COURSE CODE:	VPC 402
COURSE TITLE:	VETERINARY CHEMOTHERAPY
NUMBER OF UNITS:	3 UNITS
COURSE DURATION:	TWO HOURS PER WEEK

COURSE DETAILS:

Course Coordinator:	**Dr. Olubukola Tolulope Adenubi D.V.M., M.Sc**
Email:	**bukioguns@yahoo.com**
Office Location:	**Dept. of Veterinary Physiology and Pharmacology, COLVET**
Other Lecturers:	**Prof. R.O.A. Arowolo, Dr. J.O. Olukunle, Dr. K.T. Biobaku**

COURSE CONTENT:

Guidelines to the principles of antimicrobial therapy, antibacterial agents – penicillins, cephalosporins, aminoglycosides, tetracyclines, chloramphenicol, macrolides, lincosamides and sulphonamides; miscellaneous antibacterial agents; antiseptics, disinfectants and growth promoters; anthelmintic drugs; antineoplastic drugs; antiviral drugs; antifungal drugs; antiprotozoan agents.

COURSE REQUIREMENTS:

This is a compulsory course for all veterinary medical students in the University. In view of this, students are expected to participate in all the course activities and have minimum of 75% attendance to be able to write the final examination.

READING LIST:

Aliu, Y.O (2007) Veterinary Pharmacology (1st edition): 409-427; 448 – 462.

Boothes M. (2001). Veterinary Pharmacology and Therapeutics for small animals.

Nicholas H.B. (1988). Veterinary Pharmacology and Therapeutics. IOWA University Press.

Onyeyili, P. A. and Egwu, G. O. (1995). Chemotherapy of African Trypanosomosis: Historical perspective. *Pot Abstracts* 19(5): 230-241.

Wanamaker B.P and Kathy L.M (2009). Applied Pharmacology for Veterinary Technicians 333 -335.

LECTURE NOTES

GUIDELINES TO THE PRINCIPLES OF ANTIMICROBIAL THERAPY

DEFINITIONS

- **Chemotherapy:** The use of chemical compounds in the treatment of infectious and neoplastic diseases.
- The chemotherapeutic drugs include antibacterial, antiprotozoal, antifungal, anthelmintic, ectoparasiticidal, antiviral, and antineoplastic compounds.
- Antimicrobial therapy is based on the selective toxicity of a drug for invading organisms, i.e ability to kill or inhibit an invading microorganism without harming the cells of the host. Selective antimicrobial therapy takes advantages of the biochemical differences that exist between microorganisms, animals and man.

CLASSIFICATION OF ANTIMICROBIAL AGENTS

Classification is commonly based on chemical structure and site of action.

Classification based on site of action:

Inhibition of cell wall synthesis: eg penicillins, cephalosporins.

Impairment of cell membrane function: eg polymyxin, tyrocidin, and the polyene antifungal agents, nystatin and amphotericin B that bind to cell-wall sterols.

Reversible inhibition of protein synthesis: affect the function of 30s or 50s ribosomal subunits, and are bacteriostatic drugs which include chloramphenicol, tetracyclines, macrolides (eg, erythromycin) and clindamycin.

Alteration of protein synthesis: bind to the 30s ribosomal subunit and affect cell membrane permeability which eventually leads to cell death, eg aminoglycosides (eg; streptomycin, gentamicin).

Inhibition of nucleic acid function or synthesis: eg rifamycins (rifampin) which inhibit DNA-dependent RNA polymerase, and quinolones (eg; oxolinic acid). **Interference with microbial metabolism:** eg sulphonamides, trimethoprim. **Inhibition of viral enzymes:** These agents block the viral enzymes that are essential to DNA synthesis, thus halting viral replication, eg nucleic acid analogues (zidovudine, acyclovir, and vidarabine).

ANTIMICROBIAL ACTIONS

- Either bactericidal (ie, they kill bacteria) or bacteriostatic (ie, they arrest the growth and replication of bacteria to allow the immune system to attack and eliminate the bacteria).
- Agents that alter microbial cell wall or membrane permeability are generally bactericidal. These include the penicillins, cephalosporins, aminoglycosides and polymyxins.
- Essentially bacteriostatic agents inhibit bacterial protein synthesis, eg, chloramphenicol, macrolides and tetracyclines.

SPECTRUM OF ACTIVITY

- The chemotherapeutic spectrum of a particular drug refers to the species of organisms affected by that drug.
- The spectrum of activity depends upon their mode of action and the ease with which they can penetrate the organism.
- Antibacterial agents may have a narrow, medium or broad-spectrum of activity.

SELECTION OF ANTIMICROBIAL AGENTS

- Selection of appropriate antimicrobial agent requires knowledge of the offending organism and its sensitivity to the agent, the site of infection, the safety of the agent, and the cost of therapy.
- Effective antimicrobial therapy requires consideration of the total clinical problem, including the condition of the patient. Treatment may necessitate drainage of abscesses or haematomas, debridement of devitalized tissue, removal of foreign bodies or irrigation of cavities.

ANTIMICROBIAL COMBINATIONS

- The possible indications for co-administration of two or more antimicrobial drugs include:

- overwhelming infections
- mixed or obscure infections to broaden the spectrum of activity, such as the use of a mixture of macrolide (eg, tylosin) and a sulphonamide (eg, sulphadimidine) for enteric and respiratory disease in pigs, or a bacitracin; polymyxin B and neomycin combination in the treatment of superficial wound infections.
- to avoid rapid emergence of resistant mutants, especially in prolonged therapy with drugs such as streptomycin which tend to induce rapid bacterial resistance
- to prevent inactivation of the antimicrobial agent by bacterial enzymes, eg, the use of co-amoxiclav, a combination of amoxycillin and clavulanic acid, an α-lactamase inhibitor
- to achieve a synergistic effect, as is exemplified by co-trimazine, a combination of sulphadiazine and trimethoprim
- to reduce the severity or incidence of adverse reactions where the organisms are fully sensitive to each drug.
- However, the concomitant administration of two or more antimicrobial agents may increase the risk of adverse effects.

COMPLICATIONS OF ANTIMICROBIAL THERAPY

- Bacterial resistance - Enzyme production, decreased cell wall permeability, altered receptor site, enzyme adaptation, *a*lternative pathways.
- Cross-resistance
- Super-infection
- Antimicrobial prophylaxis
- Extra-label use of antimicrobial agents
- Antimicrobial dosage
- Adverse effects

ANTIBACTERIAL AGENTS – PENICILLINS, CEPHALOSPORINS, AMINOGLYCOSIDES AND TETRACYCLINES

PENICILLINS

- The discovery of penicillin, the first of the antibiotics, was in 1928 when Alexander Fleming (1881-1955) of St. Mary's Hospital, London, observed

that a Penicillium mould contaminating a culture plate of Staphylococcal colonies was surrounded by a clear zone, free of growth.

