudomonas)).*

4) Neomycin

Used in infections of the gastrointestinal tract (no absorption at this level: local activity).

Toxic to the kidneys (no parenteral forms).

Reserved for the treatment of local conditions (enteritis, otitis, superficial dermatitis, conjunctivitis, mastitis) caused by susceptible germs, due to their excessive general toxicity.

5) Kanamycin

It is a perfect aminoside for use in combination with beta-lactams.

It has a good spectrum and good tolerance in all species.

Used against infections caused by staphylococci, streptococci, and Pseudomonas (except *aeruginosa).*

(septicemia, mastitis, respiratory and urinary tract infections).

6) Spectimiomycin

It is an aminoglycoside related to aminoglycosides, characterized by a bacteriostatic action and low toxicity, widely used in gastrointestinal and respiratory pathology in poultry.

It is used in livestock for mycoplasma and Gram- infections.

5.3.2. Tetracycline Family: T4Cy

General characteristics

T4Cy antibiotics are widely used in veterinary medicine; they are antibiotics of choice for... carnivores and ruminants.

Their antibacterial activity is very high; they concentrate strongly in the cell bacterial (good action on germs with intracellular localization).

T4Cy antibiotics are broad-spectrum bacteriostatic antibiotics, including most of the Gram-positive and Gram-negative bacteria encountered in veterinary medicine, as well as mycoplasmas, chlamydia and rickettsia.

Main molecules

First-generation T4Cy (Natural Tetracyclines):
- Tetracycline
- Oxytetracycline (Terramycin*, Tenaline*, Duphacycile*)
- Chlortetracycline (Aureomycin*): for external use only

Second-generation T4Cy (Semi-synthetic Tetracycline):
- Doxycycline (Ronaxan *)

Pharmacokinetics:

Absorption: incomplete digestive absorption (chelating molecules of cations, in particular dietary calcium (meat, milk) which forms compounds with tetracyclines insoluble, non-absorbable). Absorption improved by Doxycycline.

Diffusion: Lipid-soluble molecules diffuse well in extracellular environments and intracellular except in the CNS, CSF and joints.

Elimination: enterohepatic circulation, fecal, biliary and milk elimination.

Instructions:

General uses: septicemia, pulmonary and digestive infections.

Local indications: ocular, auricular, dermatological, metritis and mastitis in cows,
Foot infections.
Specific diseases: Leptospirosis, Mycoplasmosis, Turkey Histomoniasis (doxycycline)
Widely used in industrial livestock farming (calves, poultry) as a preventative or curative measure.
Usual dose: 10-20 mg/kg

Side effects and contraindications:

Tetracyclines chelate calcium ions in bones and teeth (bone malformation and dental: weakening - abnormal wear).
Tetracyclines are contraindicated in carnivores during the last three weeks gestation under risk of discoloration and dental hypoplasia of the deciduous teeth, thus than in kittens and puppies during the first few months due to the risk of affecting the adult teeth. This dental toxicity would be non-existent with doxycycline.
Their digestive absorption is incomplete; some remains in the intestine and can cause Changes in the gut flora (digestive problems). Therefore, they should be avoided in Species with fragile cecal flora (Horse, Rabbit): Fatal dysenteric enterocolitis (horse).
A nephrotoxic molecule, especially in older animals.
Due to their oily nature, their administration by IV route is prohibited (risk of Thrombophlebitis at the injection site). IM or S/C injection is painful and may even cause necrosis. (local intolerances).

5.3.3. Macrolide Family

General characteristics

Bacteriostatic antibiotics, with a narrow spectrum primarily directed against Gram-positive bacteria, intracellular germs (toxoplasmosis, typical mycobacteria) and, for some compounds with regard to Pasteurella.
They replace penicillins in cases of allergy. They are antibiotics with very low toxicity. exploited in prolonged treatments.
Macrolides are a first-line treatment for respiratory infections.
(caused by *Legionella, Mycoplasma* and *Chlamydia spp)* and digestive, pharyngitis Streptococci in patients allergic to ÿ-lactams, chlamydia, infections of skin and soft tissues.

Pharmacokinetics:

Macrolides are lipid-soluble, basic compounds. Their gastrointestinal absorption is rapid and complete (with the exception of erythromycin, the most unstable, which is partially (broken down in the stomach)

Significant intracellular and extracellular distribution except in the CSF, passage placental.

