

Therapeutic efficacy of erythromycin-based conditioning in respiratory disease in young cattle

Eficacitatea terapeutică a unei condiționări pe bază de eritromicină în afectul respirator la tineretul bovin

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Cuvinte cheie: macrolide, eritromicină, afect respirator, viței.

Abstract

The phenomenon of bacterial antagonism was noted by Pasteur, who observed that a culture of *Bacillus anthracis* is arrested in development in the presence of the pyocene bacillus. Research to find new sources of antibiotics is mainly focused on new drugs that can successfully cope with resistance phenomena. The macrolide group includes large-molecule antibiotics, which include large lactone rings, linked together by dimethylated oses. They are antibiotics with a narrow but deep spectrum of action. The action is bacteriolytic or bactericidal, depending on the dose. It does not influence the normal intestinal flora. In high doses it acts on rickettsiae and treponema. In the present study, investigations were carried out on cattle, knowing the recommendations from the specialized literature and from various manufacturing companies. Therefore, it was preferred to study aspects related to respiratory diseases with recent and older evolution, which appeared in the visited units. The product Erythromycin PF 5% was studied on a total number of $n = 26$ animals. The tests were carried out in two studies: Experiment 1 (on animals that were not treated with antibiotics) and Experiment 2 (on animals that were treated with antibiotics), in two cattle breeding units and one for finishing young cattle, in Alba County in: Câmpeni (F1), Abrud (F2) and Ciuruleasa (F3). In the case of cattle, the preparation is preferable for the categories of young cattle for fattening (6-10 months). The results revealed the efficacy of erythromycin. The analysis of the post-treatment clinical condition confirms the results obtained in the three units and strengthens the conclusion that the product used was effective. The price-quality ratio for the product Erythromycin FP 5% injectable solution makes the product an economical and effective choice, especially for incipient or recently evolving, even associated, bacterial respiratory diseases.

Rezumat

Fenomenul de antagonism bacterian a fost remarcat de Pasteur, care a observat că o cultură de *Bacillus anthracis* este oprită în dezvoltare în prezența bacilului pioceanic. Cercetările pentru a găsi noi surse de antibiotice sunt calate mai ales pe noi medicamente care să facă față cu succes fenomenelor de rezistență. Grupa macrolidelor cuprinde antibiotice cu moleculă mare, care cuprinde inele lactonice mari, legate între ele prin oze dimetilate. Sunt antibiotice cu un spectru îngust de acțiune dar adânc. Acțiunea este bacteriolitică sau bactericidă, în funcție de doză. Nu influențează flora intestinală normală. În doze mari acționează asupra rickettsiilor și treponemelor. În prezentul studiu s-au făcut investigații pe bovine cunoscându-se recomandările din literatura de specialitate și a diverselor firme producătoare. De aceea, s-a preferat studierea unor aspecte legate de afecțiunile respiratorii cu evoluție recentă și mai vechi, care au apărut în unitățile vizitate. Produsul Eritromicină PF 5% a fost studiat pe un număr total de $n = 26$ de animale. Testările au fost efectuate în două studii: Experimentul 1 (pe animale care nu au fost tratate inițial cu antibiotice) și Experimentul 2 (pe animale care au mai fost tratate inițial cu antibiotice), în două unități de creșterea bovinelor și una de finisarea tineretului bovin, din județul Alba din: Câmpeni (F1), Abrud (F2) și Ciuruleasa (F3). În cazul bovinelor, preparatul este preferabil pentru categoriile de tineret bovin la îngrășat (6-10 luni). Rezultatele au relevat eficacitatea eritromicinei. Analiza stării clinice post-tratamente confirmă rezultatele obținute în cele trei unități și întărește concluzia că produsul folosit a fost eficient. Raportul preț-calitate pentru produsul Eritromicină FP 5% soluție injectabilă face ca produsul să fie o alegere economică și eficientă mai ales pentru afecțiunile de tip bacterian respirator incipiente sau cu evoluție recentă, chiar asociate.

1. Introduction

The first active antibiotic, benzylpenicillin, was discovered by Fleming in 1921 as an inhibitor of bacterial growth *in vitro*. Penicillin G was used only later, after Chain and Florey succeeded in 1940 in isolating penicillin in a pure, crystallized form and studying its properties. Research on human subjects was a resounding success and inaugurated the antibiotic era. After this, numerous antibiotics appeared: in 1944 streptomycin, discovered by Waksman; chloramphenicol in 1947; chlortetracycline in 1948; semisynthetic penicillins in 1958; cephalosporins in 1960; fluoroquinolones in 1980, etc. The sources of antibacterial agents are:

- synthetic,
- fungal metabolites (e.g., *Penicillium spp.*, *Streptomyces spp.*),
- bacteria (e.g., *Bacillus spp.*), or
- semisynthetic variants of certain natural products (e.g., the formation of amoxicillin from benzylpenicillin).

The directions for the development of research in the current decade related to antibiotics are increasing potency against highly pathogenic organisms (e.g., *Pseudomonas spp.*) and increasing drug

concentrations at specific sites of action (e.g., joints, the nervous system, etc) [3,5,10,15,16,19].

1.1. Classification of antibiotics into groups

Today, several thousand antibiotic precursors are known, of which over 100 have recognized therapeutic efficacy. [1,3,17,21,23].

According to the spectrum of action, there are antibiotics that are *antimicrobial, antifungal, antiprotozoal, antiviral, and antitumoral*, with the spectrum depending on the types of antibiotics used (Table 1.1.).

- I. **β -Lactams** – extraction-derived penicillins, semisynthetic penicillins, and cephalosporins
- II. **Aminoglycosides** – substances with streptomycin as the prototype
- III. **Macrolides** – substances with erythromycin as the prototype
- IV. **Cyclic polypeptides** – substances with polymyxin B as the prototype
- V. **Tetracycline group** – substances with tetracycline as the prototype
- VI. **Chloramphenicol group** – substances with chloramphenicol as the prototype
- VII. **Synergistins**
- VIII. **Miscellaneous antibiotics** – antibiotics that cannot yet be structurally and chemically classified.