- Penicillins are now obtained from *Penicillium chrysogenum*, which produces a much higher yield. More than 40 natural penicillins have been identified and called penicillins F, G, K, X, O, V, etc. Of these, penicillin G (benzylpenicillin) proved to be the most potent.

Chemistry: Penicillins are β-lactam antibiotics. Their basic nucleus is 6-amino-penicillanic acid comprised of a thiazolidine ring connected to a beta-lactam ring that carries a free amide group (CONH) on which a substitution and a side-chain (R_1) are made. Various constituents are added at the amide side chain (R_1) to produce agents with different properties, such as expanded antimicrobial spectrum, stability to gastric acid, and resistance to bacterial degradative enzymes (β-lactamases).

General properties: Penicillins are weak acids and their salts are fairly stable in the dry state but are unstable in solution as they loose their activity rapidly and must be prepared fresh for potential administration. Conversion to salt esters stabilizes the penicillins and affects solubility and absorption rates e.g sodium penicillin G is highly water-soluble and is absorbed rapidly following subcutaneous or intramuscular injection, but gives effective plasma concentration for no more than 4 hours. Organic salts in microsuspension such as procaine or benzathine penicillin G are gradually absorbed over 1-3 days from injection sites.

Mode of action: Penicillins interfere with the synthesis of the bacterial cell wall peptidoglycan (the major constituent of G+ve bacteria cell wall). After attachment to binding sites on bacteria, they inhibit the transpeptidase enzyme involved in cross linking of the peptidoglycan chain, the 3rd and final stage of bacterial cell wall synthesis.

Selective toxicity: Mammalian cells lack peptidoglycan in their cell wall.

Antibacterial Spectrum: G+ve aerobes and anaerobes. The broad spectrum, semisynthetic penicillins are effective against some G-ve bacteria.

Pharmacokinetics: Penicillins are rapidly absorbed parenterally. Only some penicillins (eg, penicillin V, ampicillin, amoxycillin, combined with clavulanic acid) are acid stable and can be administered per os (penicillin G is rapidly destroyed by gastric acid).

Fate: Following absorption, penicillins are widely distributed to tissues and transcellular fluids, except those of the CNS and the eye. They enter well into the CSF if the meninges are inflamed. They cross the placenta but none has been shown to be teratogenic. More than 90% of an administered dose is excreted unchanged in the urine by glomerular filtration and active tubular secretion. The remainder is metabolized by the liver to penicilloic acid derivatives, which may act as antigenic determinants in penicillin hypersensitivity. The renal elimination of penicillin G is very rapid, resulting in high urine concentrations and with a half-life of 1/2 -1 hour. This is of clinical use in the case of the broad-spectrum penicillins like ampicillin. Probenecid inhibits the renal secretion of penicillins when they are administered concurrently prolonging their duration of action. Nafcillin and ureidopencillins (eg, azlocillin) are primarily eliminated through the biliary route. A small fraction of penicillin G is excreted via bile and milk. The presence of penicillin in the milk of lactating cows may induce allergic reactions in susceptible human beings that consume such milk.

Semisynthetic penicillins

Four groups of semisynthetic penicillins are available:

Acid-stable penicillins- These agents, including phenoxymethyl penicillin (penicillin V), phenethicillin, propicillin and phebencillin are gastric acid-stable and, thus, suitable for oral administration.

β -Lactamase resistant penicillins **-** The isoxazolyl penicillins (eg, cloxacillin, flucloxacillin, methicillin, nafcillin, oxacillin, dicloxacillin) have antibacterial spectrum similar to that of penicillin G. In addition, they resist degradation by β-lactamases and gastric acid, and may be administered per os.

β -Lactamase inhibitors **-** Clavulanic acid, sulbactam, tazobactam) are β-lactam molecules, but have minimal antibacterial action. Instead, they bind to and inactivate bacteria β-lactamases, thereby protecting the antibiotics and potentiating them against bacteria that owe their resistance to production of β-lactamases.

Broad-spectrum penicillins **-** Ampicillin, amoxycillin, hetacillin, carbenicllin, ticarcillin and piperacillin are active against many gram-negative aerobes (eg, *E. coli*, *Proteus* species, *Haemophilus* species) as well as gram-positive pathogens. They are therefore referred to as extended-spectrum penicillins.

Pivmecillinam is unusual semisynthetic penicillin, being active only against gram-negative bacteria. It may affect bacterial cell differently from other penicillins. For example, instead of producing filamentous forms of *E. coli* (as does ampicillin) or rapid cell lysis (as does amoxycillin), pivmecillinam causes formation of ovoid forms, which are stable osmotically, but die after they become round.

Antipseudomonal penicillins

Carboxy penicillins

Ureidopenicillins

Therapeutic uses of penicillins: The most important animal diseases for which penicillins are the drugs of choice include streptococcal infections; bovine mastitis; anthrax; bovine pyelonephritis; ovine foot rot; erysipelas of sheep; pigs, and birds; strangles and joint ill of horses; some clostridial diseases of cattle and sheep, such as tetanus, black leg, bacillary haemoglobinuria and botulism; avian spirochaetosis and pasteurellosis.

Dose

Na+ or K+ penicillin G-

All species 10,000-20,000 IU (6-12 mg)/kg IV or IM, 4 times per day

Procaine penicillin G

All species 17,000-25,000 IU (10-15 mg)/kg IM or SC, 1-2 times per day

Benzathine penicillin G

Horse, cow 40,000 IU (24mg)/kg IM (horses), SC (cattle) every 2-3 days

Dog, cat 40,000 IU/kg IM, every 5 days.

Penicillin V

Small animals 15,000-17,000 IU (8-10mg)/kg PO, 3 times per day

Pigs and Poultry 30,000 IU (16 mg)/kg PO, 2 times per day

Oxacillin, cloxacillin

All species 10mg/kg PO, 4 times per day

Large animals 1-2mg/kg IM, 4 times per day

Small animals 4-10 mg/kg IM, 4 times per day

Adverse effects: Allergic reactions may occur in small animals, thin-skinned horses and cattle. Signs include skin eruptions, angioedema, and anaphylaxis. Hyperkalaemia and cardiac arrhythmias may result from intravenous administration of potassium penicillin. Procaine salts of penicillin should not be used in birds, snakes, or turtles

because these species are sensitive to procaine. Small herbivores (eg, rabbits, guinea and pigs) may exhibit serious reactions to penicillin. These animals may die within a few days of a single dose, apparently from an enterotoxaemia resulting from the effect of the antibiotic on the normal gut flora and the development of a pseudomembranous colitis-like condition due to an invasion of *Clostridium difficile*. A significant percentage of the human population show serious and even fatal allergic reactions to penicillin G.