Hepatic metabolism (possibility of hepatotoxicity, but rare)

Fecal and biliary elimination in active form, at high concentrations in secretions acids (milk of all species, urine and saliva of carnivores).

****NB: Related to macrolides:** Antibiotics related to strict macrolides by their activity antibacterial, and not by their composition.

Main molecules

Strict macrolides: •

Erythromycin (base, estocelate, thiocyanate) • Spiramycin (Suanovil*, Rovamycin) • Tylosin (Tylan*) • Josamycin (Alpacin*) • Tilmicosin (Micotil*)

Related to macrolides: •

Staphylomycin

• Rifampicin (Rifaximin) • Lincosamides:

Clindamycin (Antirobe *)
Lyncomycin (Lincocine *)
Pirlymicin (Pirsue*) •

Pleuromutilins: Tiamulin (Cevamuline*): rabbit enterocolitis • Others: Novobiocin, Fustidic acid

1) Tylosin

This is the veterinary-specific macrolide :

It has good diffusion in all tissues (even in eggs)

The molecule is relatively non-toxic.

For cattle: treatment of pneumonia, interdigital whitlow, mastitis, metritis, contagious pneumonia and necrobacillosis of calves.

For sheep and goats: treatment of Gram-positive metritis, contagious agalactia (acute forms) and acute), caprine pleuropneumonia.

Administer by IM or slow IV injection. Subcutaneous injection may cause painful irritation. with a local reaction/edema.

Do not administer to equines (injection is fatal).

2) Spiramycin

It is very slightly toxic and is used:

In animals

In all species and as a feed additive in livestock.

In humans

Used in cases of Toxoplasmosis in pregnant women and as prophylaxis against meningitis.

3) Erythromycin

Good dissemination in the tutorial: Oral forms have a good general effect

Good diffusion into the mammary parenchyma: Systemic treatment of the breast

4) Tilmicosin

It is used to treat pneumonia in sheep, pigs and cattle.

Risks of cardiac toxicity (dog, horse, goat, pig, primates)

5) Staphylomycin

ATB is widely used in topical application and intramammary injections for mastitis.

staphylococcal.

6) Rifampicin

A molecule used in the treatment of tuberculosis in humans, but this use is prohibited by the Animal legislation.

5.3.4. Family of Phoenicolates

Main molecules

- Chloramphenicol: Broad spectrum including against Chlamydia and Rickettsia: Cysticat*, Sogeval* (withdrawn from the market in 1994 for livestock) -Thiamphenicol: local use (Negerol* aerosol) -Florfenicol (Nuflor*)

In veterinary medicine, **Chloramphenicol** has both advantages and disadvantages:

Benefits :

Broad spectrum, low cost and low toxicity

Very good diffusion in all tissues and especially in the CSF.

It is distributed throughout the body via the blood and lymph, allowing it to reach the microorganisms that concentrate in the lymph nodes.

Disadvantages:

High sensitivity in cats

Administration prohibited in kittens: Disruption of hematopoiesis

In humans: Chloramphenicol has very high toxicity; it is known to be hematopotoxic.

It disrupts the blood count and causes severe anemia; in humans, it is reserved only for

cases of severe meningitis.

Practical conclusion:
Due to its broad spectrum, Chloramphenicol is an excellent antibiotic for veterinary use, but its potential toxicity in humans limits its use in slaughter animals because of the residual problem in meat, milk and eggs (Chloramphenicol residues resist even cooking temperature).

5.4. Antibiotics inhibiting nucleic acid synthesis

These molecules generally have a narrow spectrum, low toxicity, rapid pharmacokinetics and elimination is primarily renal.

5.4.1. Quinolone Family

General characteristics and main molecules:

• An interesting family of antibiotics for veterinarians:

Bactericidal antibiotics (ATB)

Broad antibacterial spectrum (G+ and G-)

Wide distribution throughout the body

Rarity of bacterial resistance

Various indications

Low toxicity

4 Generations: According to

– Their appearance on the market
– The strength of their antibacterial activity –
The improvement in pharmacokinetics **1.**

First-generation quinolones:

• Nalidixic acid: NEGRAM® (Human medicine) • Oxolinic acid: OXOMID®

2. Second-generation quinolones:

• Flumequine •
Pipemidic acid **3. Third-generation quinolones:**

• Enrofloxacin: BAYTRIL
• Marbofloxacin:MARBOCYL®
• Difloxacin •
Orbifloxacin ORBAX®
• Ibafloxacin *IBAFLIN*®

4. Fourth generation quinolones;

• Pradofloxacin VERAFLOX®

• Several derivatives have been synthesized (approximately 1000 derivatives): Artificial compounds: Total synthesis from Quinolone. • They are widely used in human medicine, particularly for urinary tract infections.