Table 1.1.

Microbial spectrum and the diseases associated with it (Summary)

Genus	Color	Species	Disease	
<i>Actinobacillus</i>	↑ Gram pozitiv ↓	<i>lignieresii</i>	Actinobacillosis	
<i>Actinomyces</i>		<i>bovis</i>	Actinomycosis	
<i>Bacillus</i>		<i>anthracis</i>	Anthrax	
<i>Clostridium</i>		<i>tetani</i>	Tetanus	
<i>Corynebacterium</i>		<i>pyogenes</i>	Abscesses, mastitis	
<i>Erysipelotrix</i>		<i>rhusiopathiae</i>	Erysipelas (swine)	
<i>Listeria</i>		<i>monocytogenes</i>	Listeriosis (sheep)	
<i>Micobacterium</i>		<i>tuberculosis</i>	Tuberculosis	
<i>Peptostreptococcus</i>		<i>indolicus</i>	Abscesses, mastitis	
<i>Staphylococcus</i>		<i>aureus</i>	Abscesses, mastitis	
<i>Streptococcus</i>		<i>uberis</i>	Mastitis	
<i>Bacterioides</i>		↑ Gram negativ ↓	<i>fragilis</i>	Anaerobic abscesses
<i>Bordetella</i>			<i>bronchiseptica</i>	Kennel cough
<i>Brucella</i>			<i>abortus</i>	Brucellosis
<i>Campilobacter</i>	<i>jejuni</i>		Diarrhea (canines)	
<i>Escheria</i>	<i>coli</i>		Diarrhea	
<i>Fusibacterium</i>	<i>necrophorus</i>		Diarrhea (canines)	
<i>Haemophilus</i>	<i>suis</i>		Arthritis, meningitis	
<i>Klebsiella</i>	<i>aerogenes</i>		Mastitis	
<i>Moraxella</i>	<i>bovis</i>		Hemorrhagic ophthalmia	
<i>Pasteurella</i>	<i>haemolytica</i>		Journey fever	
<i>Proteus</i>	<i>mirabilis</i>		Diarrhea	
<i>Pseudomonas</i>	<i>aeruginosa</i>		Otitis	
<i>Rickettsia</i>	<i>bovina</i>		Tick fever	
<i>Salmonella</i>	<i>typhimurium</i>		Salmonellosis	
<i>Treponema</i>	<i>hyodisenteriae</i>			

1.2. Mode of action of antibiotics

It can be: *germistatic*, *germicidal*, *germilytic (bacteriolytic)*. According to the mode of action, antibacterial agents can be divided into four major groups, depending on the disruption of: nucleic acid synthesis, protein synthesis, and cell wall or cell membrane formation. The mode of action depends on the concentration of antibiotics, with internationally recognized expressions established.

However, there is a characteristic of each group, taking into account the moment when it acts on bacteria (during the logarithmic growth phase / slow growth phase). Tables 1.2 and 1.3 present the absorption, distribution, and kinetics of the most important antibiotics in veterinary therapeutics, showing: chemical nature, plasma protein binding rate, half-life, excretion rate, and route of administration..

Table 1.2.

Absorption and distribution of common antibiotics (*Brander and col., 1991*)

Antibiotic	Absorption and Distribution
Penicillins	
Ampicillin	Easily diffusible, partially absorbed orally
Amoxicillin	Well absorbed orally
Benzylpenicillin	Easily diffusible i.m., not orally (destroyed by gastric juice)
Carbenicillin	Not absorbed orally, well distributed after i.v. or i.m. administration
Cloxacillin	Incompletely absorbed orally, well absorbed after i.v. or i.m. administration
Cephalosporins	
Cephalothin	Poorly absorbed orally, must be administered i.v. or i.m.
Cephaloridine	Poorly absorbed orally, must be administered i.v. or i.m.
Cephalexin	Well absorbed orally
Rifamycins	Well absorbed orally, intracellularly active, high blood level after the EH circuit.
Macrolides	
Erythromycin	Oral, variable absorption, lactobionate salt very effective i.v.
Lincosamides	
Lincomycin	Rapid oral and i.m. absorption
Tylosin	Well absorbed orally
Tetracycline	
Tetraciclina	Absorbție incompletă pe cale orală. Nivelurile prelungite se pot obține prin administrările pe cale i.m.
Oxiteraciclina	
Aminoglicozide	
Gentamicin	They are not absorbed orally, the best absorption being obtained through administration
Streptomycin	
Neomicina	

Table 1.3.

Kinetics of some common antibiotics in veterinary medicine (*Brander and col., 1991*)

Antibiotic	Acid/ Base	% Plasmatic coupling	Half-life	% Unchanged excretion	Route of administration
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.
Benzylpenicillin	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.
Cefalosporins					
Cefalotin	Acid	56	0,5 – 1	60 – 90	i.m., i.v.
Cefaloridin	Acid	5	1 - 2	70	i.m., i.v.
Rifamycinel	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					
Tetracyclina	Base	50	10	60	p.o., i.m.
Oxiteracyclina	Base	30	10	70	p.o., i.m.
Aminoglycosides					
Gentamicina	Base	25	2,5	90	i.m., i.v.
Streptomycina	Base	30	2,4	80	p.o., i.m., i.v.

¹ *Minimum Inhibitory Concentration (MIC)* = this gives a quantitative measure of the sensitivity of a bacterium to a particular antibiotic. It is of course a report in vitro, but

reportable to field conditions and is considered the most well-known quantitative method for evaluating the spectrum of an antibiotic. MIC has as its principle the determination of the growth of bacteria at different concentrations of antibiotic.

1.3. Antibiotic resistance

The emergence of antibioretistance is due to the abusive and irrational use of antibiotics. Antibioretistance can be **natural** or **artificial**.

Natural antibiotic resistance is the one that determines the antibacterial spectrum. For example, penicillin is inactive against G-bacteria, which have natural resistance to penicillin.