CEPHALOSPORINS AND CEPHAMYCINS

Cephalosporins are a large group of β-lactam antibiotics that have 7-aminocephalosporanic acid nucleus similar to the 6-APA nucleus of penicillins. The cephalosporins were first isolated from a filamentous fungus, *Cephalosporium acrimonium*, and many synthetic forms have since been introduced.

The cephalosporins have certain therapeutic advantages over penicillins which include their relative resistance to β-lactamase, their broad-spectrum of activity, their ability to reach the CNS, and less likelihood to cause allergic reactions, hence they are suitable for use in rabbits, guinea pigs, and reptiles.

Since a large number of cephalosporins have been developed, they are loosely categorized into 'generations', based on their date of introduction, increased spectrum of activity, particularly against *Pseudomonas*, stability to β-lactamases, and ability to penetrate the CNS.

First-generation cephalosporins: Includes cefadroxil, cefalexin, cefazolin, cephacetril, cephradine and cephaxazole.

Second-generation cephalosporins: Includes cefaclor, cefamadole, cefmetazole, cefonicid, ceproxil, and loracarbef. They also include the cephamycins; cefotetan and cefoxitin.

Third-generation cephalosporins: Includes cefdinir, cefixime, cefoperazone, cefotaxime, ceftizoxime, and ceftriaxone.

Fourth-generation cephalosporins: Examples are cefepime and cefpirome. They have a wide antibacterial spectrum e.g. *Enterobacter, Escherichia, Klebsiella, Proteus, Pseudomonas*. Cefepime is highly resistant to β-lactamases.

Mode of action: They inhibit the β – lactam-binding proteins involved in bacterial cell wall peptidoglycan synthesis, hence are bactericidal.

Pharmacokinetics: Most cephalosporins are unstable in gastric acid and must be administered parenterally except cephalexin and cefadroxil which are acid-stable and are well absorbed orally. Cephalosporins distribute well into body fluids and adequate therapeutic levels in the CSF are achieved with third-generation cephalosporins, regardless of inflammation. Metabolism of cephalosporins is not significant as some eg cefotaxime are deacetylated by the liver. Renal elimination occurs through glomerular filtration and active tubular secretion.

Adverse effects: Bleeding can occur with cefoperazone, because of anti-vitamin K effects; nephrotoxicity may develop with prolonged administration.

Others: Oxacephems, Carbapenems, Monobactams.

AMINOGLYCOSIDES

- The aminoglycosides are a group of antibiotics of complex chemical structure, consisting of a hexose nucleus, either streptidine (in streptomycin) or deoxystreptamine (other amino-glycosides), to which two amino sugars (streptose and glucosamine) joined in glycosides linkage are attached.
- The group includes streptomycin, dihydrostreptomycin, neomycin, tobramycin, kanamycin, framycetin, gentamicin, amikacin, netilmicin, and such others as sisomicin, paromomycin and viomycin that have not found wider use.

Mode of action: They bind to the 30S ribosome and inhibit the rate of bacterial protein synthesis and the functionality of mRNA translation, resulting in the synthesis of abnormal proteins. Aminoglycosides alter cell membrane permeability causing nonspecific membrane toxicity. Their effect is bactericidal and is enhanced by agents that interfere with cell wall synthesis (eg, β-lactam antibiotics).

Selective toxicity: The bacterial ribosome is smaller (70S) and composed of 50S and 30S subunits, as compared to the larger (80S) mammalian cytoplasmic ribosome, which is composed of 60S and 40S subunits.

Antibacterial spectrum: They are effective against many aerobic G-ve and some G+ve organisms; *Leptospira* spp are also affected.

Resistance: Bacterial resistance may be plasmid-mediated and may develop quickly. Inactivation by bacterial enzymes is the most common form of resistance. More than 20 enzymes, which modify or inactivate aminoglycosides, have been identified.

Netilmicin and amikacin are more resistant to enzymatic degradation than other members of the group.

Pharmacokinetics: The aminoglycosides are poorly absorbed from the gastrointestinal tract, thus, oral administration is of use in the sterilization of the bowel before surgery and to treat intestinal infections. They (except neomycin) are usually given IM to achieve adequate serum levels; peak plasma concentrations are attained within 30-90 minutes. Aminoglycosides are often applied topically to treat ear and eye infections, but penetration into CNS and ocular tissues is minimal. Absorption through the intact skin is minimal but can be increased greatly where open wounds are present. Because of their polarity at physiologic pH, they are distributed primarily to the extracellular and transcellular fluids (eg, pleural, joint, and peritoneal fluids). They tend to accumulate in the renal cortex and otic endolymph predisposing these tissues to toxicity. Aminoglycosides are excreted unchanged by glomerular filtration, and attain high concentrations in the urine. Plasma half-lives are 2-5 hours in most species, but effective plasma levels are maintained for 8-12 hours following a single injection.

Therapeutic uses: Aminoglycosides are most widely used against G-ve enteric organisms and in sepsis. In man, streptomycin in combination with isoniazid and rifampin is used to treat non-disseminated pulmonary tuberculosis. It is also combined with the tetracylines in the treatment of human brucellosis. Animals with tuberculosis or brucellosis are usually culled and not treated as veterinary policy is directed at eradicating these diseases. More recently, gentamicin, amikacin and tobramycin are used in the treatment of *Pseudomonas* infection. Due to their nephro and ototoxicity, neomycin and kanamycin are largely limited to topical application or oral use to sterilize the bowel before surgery.

Dose

All mammals	10mg/kg IM, twice daily
Poultry	0.1-0.2 mg/bird IM, as a single dose

Extended-spectrum aminoglycosides

Gentamicin was isolated from *Micromonospora purpurea*. It is the most active of the aminoglycosides. It is active against aerobic G-ve bacilli including *Escherichia coli*, *Enterobacter, Corynebacterium, Pseudomonas, Klebsiella*, and *Proteus* species. Gentamicin is a drug of choice for serious infections in dogs and cats due to G-ve bacilli and penicillin-resistant staphylococci. It has been used to treat pneumonia,

genital tract infection and infectious joint disease in horses. Pseudomonad infections are best treated by the synergistic effect of gentamicin and ticarcillin and gentamicin is incorporated into a number of topical preparations for treatment of superficial infections of the ear and eye.