The presence of contiguous oxygenated functions gives rise to **chelating properties that are not possible only with certain divalent cations** (= bivalents) such as magnesium and copper => Formation of insoluble chelates.

Pharmacokinetics

• **Resorption**

Per os:

Fast and thorough in the small intestine

Bioavailability: 90–100%

Decrease in the presence of divalent cations in the digestive tract:

- Food intake
- Antacid medications

Administration on an empty stomach / outside of mealtimes

Parenteral (IM) route:

Quick and thorough, but the injection is irritating.

• **Distribution**

Low plasma protein binding (<50%)

1st Generation

Weak acid

Extracellular distribution

Tissues and organs with rich blood vessels

2nd, 3rd Generation

Amphoteric character

Distribution: extracellular and intracellular

Multiple indications

• **Biotransformations:**

Quinolones undergo relatively little biotransformation in the body

• **Disposal**

Urinary tract ++ : Glomerular filtration and active tubular secretion => use for the Treatment of urinary tract infections

- First-generation quinolones (weak acids) => Acidic urine of carnivores (Passive tubular reabsorption and slow elimination)

Biliary tract (2nd and 3rd generation quinolones)

Rapid elimination without problems of residue accumulation in animal production

Milk: Low: (Pay attention to waiting time) for: 0.2% Enrofloxacin and 1% Marbofloxacin

Therapeutic uses

First generation quinolones (oxolinic acid):

• **Treatment of bacterial infections**

Urinals

Digestive issues, e.g., neonatal diarrhea in calves and lambs

Infectious diseases of fish: Furunculosis, vibriosis, yersiniosis…etc

Avian colibacillosis

2nd and 3rd generation quinolones

• **Treatment of general bacterial infections:**

Septicemia

Bronchopulmonary

Avian mycoplasmas (Enrofloxacin)

Cutaneous: Deep staphylococcal pyoderma (Marbofloxacin)

Osteo-articular

Treatment of localized bacterial infections : Mastitis, Metritis, Meningitis, Conjunctivitis

Side effects

\+

a. Local intolerances at the injection site (First generation quinolones)

Inflammatory reaction – Abscess

Horse: the most sensitive species

c. Neuromuscular disorders:

The most serious accidents

In cases of overdose in calves: Poor dilution of medicated premixes => Convulsions

Follow the dosage instructions.

b. Joint damage:

In case of prolonged treatment / Overdose

Arthropathies: degeneration of articular cartilage

Beware of the young animal

d. Retinal damage:

\-

In cases of overdose in **cats, the dose is 5 times** the therapeutic dose (Danofloxacin).

5.4.2. Sulfonamide or Sulfonamide Family

General characteristics:

Sulfonamides are bacteriostatic derivatives of para-aminobenzoic acid with broad-spectrum effects.

antibacterial spectrum (G+ and G- bacteria).

They act by disrupting Folic Acid, which is necessary for the synthesis of nucleic acids.

of the microorganism.

Sulfonamides can be administered orally, intravenously, intramuscularly, intraperitoneally, or locally, depending on the galenic preparation.

Pharmacokinetics:

Good digestive absorption.

Lipid-soluble and acidic substances have good tissue diffusion and are found in the CSF.

Hepatic metabolism by acetylation.

Elimination is primarily urinary.

Instructions:

These are low-toxicity antibiotics, used in minor infections and

acute systemic or local infections (digestive, urinary, genital, respiratory,

toxoplasmosis, Listeriosis, bites, interdigital abscesses, skin, eye, ear).