Acquired antibiotic resistance appears more rapidly or more slowly for all antibiotics.

This also represents the reason why a number of antibiotics that have been discovered, synthesized, extracted, and therapeutically studied are not introduced into clinical use. These are called **reserve antibiotics**.

Resistance can be limited to the specific antibiotic (**non-cross**) or can extend to other antibiotics (**cross-resistance**). Antibiotic resistance can occur through changes in the genotype. Spontaneous or antibiotic-induced mutations can change the bacterial genotype or cause modifications during sexual reproduction, when genetic material is exchanged.

Phages can carry out **transductions** in bacteria, which confer resistance. Phenotypic changes refer especially to the modification or interference of certain enzymes in bacterial metabolism. This includes the induction of hydrolyzing enzymes (penicillinases), the inhibition of bacterial enzymes, or the alteration of metabolic pathways in the bacterial cell [3,18].

1.4. Secondary and toxic effects produced by antibiotics

There are a number of secondary phenomena, **direct** or **indirect**, produced by antibiotics during antibiotic therapy: Some antibiotics from the **aminoglycoside group** act toxicly on the eighth pair of cranial nerves.

Others, such as streptomycin, affect its vestibular branch, causing balance disorders, while others, such as

dihydrostreptomycin, alter the cochlear branch, producing deafness or reduced hearing acuity.

Aminoglycosides also have nephrotoxic effects, causing degenerative processes in renal excretion.

Penicillins, in very high doses, act toxicly on the central nervous system.

Tetracyclines, especially chlortetracycline, act toxicly on the liver, causing degenerative changes in hepatocytes. Tetracyclines accumulate in bones and teeth, leading to their weakening.

Chloramphenicol, in high doses or during prolonged treatments, causes degenerative changes in hematopoietic organs (bone marrow).

A number of antibiotics (penicillin and β -lactams) cause sensitization reactions.

These sensitization reactions can range from local effects, such as maculopapular rashes and eczematous dermatitis, to generalized reactions, including anaphylactic shock, especially with parenteral administration.

Among the indirect phenomena is the bacteriolytic effect of penicillin, which leads to the release of bacterial endotoxins through cell lysis, including the Jarisch-Herxheimer reaction.

Another indirect phenomenon is superinfections. The ecological triangle of **bacteria–fungi–viruses** must be considered, as it increases the risk of fungal and viral infections when antibacterial antibiotics are used.

For example, after prolonged and intensive oral antibiotic treatments, superinfections with fungi (especially *Candida albicans*) can occur.

1.5. About the macrolide group

Erythromycin is extracted from cultures of *Streptomyces erythraea*. It is slightly soluble in water and is hydrolyzed by gastric juice. It is prepared for oral use in enteric-coated tablets. Its spectrum of action is approximately the same as that of penicillin. It is active against G+ bacteria, G+ cocci, and G- bacteria.

The indications are for respiratory diseases caused by infectious illnesses, genitourinary infections, enteritis, etc [4, 6, 9].

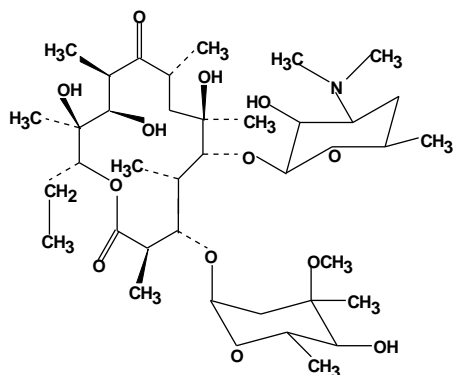


Figure 1.1. Erythromycin A

Erythromycin lactobionate

This form is the salt of lactobionic acid, containing 300 mg of erythromycin base in each vial. It dissolves well in distilled water or in 20–33% glucose solution. It does not dissolve in physiological saline, as it precipitates. It is administered intramuscularly, rarely intravenously. It is used in anthrax, strangles, foal septicemia, mastitis, or suppurative conditions.

The doses are 1–3–5 mg/kg in large animals and 5–8 mg/kg in young and small animals. The doses are repeated every 8–12 hours. In erysipelas, 300 mg (300,000 IU) is administered once together with anti-erysipelas serum at 0.25–0.50 ml/kg.

Erythromycin thiocyanate (Galimycin)

It is available in two forms: an injectable solution for mammals and another for birds. The one for mammals contains 100 mg/ml, while the one for birds contains 50 mg/ml.

It is used especially in diseases caused by organisms from the PPLO group (avian mycoplasmosis, infectious coryza, infectious sinusitis of turkeys). They are used in infections of the respiratory system. Administration is one level teaspoon per 4 liters of water for 5 days (250 g per 200 liters of water) to combat stress, and for the prevention and control of mycoplasmosis in the first days, a double dose is given.

Imported Galimycin is available as a 5% and 10% injectable solution. It is

administered at 24-hour intervals. In pigs, it is administered for pneumonia, acute bronchitis, rhinitis caused by PPLO organisms, leptospirosis, metritis, mastitis, etc. In cattle, it is administered for respiratory diseases, metritis, mastitis, postpartum infections, and infectious pododermatitis. The doses for pigs are 0.25 ml/kg, curatively 0.4 ml/kg, and for cattle 1–2 ml per 50 kg [12,13,14].

Tylosin (Tylocine)

It is an analog of erythromycin, isolated from *Streptomyces* cultures. It is presented as a white powder, insoluble in water. In the form of a salt, it becomes water-soluble and can be administered parenterally.

It is recommended for avian mycoplasmosis and for diseases caused by organisms from the PPLO group. In our country, it is produced as tylosin phosphate, called Disacilin, with doses of 1–3 ml per 50 kg at 24-hour intervals. It can be supplied as a powder mixed into feed, as a growth promoter. It is absorbed only to a very small extent. Foreign products are available under the names Tylocin or Tylan.