Dose

Dog, cat	5mg/kg IM or SC, every 12 hours for day 1, then once daily
Horse	4.4 mg/kg IM or IV, every 12 hours

Spectinomycin, an aminocyclitol, is produced by *Streptomyces spectabilis*. Unlike the aminoglycosides, aminocyclitols are bacteriostatic. They are effective primarily against G-ve coliforms and *Mycoplasma* species.

Dose

Horse, cow, dog	20 mg/kg IM, times daily

Adverse effects: The aminoglycosides are relatively more toxic than other classes of antimicrobials. Toxicity is reversible if treatment is stopped early. Oto- and nephrotoxicity may occur. Ototoxicity results from damage to cochlear sensory cells (causing deafness); damage to vestibular cells causes ataxia. The cat is most sensitive to the vestibular damage caused by streptomycin. There is first ataxia of the hind legs and then of the front legs, and a progressive loss of rotational nystagmus. Dose-related nephrotoxicity occurs in renal tubular cells, where aminoglycosides accumulate. Aminoglycosides may impair neuromuscular transmission and cause flaccid muscular paralysis, and respiratory paralysis. Contact dermatitis is a common reaction to topically applied neomycin.

Polypeptide antibiotics

Bacitracin, polymyxin B and colisten (polymyxin E) are mixtures of polypeptides derived from bacilli- bacitracin from *Bacillius subtilis*, and polymyxins from *Bacillus polymyxa*. They are frequently combined with neomycin in ointments and solutions to treat topical infections, such as wounds, eczema, dermal ulcers, eye and external ear infections. They are rarely used in any systemic conditions because they are nephrotoxic even in small doses.

TETRACYCLINES

- Following the discovery of penicillin and streptomycin, the tetracyclines produced by species of the fungus *Streptomyces* were introduced as a result of extensive search for antibiotics active against a wider range of bacteria. Two

of the most important tetracyclines discovered are the widely used oxytetracycline isolated from *Streptomyces rimosus* and the less frequently used chlortetracycline isolated from *Streptomyces aureofasciens*. Tetracycline, demeclocycline, doxycycline, methacycline, and minocycline are semisynthetic derivatives.

Chemistry: The tetracyclines are polycyclic compounds that are amphoteric and fluoresce when exposed to ultraviolet light. Most are prepared as hydrochloride salts.

Mode of action: Tetracyclines are bacteriostatic; they inhibit microbial protein synthesis by binding to 30S ribosome and block the attachment of aminoacyl tRNA to the mRNA-ribosome complex. As a result, they block the addition of amino acids to the growing peptide chain.

Antimicrobial spectrum: Includes G+ve and G-ve bacteria, spirochaetes, rickettsiae (eg, *Anaplasma*, *Cowdria*, and *Ehrlichia* species), mycoplasmae, chlamydiae, amoebae, and some protozoa (eg, *Theileria* and *Babesia* species).

Bacterial Resistance: Widespread resistance to tetracyclines is found in all domestic animals. Resistance is plasmid-mediated and usually involves decreased drug uptake or active transport of the drug out of the bacterial cell. Bacteria that have become resistant to one tetracycline exhibit cross-resistance to the others.

Pharmacokinetics: Oral absorption of tetracyclines ranges from 60-90% of the administered dose, except for chlortetracycline, which is only 35% absorbed. They form nonabsorbable chelates with cations such as calcium, magnesium, iron, and aluminum, which impair their oral absorption. Thus, milk, antacids, or iron salts should be avoided 3 hours before and after oral administration. This is less of a problem with the more lipophylic doxycycline and minocycline that are absorbed more completely. Adult ruminants absorb oral tetracyclines poorly and should not be given by this route. Also the broad antibacterial spectrum of these drugs makes it likely that fermentative digestion in the rumen will be disturbed. IV and IM injections are common routes of administering tetracyclines in veterinary practice. In the blood, tetracyclines bind to plasma proteins to an extent that varies from about 30% (oxytetracycline) to over 90% (doxycycline). Plasma half-lives range from 6-12 hours. Distribution is wide and includes all tissue except those of the CNS. Doxycycline and minocycline penetrate the CNS, eye, and prostate gland at therapeutic concentrations. As a result of chelation with calcium, tetracyclines bind to tissues undergoing calcification (growing bones and teeth), causing discolouration and

damage to them. Tetracyclines cross the placenta and concentrate in foetal bone and dentition.

Therapeutic uses: Due to their wide antibacterial activity and the difficulty of accurate bacterial diagnosis in field practice, tetracyclines have been used in a great variety of local and systemic infections, often indiscriminately. Such diseases as enteritis in pigs and white scours in claves; strangles in horses; actinomycosis and actinobacillosis; anthrax; pasteurellosis; clostridial diseases; respiratory and urinary tract infections in dogs and cats; psittacosis in birds, rickettsial diseases; bovine anaplasmosis, caprine heartwater, canine ehrlichiosis, mycoplasma infections of poultry including borreliosis, coryza and erysipelas all respond to tetracycline therapy. Local application of oxytetracycline pessaries into the uterus has been used in bovine endometriosis. Tetracyclines are used in aerosol form with a dye marker (eg, gentian violet) for the treatment of foot rot and scald in sheep. Infectious keratoconjunctivitis of cattle and sheep usually responds to a single injection of oxytetracycline beneath the externa and pyogenic skin infections in dogs.

Dose

Oxytetracycline;

Cattle, sheep	5-10 mg/kg IM, SC or IV, daily
Pig	10-20 mg/kg PO, twice a day
Dog, cat	5-10 mg/kg IM, SC or IV, daily
	20 mg/kg PO, twice a day

Chlortetracycline:

Cattle, sheep, pig	10-20 mg/kg PO, daily
Dog, cat	20-50 mg/kg PO, daily

Long-acting oxytetracycline:

All species	20 mg/kg IM, SC, every 3-5 days

Adverse effects: Tetracyclines are relatively safe drugs, except in horses and young animals. The toxic effects reported are referable to the ability of the drugs to suppress the gut microflora and to chelate metal ions. Oral therapy in ruminants may cause diarrhea initially due to alteration in the normal microbial flora of the digestive tract, but animals soon get over it. In man, secondary overgrowths or super-infection with yeasts or moulds in the vagina and other mucous membranes, or of resistant micrococci frequently follow oral administration. Tetracyclines may cause

hypersensitivity reactions in small animals, horses and cattle, especially following rapid intravenous injections. Deposition in the bone and primary dentition occurs during calcification; this may cause discolouration of growing teeth and bones in puppies when tetracyclines are given to the bitch during the last 2-3 weeks of pregnancy or to puppies during their first month of life. Extensive hair loss has been reported in cats. Tetracycline preparations whose potency has expired can cause renal tubular necrosis. Vestibular problems eg, dizziness, nausea, and vomiting can occur with minocycline, which concentrates in the endolymph of the ear and affects auditory function.