They also possess excellent coccidiostatic action and are used in pathology.

avian as **anticoccidials.**

Main molecules:

Short-acting sulfonamides (3 to 6 hours):

- Sulfamethizole (with urinary action)
- Sulfathiazole (for local application: in wounds)
- Sulfadimidine (sulfadimerazine): anticoccidial

Semi-delayed sulfonamides (6 to 10 hours):

- Sulfamethoxazole (+ Trimethoprim: Cotrimoxazole BACTRM (ND))
- Sulfadiazine (for local action: in burns)
- Sulfalinamide
- Sulfapyridine

Delayed sulfonamides (10 to 24 hours):

- Sulfadimethoxine: anticoccidial
- Sulfamethoxypyridazine
- Sulfadoxine

Sulfonamides with digestive action (are not absorbed via the digestive tract):

- Sulfaguanidine: anticoccidial
- Phthalisulfathiazole

5.4.3. Diaminopyrimidines (Trimethoprim, Pyrimethamine):

Trimethoprim: related to sulfonamides, it is much more of an anticoccidial; it constitutes a excellent combination with Sulfamethoxazole to give Co-Trimoxazole, drug of choice in avian pathology.

**** On the other hand, the combination of trimethoprim and sulfonamides is not always well tolerated. in cats, in which it can cause anorexia, leukopenia and at usual doses anemia.

Pyrimethamine: combined with sulfonamides to treat protozoal infections such as Leishmaniasis or Toxoplasmosis.

5.4.4. Nitrofuran Family

General characteristics and main molecules:

Mixed activity: broad-spectrum antibacterial (bactericidal) (G+ and G-) and antiparasitic Antiprotozoal agents: Trichomonas digestive tract of poultry, Histomonas liver of turkeys, Coccidia (Nitrofural, Furazolidone).

Main molecules:

- **Furfurylidene series**
  - Nitrofurazone (Nitrofural)
  - Furazolidone
  - Furaltadone
  - Nitrofurantoin
  - Nifursol •

Vinyl Series

- Nifurprinol

Pharmacokinetics

- **Resorption:**

Overall poor absorption orally

Use for local infections of the TD

Furaltadone and Nitrofurantoin: Satisfactory gastrointestinal absorption

No injectable presentations

Their low solubility explains their general difficulty in crossing membranes. biological

- Few biotransformations in the body
- **Disposal:**

Nitrofurans used orally are mostly eliminated directly by digestive tract.

Nitrofurantoin, due to its acidic nature, is primarily eliminated via renal by active tubular secretion

Indications

Nifurprinol was widely used in the treatment of infectious fish diseases

Furazolidone was indicated only for the local treatment of digestive infections.

Nifursol is authorized as an antibiotic supplement for the prevention of Histomoniasis of turkey

Nitrofurantoin is used in carnivores orally (tablets) in the treatment urinary tract infections

Note: **Nifuroxazide (Ercefuryl®)** is a substance belonging to the nitrofuran family. It is used as an intestinal antiseptic.

Contraindications

Nitrofurans are all prohibited in livestock (mutagenic potential and carcinogenic)

Before their ban in livestock, nitrofurans were contraindicated. absolutely in waterfowl due to their particular sensitivity

Their combination with chloramphenicol is strongly discouraged due to the risk of potentiation of bone marrow blood toxicity

5.4.5. Nitroimidazole derivatives

General characteristics and main molecules:

Mixed activity: antibacterial (narrow-spectrum bactericidal antibiotic (aerobic and Gram-positive anaerobes) and antiparasitic (Trichomonas in poultry and Histomonas in turkeys)

Nitroimidazoles are **all prohibited for therapeutic use in animals. production/residues** in food and the risk of teratogenic effects and carcinogens observed in humans. For this reason, they are prohibited in women during the pregnancy and breastfeeding and are only used for short-term treatment.

They are authorized for therapeutic use only in domestic carnivores and the hobby pigeon in tablet or oral powder form

Main molecules used in veterinary practice:

• **Metronidazole :** oral infections in pigeons (Metronidazole + Spiramycin) • **Carnidazole :** trichomoniasis in pigeons • Ronidazole

• Dimetridazole

More fat-soluble derivatives (Dimetridazole) +++

Use in combination with spiramycin

Concentration in acidic secretions

Metronidazole is found in high concentrations in the saliva of carnivores.

Elimination: renal and biliary

4.5. Antibiotics incorporated into animal feed as feed additives

These antibiotics are both bactericidal, narrow-spectrum (G+ bacteria), and antibacterial. protozoa (anticoccidials), used exclusively as food additives as factors of growth and anticoccidials.