Spiramycin (Rovamycin)

It is extracted from cultures of *Streptomyces ambofaciens*. It is slightly soluble in water, forming salts with acids (spiramycin sulfate – Rovamycin). It is resistant to digestive juices and has a bacteriostatic action. In high doses, it may be bactericidal for some organisms. The spectrum of action is similar to that of erythromycin, acting on G+ and G- cocci. It is very active against anaerobes, rickettsiae, and spirochetes.

It may show cross-resistance with erythromycin, oleandomycin, and carbomycin. The indications are similar to those of erythromycin.

The phenomenon of bacteriostasis occurs. After oral absorption of spiramycin, maximum levels are reached at 3 hours and are neutralized within 12 hours. Tissue levels are good and higher than blood levels (tissue concentration).

It does not cross the blood-brain or blood-eye barriers. It concentrates in the bile, is metabolized, and is eliminated through bile, feces, and urine.

Carbomycin (Magnamycin)

It is extracted from cultures of *Streptomyces halstedii*, with a high molecular weight (842 Å). It is a yellowish, microcrystalline powder, slightly soluble in water. It appears as salts or esters (succinate, phosphate and hydrochloride), is soluble, and can be administered intramuscularly. Its action is similar to that of penicillin, with a broad spectrum against G+ bacteria. It acts bactericidally or bacteriostatically. Resistance develops slowly. Sometimes it shows cross-resistance with erythromycin, oleandomycin, and spiramycin. It has good oral absorption. Tissue and blood levels are low. It concentrates in the liver, bile, and kidneys, and is eliminated via these routes. Oral tolerance is fairly good. In injectable form, it is painful. It is supplied as 0.25 g capsules for oral administration.

Staphylycin (Stafilocillin) is extracted from cultures of *Streptomyces virginiae*. It is a light yellow, bitter powder, resistant to gastric juice. It has a bacteriostatic action and a spectrum of activity similar to that of streptomycin. It does not show cross-resistance with other antibiotics. It acts strongly against staphylococci. Oral activity is good. Its effect lasts for 6 hours. It is eliminated through the urine. It is available as 0.150 g capsules, powder, ointment, 1% eye drops, or 15% suspension.

Oleandomycin is extracted from cultures of *Streptomyces antibioticus*. It has a spectrum similar to that of erythromycin. Maximum activity occurs at pH = 8. It is absorbed very rapidly. Maximum blood concentrations appear at 1–3 hours. Therapeutic concentrations should reach 0.8–1.6 g/l. It is largely eliminated through bile and to a lesser extent (5–12%) through urine. It is usually administered orally at 6-hour intervals, in doses of 25 cg/kg per day, divided into 4

daily doses.

Antibacterial activity is expressed in IU. The international standard comprises 880 IU/mg. Oleandomycin is usually used as the sulfate or phosphate, in the form of a white powder or triacetyl oleandomycin (T.A.O). It is poorly soluble in water. For injection, the phosphate is used in vials containing 500 mg of dry substance, dissolved in physiological saline or glucose solution.

Oleandomycin is frequently combined with tetracycline, the two antibiotics acting synergistically, enhancing each other's effect. A combination of one part oleandomycin and two parts tetracycline is called sigmamycin.

Sigmamycin

It is a preparation composed of one part oleandomycin and two parts tetracycline. Due to its synergistic effect, Sigmamycin has high antimicrobial activity. Tetracycline, with its broad spectrum, acts on G+ and G- organisms, while oleandomycin acts on G+ bacteria (cocci, pneumococci, staphylococci, streptococci).

Sigmamycin is used for bronchitis, pneumonia, bronchopneumonia, genitourinary infections, external infections, and infectious diseases. It is supplied as a soluble powder. It can be dissolved in drinking water, mixed into feed, or administered as a drench. It is administered to calves at 10 mg/kg of active substance and 20 mg of active substance per kg body weight.

Taocycline is a preparation composed of one part oleandomycin – triacetyl oleandomycin – and two parts tetracycline. It is a 10% soluble powder. It is used especially in birds. It is administered mixed in feed or drinking water: 500 mg of active substance per 6 liters of water. It can also be used in calves, foals, piglets, lambs, dogs, and cats.

Lincomycin (Lincocin) is extracted from cultures of *Streptomyces lincolnensis*. It is used as lincomycin hydrochloride. It acts on G+ and G- cocci and G+ bacteria. It is very active against B. anthracis. G- bacteria are not sensitive to lincomycin. It is administered

orally in coated capsules. It gives good results in mastitis, either alone or in combination with neomycin. Sometimes it is used with a cortisone preparation (prednisolone).

Clindamycin

It has an action similar to lincomycin and is most frequently used in the treatment of mastitis. The present investigations aimed to establish the effectiveness of treatment with erythromycin FP 5% injectable solution for veterinary use, produced by Pasteur, Filipești de Pădure branch, in early respiratory conditions in multiple animal species, taking into account primarily the indications and

contraindications provided by the manufacturer (Table 1.4.).

In addition to therapeutic effectiveness, evaluations were also made regarding the possibility of local or general reactions following administration of the product under testing.

Clinical testing was carried out in accordance with the testing protocol and the product sheet, which received approval from A.N.S.V.S.A. of M.A.A.P. The criteria for clinical testing of the erythromycin FP 5% product were established in agreement with the representatives of I.C.B.M.V. Bucharest.