CHLORAMPHENICOL, MACROLIDES, LINCOSAMIDES AND SULPHONAMIDES

CHLORAMPHENICOL

- First isolated in 1947
- First synthesized in 1949
- It is the first commercially synthesized antibiotic.

Source:

- It was first isolated from *Streptomyces venezuelae*
- Later synthesized artificially.

Chemistry:

- Chemically, it is derived from dichloroacetic acid containing a nitrobenzen moiety.
- It is a neutral stable compound.
- Plamitate salt is its form of salt and it is water insoluble thus, it is administered orally.

Mode of action:

- Chloramphenicol binds with the 50 s ribosomal subunit to inhibit peptide bond formation and protein synthesis in the bacterial or disease causing organism.

Antimicrobial Spectrum

Chloramphenicol is a broad-spectrum bacteriostatic agent active against many gram-positive and gram-negative bacteria, *Rickettsia*, *Mycoplasmas*, and *Chylamydia*. It has an excellent therapeutic activity against *Salmonella*.

Resistance: The resistance bacteria inactivate chloramphenicol by *acetyl-transferase* and other enzymes.

Pharmacokinetics:

- Following oral administration, chloramphenicol is rapidly absorbed especially in monogastrics.
- The peak plasma concentration is attained in dog about 30 minutes after an intramuscular injection.
- The drug becomes widely distributed in the tissues including those of the eye.
- The circulatory chloramphenicol becomes bound to red blood cells and plasma proteins producing similar concentration in cells as in plasma.
- The drug is widely metabolized in the liver by nitro-reduction and glucuronide conjugation. This metabolism is rapid in the horse.
- The drug is eliminated entirely in-active in its metabolites in urine and faeces via the entero-hepatic shunt.

Therapeutic Uses:

- Its use is restricted to life-threatening infections, such as systemic *salmonellosis* and respiratory disease in claves.
- The drug is used in humans in typhoid fever.
- 1% topically or 0.5% solution is used in the treatment of acquire *Dermatophilus* infection.
- Ovine foot rot.
- Mastitis in cattle
- In skin and eye infections.

Adverse Effects:

- The effect of chloramphenicol via its protein synthesis inhibition might be on specific to the cells of bacteria thus, since the mitochondrial ribosomes of mammals or the host is similar to the bacteria, this might predispose to toxicity of bone marrow.
- There is a dose-related anaemia associated with the use of this drug especially in cats, ducks and dogs.
- In man, the drug is said to produce blood dyscrasia, aplastic anaemia and super infection with overgrowth of *candida* or mucuous membranes

Newer, safer derivates of chloramphenicol derivates are: *florfenicol*, *thiamphenicol*.

Dose:

Oral administration

Dog, foal, calf,	-	50mg/kg every 12 hours
Cat	-	25mg/kg every 12 hours

Parenteral administration

Dog	-	50mg/kg I.M, SC slow I.V. every 12 hours
Cat	-	25mg/kg I.M. Sc. Or slow I.V. every 12 hours
Horse	-	30-50mg/kg I.M. every 12 hours.
Ruminant	-	10-25mg/kg I.M. every 12 hours
Pig	-	10-25mg/kg I.M. daily

MACROLIDE ANTIBIOTICS

History: Erythromycin which is a prototype macrolide was isolated from *Streptomyces erythreus* in 1952.

Chemistry: The Macrolides are group of antibiotics with macrocyclic lactone ring to which deoxysugars (desoamines and caldinose) are attached. Other examples include; oleandomycin, tylosin, carbomycin, spiramycin, tiamulin, tilmicosin.

Newer ones: roxithromycin, and dithromycin.

Mode of action of the drug:

It inhibits bacterial protein synthesis by binding to the 50s ribosome, preventing translocation of amino acids to the growing peptide.

Antimicrobial spectrum: It is effective against gram positive organisms such as *staphylococci, mycoplasma, spirochaetes,* and certain mycobacteria are sensitive to the group.

Resistance: Resistance to macrolides can develop rapidly, it may be chromosomal or plasmid – mediated and results from decreased drug binding by the 50s ribosome. This occurs as a result of resistance and Methylase enzymes which alters the ribosomal binding site for erythromycin.

Pharmacokinetics:

The erythromycin is destroyed by gastric acid, thus either enteric coated tablets or stable exterified salts (*stearate, tartrate, estolate or lactobionate*) are administered and allow oral absorption. The Newer ones (marcolides) are stable to

gastric acids and are readily absorbed. The drug diffuses throughout the tissues of the organs except those of C.N.S.

The macrolides accumulates in the macrophages. The Macrolides are concentrated in the lung tissue at levels sixty times higher than serum levels.

Erythromycin is metabolized by the liver and excreted in bile. The remainder is excreted in active form in urine and bile.

Tylosin and timicasin are excreted in unchanged in bile and urine.

Azithromycin is primarily concentrated and excreted in active form in the bile. Minor amounts are eliminated in the milk of lactating animals.

Roxithromycin is long acting with a half-life of 12 hours and it is becoming an alternative to erythromycin for respiratory, genital tract, skin and soft tissue infections.

Adverse effects:

Alteration of gastrointestinal flora following biliary excretion. The effect of distortion of microbial flora is very common in horses and might cause diarrhea.

Dose:

All Species: 10mg/kg I.M. daily

Dog: erythromycin 15mg/kg P.O. 3 times per day

Swine: tylosin 7mg/kg, in feed; 0.2-0.5gm per litre of water

Poultry: tylosin 0.5gm/litre of drinking water, in turkeys; tylosin may be injected directly into the sinuses.

LINCOSAMIDES :

Lincomycin.

Source:- Lincomycin was isolated from *Streptomyces lincotnensis*, and its semi-synthetic derivative, clindamycin.

Chemistry: They are derivatives of a sulphur containing octose with an amino acid-like side chain.

Mode of action: Same as erythromycin and chloramphenicol.

SPECTRUM OF ACTIVITY: They are effective against gram-positive cocci, an-areroes, Toxoplasm and mycoplasma species.