Main molecules : Bacitracin,
Monensin, Lasalocide, Narasin; Salinomycin, Maduramycin;
Avilamycin, Quinoxaline N-dioxides ;
Avoparcine, Flavophospholipol, Efrotomycin

Advantages of antibiotic additives in veterinary practice:

In veterinary practice, antibiotics are introduced prophylactically as feed additives.
This practice is common, authorized by regulations, especially in intensive poultry farming (the Additives improve bird growth while preventing infections, especially diarrhea).
Antibiotics are incorporated in very low doses (10g/kg) and it is made from antibiotics not used in the treatments in both humans and animals, for this reason the risk of antibiotic resistance is practically zero.
However, this practice is prohibited in ruminants (disruption of the rumen flora), the horse and the rabbit (disruption of the cecal flora).

The 4 main dangers to humans associated with the use of antibiotics in veterinary medicine:

1. Decreased sensitivity or resistance of zoonotic pathogens passing from animals to humans either directly or via the food chain.

2. Development of resistance in commensal flora and transmission of resistance genes to humans via the food chain or the environment: **the major danger**

3. Release of active antibiotics into the environment and all its consequences. 4. Antibiotic residues in food: **a minor hazard .**

6. Use of antibiotics in animals

Antibiotics can be used for various purposes:

For therapeutic purposes: to achieve the cure of clinically ill animals and prevent the mortality.

Maintaining animal production: milk, meat, eggs

Improving animal growth and performance (feed additives).

Prevent the transmission of pathogens to other animals or even to humans.

Practicing Metaphylaxis, Antibiotic Prophylaxis and Antibiotic Prevention

Metaphylaxis

Metaphylaxis, sometimes called prevention in an infected environment, consists of treating all animals of a group (poultry, calves) when a certain proportion of them (generally 10%) has exhibited clinical signs of bacterial infection.

Antibiotic prophylaxis

Antibiotic prophylaxis is used during critical periods in the lives of animals in livestock farming. that is, when a risk factor is present, which is very often associated with development infections. These include periods associated with stress, such as during travel, grouping of animals from various farms or from weaning, but also during dry period dairy cows.

Antibiotic prevention (cover antibiotic therapy):

To prevent bacterial infections, e.g., surgery, trauma, postpartum: low risk precise, poorly identified, often debatable, risk of superinfections.

7. Criteria for choosing an antibiotic

The choice of an antibiotic should be made based on the expected effectiveness of the treatment and the need to minimize the selection for antibiotic resistance.

This choice is made based on:

From **the veterinarian's clinical experience** and knowledge of the specificities of the production.

Epidemiological history **of the livestock unit,** with regard to more particularly the antimicrobial susceptibility-resistance profiles of pathogens in cause.

Spectrum of **antimicrobial activity** against the pathogens considered and of Targeting of specific microorganisms.

From the **availability of antibiotics to the site of infection.**

** But the ATB must be determined based on the results of microbiological analyses.

8. Rules for the use of antibiotics

Three golden rules govern antibiotic therapy:

1) Act very quickly
2) Hit hard
3) Maintain the treatments for a sufficient amount of time

1) Act very quickly

It is best to intervene as early as possible so that the bacterial population does not proliferate (The earlier the

The lower the number of bacteria, the more quickly and easily the antibiotic can destroy them.

2) Hit hard

While remaining below the toxic dose, this is with the aim of destroying the germs and avoiding

the emergence of microbial resistance.

For this reason, it is often administered at the beginning of treatment, during the first 12 or 24 hours.

an "attack dose" approximately double the maintenance dose.

The values provided by pharmaceutical companies are only indicative doses.

treatments must be adapted according to the presumed sensitivity of the germ, the location of the infection, and the condition of the

immune defenses of animals, and finally the general and local tolerance of the antibiotic.

3) Maintain the treatments for a sufficient amount of time

Even after the appearance of a cure, to ensure total destruction of the germs

microbial and to prevent the reactivation of an incompletely eliminated infection.

A treatment for a general infection easily accessible by antibiotics: average duration 3 to 7 days.
Treatment with a bacteriostatic antibiotic (5 to 7 days) should in principle be longer than with a bactericidal antibiotic (3 to 5 days).
In localized infections that are difficult to reach (cutaneous or bone Staphylococcal infections), treatments are even longer and can last from 15 days to 1 month, or even longer.

Noticed:

Another important rule for antibiotic use can be added: **Target precisely ,** as the use of critical antibiotics must be based on laboratory results demonstrating no
not only their effectiveness on the isolated pathogen responsible for the clinical problems, but also the resistance of this pathogen to other usable antibiotics.