Tabelul 1.4. Fișa produsului Eritromicina FP5%

Commercial name	Erythromycin FP 5%
Authorization number	140112
Authorization status	Valid
Date of the authorization	29-05-2014
Authorization valid until	Unlimited
Active substance	Erythromycin thiocyanate
Target species	Cattle, Sheep, Pigs, Birds, Dogs, Cattle - treatment of respiratory and digestive system diseases, metritis, retained placenta, panaritium and pododermatitis, abscesses, mastitis.
Acțiune terapeutică	Sheep - in newborn lamb dysentery, anterior respiratory, mastitis. Pigs - in gastrointestinal diseases, respiratory diseases, mastitis, metritis. Chickens - in mycoplasmosis, pasteurellosis, coryza, sinusitis, synovitis, streptococcal and staphylococcal infections. Dogs - in infections caused by germs sensitive to erythromycin.
Therapeutic group	Antibiotics
Pharmaceutical form	Injectable solution
Presentation	vials × 50; 100 ml
Waiting period	Meat and offal: cattle, sheep, pigs - 7 days, chickens - 3 days. Milk: cattle, sheep - 3 days. Poultry: Do not administer to laying birds intended for human consumption.
Manufacturing company / Serial issuer	Pasteur - Filipești Branch, Romania
License holder	Pasteur - Filipești Branch, Romania
Responsible company in Romania	Pasteur - Filipești Branch, Romania

2. Materials and Methods

2.1. Erythromycin

It belongs to the large macrolide group, which includes over 40 antibiotics, the best known of which are erythromycin, carbomycin, tilmicosin, oleandomycin, and spiramycin. Erythromycin was discovered in the 1960s, when it was obtained semisynthetically by McGuire from cultures of *Streptomyces erythraea* (isolated from soil samples from the Philippines) [3,17, 31,34].

Structure

Macrolides contain a **macrolactone nucleus** (with 12–22 carbon atoms) and one or two sugar molecules (desosamine and cladinose) attached to the erythronolide, which are actually responsible for the antibiotic activity. To date, two major groups of macrolides are known: those with 14 carbon atoms (ex., erythromycin

oleandomycin) and macrolides with 16 carbon atoms (e.g., tilmicosin, spiramycin). The macrolide acts selectively as a bacteriostatic agent, with a mechanism of action similar to chloramphenicol, namely: **inhibition of protein synthesis** by blocking the transport of activated amino acids to the site of protein synthesis. [33,35].

Absorption and kinetics

Erythromycin is easily absorbed when administered either orally (starting from the upper third of the intestine) or parenterally, diffusing well into most tissues. Serum concentrations generally decrease 4–6 hours after oral administration. [3,6,11,12,20,22,24].

In the case of injectable formulations, for example at a dose of 15 mg/kg body weight, the plasma half-life was reached after 8–9 hours, with an average maximum plasma concentration of 0.5 µg/ml. Two hours after administration, the highest concentrations were found in the liver, submaxillary glands, lungs, and kidneys.

Erythromycin does not cross the blood–brain barrier in the case of normal meninges or cerebrospinal fluid (which is why it is not indicated for meningitis), but diffusion occurs in the placenta, pleura, peritoneal cavities, and more slowly in the joints.

Erythromycin has also been identified in prostatic fluid and semen, at concentrations representing about one-third of the plasma level. The base antibiotic is destroyed by gastric acidity (which is why enteric-coated tablet formulations are recommended). Oral solutions for birds, to reach effective blood levels, must have a minimum concentration of 1‰. [1,3,15,30,32].

Metabolism

Erythromycin undergoes an enterohepatic cycle; about 50% of the macrolide is metabolized, while the other 50% is eliminated unchanged.

Excretion

Elimination occurs mainly via the kidneys, with high concentrations often found in urine. In the case of biliary excretion, the concentrations reached are higher compared to those in plasma. Erythromycin is also eliminated in the feces following oral administration, with Gram-positive microorganisms being strongly inhibited by the presence of the antibiotic in the feces. In Gram-negative microorganisms, this effect is negligible. Therapeutic doses ensure the bacteriostatic effect of erythromycin, while higher doses confer a bactericidal effect.

Antimicrobial and pharmacotherapeutic action

Normally, erythromycin is bacteriostatic but at high concentrations it can become bactericidal by penetrating the cell and inhibiting bacterial protein synthesis.

The antibacterial activity of erythromycin is directed mainly against Gram-positive organisms, including penicillin-resistant strains, as well as against some Gram-negative bacteria, mycoplasmas, and rickettsiae.

It is noteworthy that erythromycin is the drug of choice for the treatment of campylobacteriosis. [31,36,38].

The spectrum of activity is very broad:

Gram-positive:

- *Streptococcus spp.*,
- *Staphylococcus spp.*,
- *Bacillus anthracis*,
- *Corynebacterium spp.*,
- *Clostridium spp.*,
- *Listeria spp.*,
- *Erysipelothrix rhusiopathiae*,

Gram negative:

- *Haemophilus spp.*,
- *Pasteurella spp.*,
- *Brucella spp.*,
- *Mycoplasma spp.*,
- *Actinomyces spp.*,
- *Rickettsia spp.*,
- *Spirocheta spp. etc.*

The action of this antibiotic is related to the translation process, inhibiting the transport of activated amino acids (by aminoacyl-synthetase) to the site of protein synthesis (ribosomes). It binds competitively to the messenger RNA (mRNA) receptors located on the 50S ribosomal subunits, preventing the formation of polysomes.

Bacterial resistance occurs through modification of the ribosomal receptor sites and/or increased resistance of the cell membrane. Bacterial resistance to erythromycin develops rapidly, which is why this antibiotic is indicated only in special cases, namely when a positive antibiogram is available or in infections caused by penicillin-resistant organisms (especially staphylococci). When administered intramuscularly, effective blood concentrations are reached after approximately one hour.

Presentation of the product in the study

According to the manufacturer's datasheet, the product Erythromycin PF



5%, 1 ml injectable solution for veterinary use (Figure 3.1) has the following:

Erythromycin (thiocyanate salt) 50 mg
Benzyl alcohol 10 mg
Ethyl alcohol, sodium hydroxide, propylene glycol.

Figure 3.1. Erythromycin FP5%
(Pasteur, Filipești branch)

The formulation is presented as a colorless, transparent solution, without any sediment, and is marketed in brown vials,

protected from light, at room temperature, in 50 or 100 ml vials.

The antibiotic is a crystalline powder, white to yellowish, odorless, with a bitter taste. Its solubility in water is 1:1000 (0.2%), but it is easily soluble in alcohol and ether. Like streptomycin, erythromycin is more active at a pH of 8 compared to neutral pH and is unstable in acidic conditions. It is noteworthy that it is a liposoluble antibiotic.