RESISTANCE: Takes place as a result of altered drug binding by bacteria ribosomes is the usual form of resistance. There is a cross resistance between Lincosamides and macrolides is common.

PHARMCOKINETICS:

Lincomycin is not completely absorbed following oral administration; but clindamycin is well absorbed orally, distribution is wide, with excellent penetration of bone and soft tissues, including tendon sheath. The lincosamides accumulate in neutrophils and macrophages, but CNS levels are low unless the meninges are inflamed clindmycin is extensively protein –bound. Elimination is via hepatic oxidative metabolism primarily, with some excreted unchanged in the urine, bile and faeces. Elimination half-lives are 3-5 hours in dogs and cats.

THERAPEUTIC USES:

Lincomycin has become obsolete, clindamycin is used in dogs and cats for periodontal disease, osteomyelitis, dermatitis, and deeps of tissue infections and for treating toxoplasmosis. Lincomycin has been used in swine in the treatment of arthritis and pneumonia involving mycoplasma species. A combination of lincomycin and spectinomycin (an amino- cyclitol) is used in respiratory diseases of cattle due to mycoplasma and pasteurella.

DOSE:

Lincomycin or Clindamycin

Cow, Swine, Dogs, Cats: 10mg/kg1m, twice a day

Lincomycin

Dog, Cats : 25mg/kg P.O every 12hour
15mg/kg P.O, every 8 hours
22 mg/kg 1m, Sc daily

Pig : Feed –mix: 110 – 220gm/ tones feed

Clindamycin

Dog : 5 – 10 mg/kg P.O every 12 hours

ADVERSE EFFECTS: Lincosamides are relatively safe in dogs and cats.

- Clindamycin may cause local irritation at injection site.
- Serious diarrhea with hemorrhage colitis may occur in horses after low doses. Clindamycin is very toxic in rabbits, guinea pig and hamsters.
- Fatal pseudomembranous coltis due to over growth of Clostridium difficile in the lower bowel, which elaborates necrotizing toxins.

SULPHONAMIDES

HISTORY:-The sulphonamides originated from the dye prontosil which was shown in 1935 by Gerhard Domagk to be effective in vivo against haemolytic streptococcal infection in mice. He was awarded the 1939 Nobel Prize medicine for his discovery.

Also in 1935, four French scientists, Bovet Nitti, Trefovel and Trefouel demonstrated that the body converted prontosil to Sulphanilamide, which is the active part of the molecule since then the sulphonamide nucleus has been modified. The modifications are designed to achieve greater antibacterial potency, a wider spectrum of activity, greater solubility in urine and a longer duration of action.

In the 1970s, a synergistic combination of sulphamethoxazole with trimethoprim (Co-trimazole)

CHEMISTRY

The sulphonamides are derivatives of P-aminobenzene sulphonic acid and are structurally similar to P-aminobenzoic acid (PABA) an essential member of Vitamin B complex, and an intermediate in bacteria synthesis of folic acid.

MODE OF ACTION

Being impermeable to folic acid, many bacteria must rely on their ability to synthesise folate from PABA. Pteridine and glutamate in contrast the mammalian in cells cannot synthesize folic acid and must obtain preformed folate as a vitamin in their diet. The sulphonamides are structurally similar to PABA, the sulphonamides competitively inhibit dihydropteroate synthetase, the enzyme that catalyses the incorporation of PABA into dihydrofolic acid. The folic acid is required for pure and D.N.A synthesis which without it bacteria growth is inhibited.

ANTIBACTERIA SPECTUM: Sulphonamides have a broad- spectrum of activity against both gram- positive and gram negative bacteria, and some protozoa (coccidia, Neospora, Toxoplasm), riicketsiae.

RESISTANCE: is common in animals isolated and usually exhibit cross-resistance to the whole group. Resistance occur gradually and may be due to plasmid transfer or random mutation resulting in decrease affinity of the bacterial dihydropterate synthetase for the sulphas, decrease uptake, increased PABA synthesis by bacteria.

Classification :

Long acting – sulphamethoxypyridazine, sulphamethoxine, sulphadoxine

Enteric or gut-active sulphonamides – Phythalylsulphathiazole, Succinyl sulphathiazole, Sulpha-bromethazine, Sulphaquinoxaline, Sulsalazine, Sulphacetamide

MISCELLANEOUS ANTIBACTERIAL AGENTS: NITROFURANS, HYDROXYQUINOLONES AND NITROIMIDAZOLES

NITROFURANS:

- These are a group of closely related, synthetic, antimicrobial drugs with bacteriostatic activity against Gram positive and Gram negative bacteria, some protozoa and fungi. These include *Salmonella* spp, *Giardia* spp, Trichomonads, Amoeba and some *Coccidia* spp.
- Compared with other antimicrobial agents, their potency is not particularly great.
- They are yellowish compounds that must be protected from light, otherwise they deteriorate and turn brown.
- Absorption is complete after oral administration and is rapidly excreted in the urine.

- They are more active in acidic environment e.g acidic urine therefore not effective systemically. It is a common practice to administer a urinary acidifier with nitrofurans to promote drug ionization when treating UTI.
- Given p/o or topical (not administered parenterally)

Mechanism of action: The nitrofurans are reduced to highly reactive intermediates which inhibit various enzymes including those involved in carbohydrate metabolism. Also block the initiation of translation thereby interfering with gene expression (DNA).

Adverse Effects: GIT disturbances include vomiting, intestinal bleeding, diarrhoea. CNS involvement- peripheral nerve damage, excitement, convulsion, hypersensitivity. Allergic skin rashes, depressed spermatogenesis and poor weight gain can also occur.

Nitrofurans include nitrofurantoin, furaltadone, nifurprazine, nitrofurazone, nifuratel, furazolidone and nifuraldezone.

8-HYDROXYQUINOLONES:

- They are a group of synthetic compounds with antibacterial, antifungal and antiprotozoal activity.
- They have been widely and injudiciously used in humans for the prophylaxis and treatment of nonspecific diarrhoea, traveller's diarrhoea, dietary indiscretion etc.
- They are active against *Entamoeba, Giardia, Trichomonas*, dermatophytes, and Candida.

Classes: Iodochlorhydroxyquinolone (Quiniodochlor or Clioquinol), Di-iodohydroxyquinolone (Iodoquinol), Broxyquinolone and Hydroxyquinolone.

Pharmacokinetics: Absorption from the intestine in variable.

- Least absorbed (10-30%) and probably safest is Iodoquinol.