9. Combinations of antibiotics

Antibiotics should be used alone whenever possible; this is the general rule of monotherapy (1

ATB by anti-infective treatment).

In anti-infective therapy, two antibiotics are combined. The main reasons in veterinary medicine are:

To ensure emergency antibiotic coverage, that is, to broaden the spectrum

activity, in the face of an infection with unknown germs during poly-bacterial infections or when

The nature of the germ involved is unknown.

To delay the emergence of antibiotic resistance

In order to seek synergy

In order to limit adverse effects, particularly the toxicity of certain antibiotics in

reducing the doses of each

The combination of antibiotics should be between antibiotics having the same property with regard to their action on germs, that is to say, it is necessary to combine bactericidal antibiotics or antibiotics. bacteriostatic antibiotics. Most of the associations are demonstrated experimentally but especially confirmed by clinical experience.

When antibacterial agents are combined, three types of phenomena can result at the bacteriological level: 1) an ***additive effect,*** also described ***as indifferent,*** **equal** to that produced by the sum of the effects produced 1) by each antibiotic separately; 2) a ***synergistic effect,*** **greater** than that produced by the addition of the effects of each antibiotic separately; 3) an ***antagonism,*** an adverse effect **less** than that produced by the addition of the effects of each antibiotic separately.

Associations should, in principle, remain the exception and in practice never exceed two Antibiotics. Their choice must take into account:

-Bacteriological properties of each antibiotic to avoid antagonism phenomena. The Jawetz laws were enacted in 1953 on these properties (fig 3) (see box).

-Pharmacokinetic characteristics of each antibiotic: it is essential that antibiotics associated have similar pharmacokinetic behaviors to reach the site together of infection.

- Regarding their general or local tolerance: The combination of antibiotics that exert a toxicity to the same organ. Ex: Aminoglycosides and Polymyxins, both nephrotoxic.

- Galenic constraints to avoid potential physicochemical incompatibilities, this is This is particularly true for injectable aqueous solutions of antibiotics. Example: incompatibility chemical interaction of penicillin G with tetracyclines and gentamicin.

Laws of Jawetz 1953 (figure.3)

Bactericidal antibiotics active against growing germs (Beta-lactams) may have an **antagonistic effect** with bacteriostatic antibiotics.

Bactericidal antibiotics active against growing germs (Beta-lactams) most often have a **synergistic or indifferent effect** with bactericidal antibiotics active against germs in the resting phase (aminoglycosides, polymyxins, quinolones).

Bactericidal antibiotics that are active against germs in their resting phase have an **effect indifferent or synergistic** with bacteriostatic antibiotics (tetracyclines, macrolides, lincosamides, sulfonamides).