In Romania, erythromycin is available:

- *erythromycin lactobionate, injectable powder, for human and veterinary*
- *erythromycin ethylsuccinate, suspensible powder, for human use,*
- *erythromycin propionate, tablets,*
- *erythromycin thiocyanate, oral and injectable powder (5–10%), for veterinary use*².

In Europe, other formulations are also known, in the form of estolate, gluceptate, or stearate salts. Abuse of erythromycin can lead to the development of resistance (with a mechanism similar to that of penicillin) quite rapidly, which is why its use is recommended mainly for penicillin- and tetracycline-resistant organisms, especially staphylococci, or when a positive antibiogram is available.

It is noteworthy that the development of resistance to erythromycin thiocyanate is the slowest, and cross-resistance is observed within the group—for example with oleandomycin, tilmicosin lincosamides, etc.—but not with other antibiotics.

Indications

They are basically the same as those for penicillin, if the organisms are resistant to it (pneumonias, bronchopneumonias, bronchitis, mastitis, metritis, septicemia, abscesses, phlegmons, retained placentas, arthritis, etc.), to which specific diseases are added, such as anthrax and foot-and-mouth disease, anaerobic infections, leptospirosis, micoplasmosis

² Cel mai cunoscut sinonim internațional: Gallimycin

infectious coryza, infectious sinusitis. The manufacturer recommends erythromycin for the following conditions:

- *Chickens:* *mycoplasmosis, pasteurellosis, chronic respiratory disease, infectious sinusitis, staphylococcal arthritis, streptococcal infections, reduction of mortality due to stress.*
- *Turkeys:* *airsacculitis, infectious sinusitis, staphylococcal arthritis, streptococcal infections.*
- *Rabbits:* *pasteurellosis, streptococcal and staphylococcal infections.*
- *Pigs:* *respiratory infections, enteritis, metritis, erysipelas.*
- *Sheep:* *respiratory infections, septicemia, coryza.*
- *Calves, horses:* *infections of the respiratory and digestive systems, postpartum infections, arthritis, infectious pododermatitis.*

In the treatment of mycoplasmosis in birds, the recommended doses of medicated water are 0.25 g per liter of water. Erythromycin thiocyanate is recommended for intramuscular injection in mammals, subcutaneous injection in birds, and as sinus instillations in cases of sinusitis. Local or topical administration is not recommended due to the risk of sensitization.

Dosage, route, and method of administration

In large and medium-sized animals, the product is administered by deep intramuscular injection, while in birds it is given subcutaneously in the connective tissue of the neck, for 3–5 consecutive days, depending on the severity of the condition.

If the animals do not show improvement in health, a veterinarian should be consulted to reassess the diagnosis. The manufacturer's recommended doses are:

- *Cattle:* *5–10 ml per 50 kg bw/ day (5–10 mg a.s./kg.bw./day).*
- Sheep:* *4 ml per 50 kg bw per day (4 mg a.s./kg bw/day).*
- Pigs:* *5–10 ml/50 kg.gc./zi (5–*

10 mg a.s./kg.bw./day).

- *In newborn piglets:* *0,5 ml/kg.bw./day(25 mg a. s./kg.bw./day).*
- *Poultry:* *0,5 ml as/kg b.w./zi (25 mg a.s./kg.bw./day).*
- *Turkeys:* *1-2 ml, in sinusitis: intranasal inoculation, depending on severity (3,5-6,5 a.s./kg.bw./day).*
- *Dogs:* *1-2 ml/10 kg b.w./ at 12 hour (5-10 mg a.s./kg.bw./day).*

The data in the bibliography are similar to those proposed by the manufacturer. They indicate oral doses of 20-50 mg/kg body weight, parenteral doses of 3-5 mg/kg body weight and intramammary doses of 300 mg/patient quarter, in the case of mastitis. [25,26,27]

The doses recommended by the manufacturing company are consistent with the doses in the specialized literature we consulted, with the mention that for large species the most advantageous conditioning would be 10% conditioning..

Waiting time

The manufacturer's recommended times are:

- *Meat* *7 days;*
- *Milk* *3 days;*
- *Eggs* *2 days.*

The data in the literature present these periods in different ways for each species:

- *Cattle:* *2-14 days for meat and 3 days for milk, the tolerance level in meat and milk being 0 ppm.*
- *Sheep and goats:* *3 days for meat.*
- *Pigs:* *2 days, the tolerance level being 0.1 ppm.*
- *Poultry:* *one day for meat and one day for eggs, the tolerance level in eggs being 0.025 ppm.*

Toxicity of erythromycin thiocyanate salt,

According to bibliographic data, it is generally minor, but there are also known contraindications—for example, in horses, administration by any route is not recommended due to the risk of serious gastrointestinal disorders

arising. However, some authors recommend erythromycin (lactobionate salt) in horses as well, both orally and parenterally, at a dose of 10 mg/kg body weight twice a day for 3 days..

Some gastrointestinal disturbances (vomiting and diarrhea) may also occur in carnivores when high doses are administered orally, as well as some reversible irritation at the injection site in the case of parenteral formulations.

Contraindications, precautions, and adverse reactions

- It should not be administered to birds producing eggs for consumption.
- Treatment should be avoided in animals allergic to erythromycin or other macrolide antibiotics, or in animals with liver dysfunction.
- Possible allergic reactions, local or systemic.
- Erythromycin can be safely administered to pregnant cows and sows, without harmful effects on the development of the conceptus.
- It should be used only in accordance with the benefit/risk assessment carried out by the veterinarian.
- Erythromycin is antagonistic with lincomycin, clindamycin, and chloramphenicol by inducing staphylococcal resistance, each of these being capable of conferring resistance to the others. Therefore, they should not be administered together, as they counteract each other's action.
- Penicillin inhibits cell division by blocking bacterial cell walls synthesis
- The metabolism of methylprednisolone may be inhibited when administered simultaneously with erythromycin.
- Probenecid inhibits the tubular reabsorption of erythromycin and prolongs the maintenance of plasma levels.