Route: p/o or topical. Topical application of quiniodochlor has been used for dermatophytosis. Also as vagina cream for monilial and *Trichomonas vaginitis.*

NB: 8-hydroxyquinolones cause convulsion in cats and an iatrogenic disease in human known as subacute myelo-optic neuropathy (neurotoxic when used for prolonged periods).

Dose: Horses-1g/44.5kg p/o sid using decreasing dosage to end medication.

5-NITROIMIDAZOLES:

- A group of synthetic drugs that have a broad spectrum activity against protozoa (trichomonads, amoebae and giadia) and bacteria (anaerobic cocci and bacilli).
- They are imidazole heterocycles with a nitro group
- The prototype is metronidazole.
- Others are dimetridazole niradazole, lipronidazole, flunidazole, tinidazole, ronidazole and nimorazole.

Mode of action: A ferredoxin linked metabolite disrupts DNA synthesis in protozoa and bacteria.

ANTISEPTICS, DISINFECTANTS AND GROWTH PROMOTERS

A Good Antiseptic/Disinfectant must be;

i. chemically stable
ii. non staining with agreeable colour and odour
iii. active against all microbes – bacteria, protozoa
iv. active even in the presence of blood, pus, exudates and excreta (though action is reduced)
v. able to spread through organic films and enter folds/ crevices
vi. cheap
vii. rapid in action and exert sustained protection
viii. non-irritating to tissues, should not delay healing
ix. non-absorbable, produce minimum toxicity if absorbed
x. non-sensitizing (no allergy)
xi. compatible with soaps and other detergents
xii. non destructive to applied surfaces.

Uses of Antiseptics/Disinfectants

- Pre-operative: In surgery for the antisepsis of the surgical area, surgeon's hands, surgical instruments and apparel.
- Home and farm premises
- Water treatment/ purification
- Public health sanitation: in disease outbreaks to reduce the spread of disease hrough transport vehicles etc.
- Treating local infection e.g skin abrasion and animal husbandry procedures e.g as teat dips or in farrowing houses.
- Preservation of food and drugs

Factors affecting activity:

- Temperature and pH
- Period of contact
- Nature of micro organism
- Size of inoculum
- Presence of blood, pus and other organic matter

Therapeutic index of an antiseptic is defined by comparing the concentration at which it acts on micro organisms with that which produces local irritation, tissue damage or interference with healing.

CLASSIFICATION

Antiseptics/Disinfectants could be classified into:

1. Phenols and derivatives e.g Chloroxylenol, phenol, cresol
2. Oxidizing agents e.g Hydrogen peroxide, potassium permanganate
3. Halogens and halogen containing compounds e.g Iodine, chlorine
4. Biguanides e.g Chlorhexidine
5. Quartenary Ammonium compounds e.g cetrimide
6. Soaps e.g Na and K
7. Alcohols e.g ethanol
8. Aldehydes/Alkylating agents e.g formaldehyde, glutaraldehyde
9. Acids and Alkalis e.g boric acid, acetic acid
10. Silver salts e.g silver sulfadiazine
11. Dyes e.g Gentian Violet
12. Furan derivatives e.g nitrofurazone

GROWTH PROMOTERS/GROWTH PERMITANTS

(Natural/Non-antibiotic Growth Promoters (NGPs) or Antibiotic Growth Promoters (AGPs).

As the name implies, this refers to hormones (natural or synthetic) or antimicrobial compounds which help to improve animal performance. They act by improving growth rate and feed conversion efficiency in livestock on an optimal plane of nutrition.

Antibiotic Growth Promoters (AGPs): The antimicrobial compounds act by changing the population of microbes in the GIT of healthy animals thereby preventing disease and maintaining health in animals in an environment likely to lead to decreased performance due to increased incidence of disease. They are given at low dose rate in contrast to the dose required for therapeutic effect. They should not be used unless they are officially approved and local regulations are followed. Their use has been banned in most countries.

Antimicrobial feed additives

i. Non-ionophore antibiotic e.g avoparcin and flavophospholipol

ii. lonophore antibiotic e.g monesin and lasalocid

iii. Gut-active growth promotants e.g enzymes (amylase, lipase) and probiotics (selected strains of lactobacilli and streptococci). Probiotics are live microorganisms or viable spores which support the development of a beneficial gut microflora. Probiotic bacteria (e.g. from the genera *Lactobacillus*, *Bifidobacterium*, *Enterococcus*) counteract undesired microorganisms such as *Salmonella* or *E. coli* by blocking receptors on the gut wall, production of antimicrobial substances or activation of the immune system.

Natural Growth Promoters (NGPs) or Non-antibiotic Growth Promoters: They are commonly regarded as favorable alternatives to Antibiotic Growth Promoters (AGPs) in livestock production.

Categories of NGPs:

NGPs include predominantly acidifiers e.g organic acids, probiotics, prebiotics, synbiotics, phytogenics, feed enzymes and immune stimulants. Since the use of AGPs

has been banned, an ongoing search for alternatives has created a large variety of NGPs for pigs, poultry, ruminants and aquatic species.

ANTHELMINTIC DRUGS

- The parasitic helminthes of animals are broadly classified into nematodes (roundworms, hookworms, whipworms, pinworms, schistosomes); annelids (leeches), and acanthocephales (thorny-headed worms). In the animal body, gastrointestinal tract is the abode of many helminthes, but some also live in tissues or their larvae migrate into tissues.
- **Anthelmintics** are drugs that reduce parasite burdens in the animal to a tolerable level; they kill the parasites (*vermicide*), inhibit their growth or paralyze them (*vermifuge*). The also reduce the build-up of infective worm larva on the pasture, or eggs in the environment.

Benzimidazoles

They include **albendazole, carbendazole, fenbendazole, flubendazole, mebendazole, oxfendazole, oxibendazole, parbendazole** and **triclabendazole.** The probenzimidazoles (**fabantel, netobimin,** and **thiophanate**) are converted in the body to **fenbendazole, albendazole,** and **lobendazole**, respectively.

Anthelmintic spectrum: The benzimidazoles are effective against a wide spectrum of nematodes and have a wide safety margin. Most are effective against larval and adult roundworms.

Pharmacokinetics: Because most benzimidazoles are sparingly soluble in water, they are given per os as suspension, paste, or powder, or by intraruminal injection. Gastrointestinal absorption varies, depending on the water solubility of the compound.