Bacteriostatic antibiotics usually have an **indifferent effect on each other.**

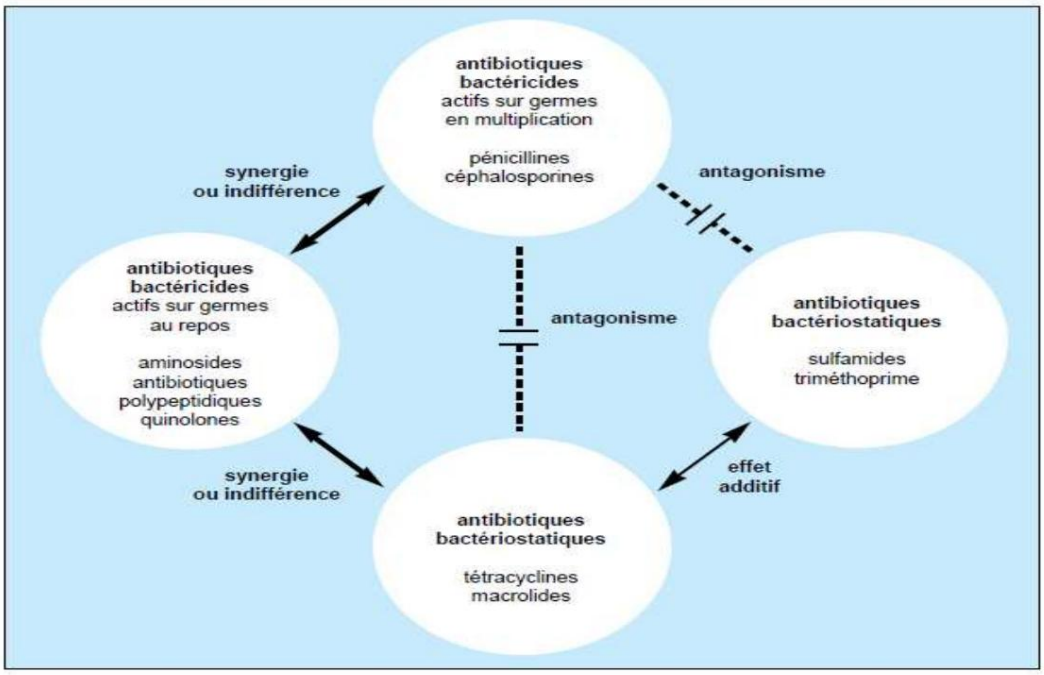


Figure 2: Combinations of antibiotics (Jawetz's laws: 1953)

10. Bacterial antibiotic resistance

10.1. Definition of resistance

The ability of a bacterium to adapt to an environment containing harmful chemical agents
It has been known for a long time. Antibiotic resistance can be defined according to different
viewpoints:

-For the clinician, a bacterial strain is resistant to an antibiotic if the treatment is not
effective (it can no longer be eradicated by antibiotic therapy).

-For the pharmacologist, a bacterial strain is resistant to an antibiotic if the concentrations
The effects at the site of action are below the minimum inhibitory concentration.

-For the microbiologist, a bacterial strain is resistant to an antibiotic if it has a
resistance mechanism increasing the value of the minimum inhibitory concentration.

-For the epidemiologist, a bacterial strain is resistant to an antibiotic if it has a
The minimum inhibitory concentration is significantly different from that of the normal population.
The phenomenon of resistance can be demonstrated, in vitro, by the growth of the germ in the presence of
antibiotic concentrations that can be achieved in therapy.

10.2. Methods of acquiring and transmitting resistance

To resist, the bacterium has developed four main strategies to prevent interaction between
the antibiotic and the bacterial target (figure.3):

1) Jamming
2) Camouflage
3) Shielding
4) Dodge

1) Scrambling : This is the most widespread mechanism in nature. *The bacterium synthesizes a an enzyme that modifies the antibiotic and renders it harmless.* Inactivation can be intracellular, in the This is the case for antibiotics whose targets are cytoplasmic (for example: aminoglycosides). In contrast, Beta-lactams target extracellular sites and must therefore be inactivated before contact with the cell. Appropriate enzymes called beta-lactamases are secreted into the medium of culture (Gram-positive bacteria: staphylococci) or in the periplasmic space (Gram-negative bacteria) and intercept the antibiotic before it even reaches its target.