- With the exception of the adverse reactions mentioned above, which occur occasionally, erythromycin is considered a drug with low toxicity.
- Erythromycin is inactivated in alkaline or acidic aqueous solutions..

2.2. Animals in the study

Investigations were carried out on cattle, based on recommendations from the specialized literature and various manufacturers, including.

For this reason, the study focused on aspects related to respiratory conditions of both recent and older onset, which occurred in the visited units.

The product Erythromycin PF5% was studied on n = 26 animals, of which:

The tests were carried out in two studies: **Experiment 1** and **Experiment 2**, in two cattle-rearing units and one young cattle finishing unit in Alba County (Figure 3.2).

- Cămpeni (F1), ■
- Abrud (F2) ■ and
- Ciuruleasa (F3) ■

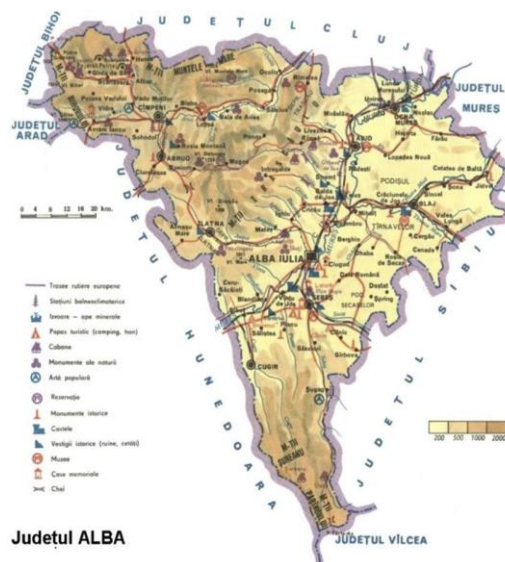


Figure 3.2. Location of the units in Alba County
Source: <https://pe-harta.ro/alba/> (39).

To standardize the method of use and the evaluation of results, the instructions for the tested product (pharmacodynamic action, indications, method of administration and dosage, contraindications and precautions, storage, etc.) were duplicated and distributed to the veterinarians involved in the testing.

Additionally, to unify the criteria for evaluating the results obtained, a datasheet was created and completed for each treated animal. This allowed the sorting of cases by species and syndromes and enabled a correct analysis of the results using the same evaluation criteria. Based on these criteria (general condition, temperature, respiratory signs), after treatment, the animals were classified into one of the following categories:



1. *Cured*
2. *Improved*
3. *Slightly improved*
4. *Not improved*

Results and Discussion

Study of Erythromycin PF 5% in Cattle

2.3. Experiment 1

In this experiment, the aim was to identify the genera responsible for acute respiratory conditions in young cattle in two units in Alba County:

- Câmpeni (F1), 
- Abrud (F2), 

Animals

It should be noted that the animals included in the study had not previously been treated with other antibiotics or sulfonamides, and the clinical courses were acute in all cases. The groups were considered uniform in weight, with animals aged between 5 and 6 months, and were

Calves of the Friesian, Romanian Spotted, and crossbred breeds.

Batch identification

The calves were identified by tattoo and also by markings on their backs, and they were housed in individual pens (F1) and a common pen (F2). Feeding and watering were provided *ad libitum*.

Methodology

In this case, the methodology included: identification of cases with symptoms of pneumonia and bronchopneumonia, sample collection using the tracheo-bronchial lavage method, bacteriological examination (by inoculation on 5% blood agar and 5% bovine serum broth), performing the antibiogram. The tests were carried out in the microbiology laboratory of D.S.V.S.A. Alba, along with treatment using Erythromycin injectable solution for 3 days, administered intramuscularly at a single site, in single doses of 5 ml per 50 kg body weight.

The follow-up of the cases after treatment was carried out over a period of 5 days.

Principalele trei semne clinice comune identificate la viței au fost:

- *hyperthermia*,
- *cough*,
- *nasal discharge and wet rales*.

From the calves included in the study, bronchial lavage samples were collected to determine the bacterial genera present in these units.

The bacterial strains were identified based on cultural and morphological characteristics (for the genus *Pasteurella*, by indole production).

The antibiogram was performed using the diffusion method, by measuring the inhibition halo (the set of antibiograms used was from Sanofi).

Table 2.1 presents the situation of the genus-level identifications and the results

³ **Bronchial lavage technique:** In calves with identified respiratory conditions, the animals were restrained, the upper third of the neck was shaved, and the area was disinfected. Then, a tracheal puncture was performed using a sterile venesection needle. Through this needle

a catheter was inserted up to the tracheal bifurcation (when the cough reflex was triggered), and 1-2 ml of tracheal exudate was aspirated with a syringe. Finally, the media were inoculated and incubated for 18-24 hours at a temperature of 37°C

of the antibiogram for the cases identified in the first two units under observation.

After identifying the bacterial genera involved (predominantly *Pasteurella* spp., *Streptococcus* spp., and *A. pyogenes*), the next step was to carry out

Treatments were administered using the manufacturer's minimum recommended dose (1 ml per 10 kg body weight) intramuscularly at a single site.

The duration of treatment in this case was three days for all monitored cases.

Table 2.1.

Bacterial genera identified and the results of the antibiogram for the units within the experiment E1

F.1.							
Calf nr.	1	2*	3	4	5*	6	7
Genus	<i>Pasteurella</i> spp.	-	<i>Streptococcus</i> spp.	<i>Pasteurella</i> spp.(1) <i>A. pyogenes</i> (2)	-	<i>A. pyogenes</i> (1) <i>Streptococcus</i> spp. (2)	<i>Pasteurella</i> spp.
Sensitive	T, E, Amox, A, Enro**,	-	P, E, T, Amox, A, Enro, Sulf	P, E, T, Amox, A, Enro, Sulf (1) E, Amox, A (2)	-	E, Amox, A (1) P, E, T, Amox, A, Enro, Sulf (2)	T, E, Amox, A, Enro, Sulf (2)
Resistant	P, S, Sulf.	-	S	S (1) T, P, S, Sulf (2)	-	T, P, S, Sulf (1) S (2)	P, S, Sulf.