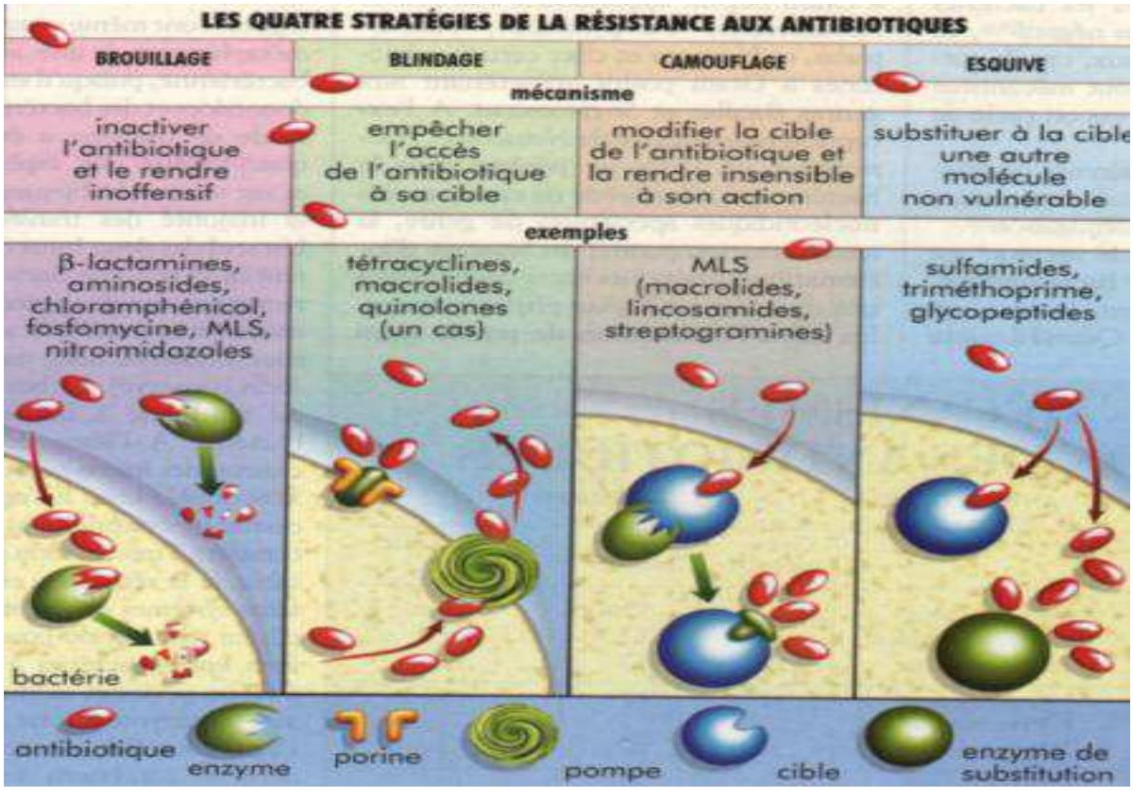


Figure 3: The four strategies of antibiotic resistance.

2) Camouflage : *the bacterium modifies the antibiotic's target to make it insensitive to its action .* This is also the case with macrolide resistance in Gram-positive bacteria. For example, the target of Erythromycin is a 23S ribosomal RNA molecule. In this case, the bacteria synthesize a methylase which This modifies the bacterial ribosomal RNA. The antibiotic no longer has an affinity for the ribosome. amended

3) Shielding : This involves *preventing the antibiotic from reaching its target.* To do this, the bacterium can shrink. or close the channels that make the membrane permeable, or synthesize a membrane pump

(efflux pump) which expels the antibiotic out of the bacteria. Its intracellular concentration will remain insufficient to be toxic. This is the case, for example, with tetracycline resistance.

4) Evasion : *the bacterium substitutes another, non-vulnerable molecule for the target.* It establishes a Metabolic derivation. Two different molecules (one sensitive, the other not) possessing the same functions then coexist in the same bacterium. It is important that the resistant phenotype dominates the sensitive phenotype for resistance to be observed (case of resistance to Sulfonamides, Trimethoprim)

We distinguish between natural or intrinsic resistance and acquired resistance (figure.4).

The first is present in all strains of the species in question and pre-exists the use of antibiotics. It is a characteristic specific to the species and defines the spectrum of activity of antibiotics. On the other hand, acquired resistance is only present in a few strains of a species normally susceptible and appears following the use of antibiotics. Genetically, two mechanisms have been identified:

A. Either a genetic mutation occurs on the bacterial chromosome in the repeated presence of
In this case, antibiotic resistance is transmitted only to offspring.
(vertical transmission).

B. Either the bacterium acquires genetic information from another bacterium already
resistance via plasmids or transposons; in this case, resistance is also transmitted
from one bacterium to another (horizontal transmission) and from one species to another.

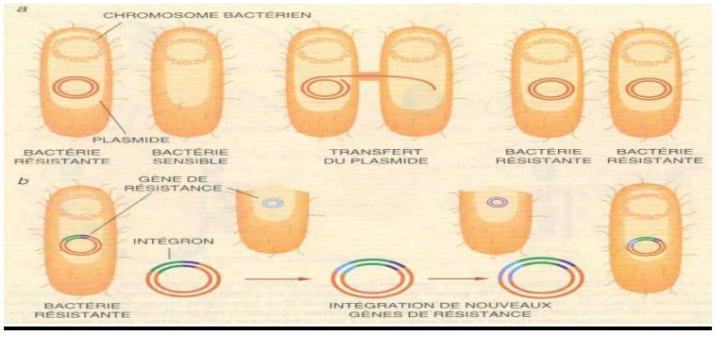


Figure 4: Resistance Mechanisms

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IMPORTANT

La traduction est assurée par Google traduction mais qui na pas encore

été corrigée. La version finale est cours…

KEEP IN MIND

The translation was performed by Google Translate, but it hasn't been corrected yet

We are currently working

on the final version.