F.2.							
Calf no.	1	2	3	4*	5	6	7*
Genus	<i>Pasteurella</i> spp.	<i>Pasteurella</i> spp.	<i>Streptococcus</i> spp.	-	<i>Pasteurella</i> spp.(1) <i>A. pyogenes</i> (2)	<i>A. pyogenes</i> (1) <i>Streptococcus</i> spp. (2)	-
Sensitive	T, E, Amox, A, Enro,	T, E, Amox, A, Enro,	P, E, T, Amox, A, Enro, Sulf	-	P, E, T, Amox, A, Enro, Sulf (1) E, Amox, A (2) S (1)	E, Amox, A (1) P, E, T, Amox, A, Enro, Sulf (2)	-
Resistant	P, S, Sulf.	P, S, Sulf.	S	-	T, P, S, Sulf (2)	T, P, S, Sulf (1) S (2)	-

Where:

* = Sterile samples

** = T = tetracycline, E = erythromycin, A = ampicillin, P = penicillin, S = streptomycin, Amox. = amoxicillin, A-Enro. = enrofloxacin, Sulf. = sulfonamides

Table 2.2

The situation of clinical outcomes on the 5th day after completing the three-day treatment, with a dose of 5 ml/50 kg body weight, intramuscularly, in the case of the Experiment E1

F.1.								
Calf no.	1	2	3	4	5	6	7	%
Cured	+	+	-	+	+	+	-	71,44
Improved	-	-	+	-	-	-	-	14,28
Slightly improved	-	-	-	-	-	-	+	14,28
Not improved	-	-	-	-	-	-	-	0

F.2.								
Vițelul no.	1	2	3	4	5	6	7	%
Cured	+	+	+	-	+	+	-	71,44
Improved	-	-	-	+	-	-	+	28,56
Slightly improved	-	-	-	-	-	-	-	0
Not improved	-	-	-	-	-	-	-	0

As can be seen from Table 2.2, in the case of the two monitored units, the vast majority of calves (71.44%) were clinically cured after 3 days of treatment with the minimum recommended dose. A significant improvement was observed in 3 calves

(21.42%), and only in one case (7.14%) was a slight improvement noted (it should be mentioned that in this case, the respiratory disorders were also associated with digestive disturbances). Notably, no local or systemic adverse reactions were observed.

generale and there were no cases of clinically unimproved animals.

In conclusion, it can be said that the results obtained were very good..

2.4. Experiment 2

In this experiment, a total of 12 fattening bulls from the Ciuruleasa unit were treated. (F3) ■

The bulls from this unit came from the collection, belonging to different breeds, mainly Romanian Spotted and crossbreeds. Their ages ranged between 6 and 10 months, and their weights varied from 195 to 280 kg.

The bulls included in the study, in this case, presented symptoms of chronic bronchopneumonia with recurrent respiratory episodes of unspecified etiology, which became increasingly frequent with the onset of the cold season.

It is noteworthy that almost all the animals in the studied group had previously been treated at least once with various antibiotics or sulfonamides, but with unsatisfactory results (also reflected in poor weight gain and the general condition of the animals).

In this case, the erythromycin administration protocol used the maximum dose (manufacturer's recommendation: 10 ml/50 kg body weight), administered intramuscularly at a single site. Treatments were carried out for 4 days. The animals under treatment were isolated in a separate pen and identified by markings.

As can be seen from Table 2.3, the clinical outcomes after treatment demonstrate good efficacy, even in cases of chronic respiratory and digestive conditions observed in the monitored unit, despite the animals having been previously treated with other medications.

Table 2.3.
Situția rezultatelor evoluțiilor clinice în a 5-a zi după încheierea tratamentelor
(for 4 days with dose= 10 ml/50 kg.bw., im.)

F.3.													
Calf no.	1	2	3	4	5	6	7	8	9	10	11	12	%
Cured	+	-	+	+	-	+	+	-	-	+	+	+	66,68
Improved	-	-	-	-	+	-	-	+	-	-	-	-	16,66
Slightly improved	-	+	-	-	-	-	-	-	-	-	-	-	8,33
Not improved	-	-	-	-	-	-	-	-	+	-	-	-	8,33

The 8 animals (66.66%) that were cured represent, in our view, a good result considering their previous clinical condition.

The animals that were improved (16.66%) and slightly improved (8.33%) exhibited both chronic respiratory and digestive signs, while the unimproved case (8.33%) was due to the animal's clinical condition prior to our treatment; this animal was also the weakest in the study group.

No local or systemic adverse reactions were observed in any treated animal.

The results obtained (on a relatively small number of animals) with the Erythromycin PF 5% injectable solution were similar to those reported in the literature for other similar products. [1,3,5,33].

We identified conflicting literature regarding the administration of the product in its thiocyanate salt form to horses, where it can cause severe gastrointestinal disturbances. For this reason, treatments are not considered safe and are limited for this species. Additionally, there is a need to expand field studies to carnivore species in our country, as this product is considered the drug of choice for campylobacteriosis. [34,37].

3. Conclusions

We note that the present conditions studied could not exhaust all the situations, species and pathological conditions in which Erythromycin is indicated, this study can be considered an efficiency study limited to the cases identified in the visited units.

- In the case of cattle, the preparation is preferable for young fattening animals (6–10 months).
- It is recommended to use erythromycin at a 10% concentration as well (for example, Gallimicin 10% and Erythro 100, 200, products by Sanofi) for larger animals, allowing for a more convenient injection volume, especially considering the single-site administration of erythromycin thiocyanate.
- Analysis of the clinical condition post-treatment confirms the results obtained in the three units and reinforces the conclusion that the product used was effective.
- The price-to-quality ratio of Erythromycin PF 5% injectable solution makes it an economical and efficient choice, particularly for incipient or recently developed bacterial respiratory infections, even when associated with other conditions.

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