Therapeutic uses: In ruminants, albendazole and oxfendazole are effective against major gastrointestinal worms (in both the adult and larval stages). In additions, they are effective against lung worms. However, they are ineffective filarial. In horses, fenbendazole, oxfendazole, oxibendazole, mebendazole, being effective against strongyles, intestinal threadworms and ascarids, but not against bots. Fenbendazole is effective against harbronema, and mebendazole against lungworms at dosages of 15-20mg/kg/day for 5 consecutive days. In dogs and cats, fenbendazole, membendazole, oxibendazole, and febantel are effective against ascarids, hookworms, and whipworms. Febantel is the only agent approved for use in cats.

Imidazothiazoles

Tetramisole, butamisole and **levamisole** are broad-spectrum synthetic imidazothiazole derivatives, which are nicotine-like. They are effective against adult and larval nematodes of the gastrointestinal tract, heart, lungs, and kidney. **Pharmacokinetics**: Levamisole is formulated for oral and subcutaneous injection in ruminants and pigs. It is rapidly absorbed orally or from the injection site. The half-life is about 4 hours after intrasmuscular administration in the cow. The liver and kidney are the main organs involved in the metabolism and excretion of levamisole. The drug is eliminated from the body in 2 days. The preslaughter clearance periods in pigs and cattle are 3days and 7 days, respectively.

Dose

Ruminants, pigs	7.5mg/kg PO (in feed) or SC
Cats	5mg/kg PO

Adverse effects: Levamisole is one of the most toxic anthelmintics; signs of toxicity include salivation and muscle tremors.

Tetrahydropyrimidines

Pyrantel, its methyl ester **morantel**, and the **metaoxyphenol** analogue, **oxantel** are effective against adult gut nematodes. They are less effective against immature forms and are not effective for treating hypobiotic larvae or lungworms. A particular attribute of morantel is its formulation. It is marked as sustained-release bolus; this provides continuous release of the drug in the recticulo-rumen for at least 90 days on oral administration. Pyrantel is formulated as a paste, suspension and granules for broad-spectrum control of adult gut nematodes in horses and dogs. Along with mebendazole, pyrantel is effective in the treatment of infections caused by roundworms, pinworms, and hookworms. Pyrantel has been combined with oxantel for their broad-spectrum anthelmintic activity. Pyrantel has a good safety margin; it is suitable for use in young puppies, and in pregnant and lactating bitches.

Organophosphate anthelmintics

Haloxon, coumaphos, dichlorvos, crumate and **napthalophos** are widely used organophosphate anthelmintics. Dichlorvos is used in horses, dogs, pigs, and cats, and **trichlorfon** (metriphonate) in horses and dogs. Haloxon is probably the safest organophosphorus anthelmintic for use in ruminants. The concentration required to inhibit cholinesterase activity of the parasite is extremely low; in addition, mammals have cholinesterase that forms unstable complexes with haloxon. It is primary action

ruminants is against parasites of the abomasums and small intestine. It is active against *Haemonchus, Trichostronglus, Cooperia, and Stronglyloides* species. Haloxon may be administered orally in bolus, drench, or paste form at a dose of 44m/kg to cattle, and 35-50 mg/kg to sheep and goats. It is rapidly absorbed from the gut, metabolism fairly rapidly, and excreted in the urine.

Avermectins

The avermectins are a group of naturally occurring macrolides (macrocyclic lactones) extracted from sytreptomyces avermitilis. **Ivermemectin, abamectin, epinomectin, moxidectin, doramectin, selamectin,** and **milbemycin oxime** are semi-synthentic avermectin derivates. *Ivermectin* is the most widely used. It has a high degree of efficiency at low doses against all major gastrointestinal worms and lungworms, as well as canine heartworm. It is also effective against all ectoparasites. It is used especially to control lice and manage mites. It is effective in visceral larva migrans, warbles in cattle, and is the drug of choice for *Onchocerca volvulus,* the cause of river blindness in humans.

Pharmacokinetics- Ivermectin is rapidly absorbed orally. It is widely distributed, but enters the eye slowly and to a limited extent. More than 95 percent of the absorbed dose is metabolism in the liver. The plasma half-life is 3days in cattle, but remains in tissues with long persistency; one dose is usually effective for 2-4 weeks. Excretion of the drug and its metabolites is almost exclusively in the faeces. Preslaughter clearance periods of ivermectin are 18 days in swine and 35 days cattle. The drug should not be administered to lactating diary cattle, but it is safe for use in pregnant animals and breeders.

Dose:

Cattle	200µg/kg SC
Pig	300µg/kg PO
Sheep	50µg/kg SC
Dog	50µg/kg SC
Dog (heartworm prophylaxis)	6µg/kg PO, monthly
Poultry	up to 160ug/kg PO

Adverse effects – Local irritation may occur following subcutaneous administration to swine. High doses may evoke CNS depression as evidences by listlessness, ataxia, mydriasis, recumbency and coma.

Piperazine

Piperazine is available as the hexahydrate (which contains about 44 percent of the base) and as a variety of salts: adipate, citrate, phosphate, tartrate or hydrochloride. It is effective against *ascarids* and nodular worms in all species; however, it use is limited in ruminants, because *ascarids* are not a significant problem in this species. Piperazine salts are well absorbed orally. The drug is partly metabolized in the liver and the remainder (30-40 percent) is excreted unchanged in the urine. Urinary excretion starts as early as 30 minutes after dosing, and is complete within 24 hours.

Dose

Horse, cow	0.2gm/kg; maximum 80 gm; foals 30 gm; yealings 60gm
Sheep, goat	0.4 -0.8 gm/kg
Pig	0.1 gm/kg in each of 3 successive feeds
Dog, cat	80-240 mg/kg PO
Poultry	up to 160 mg/kg PO

Adverse effects: Piperazine is almost free of pharmacologic action in the host. It is a very safe drug, but large doses may produce vomiting, diarrhea, and ataxia.

Phenothiazine

Phenthiazine**,** the oldest antinematodel drug, was introduced in 1938. It was used extensively in livestock but has been largely replaced by drugs with broader spectra of activity. It is still used, primarily in ruminants, in prophylactic, low level in-feed programmes. Its efficacy is best against *Haemonchus and Oesophagostomum* species in ruminants, small strongyles in horses, and the caecal worm (*Haterakis gallinarum*) of poultry.

Dose:

Single oral therapeutic doses (in food, as a drench, or by stomach tube, or in tablet form or salt lick):

Horses	10-30 gm at 3 mg/50kg
Cattle	20-60gm at 10gm/kg
Sheep, goats	5-40gm
Poultry	0.25-1 gm

Drugs for the treatment of hookworm

Bephenium, a nicotine-like quaternary ammonium compound, is used mainly in dogs and cats to treat hookworm (*Ancylostoma caninum* or *Uncinaria stenocephala*) infection. It is effective to a lesser extent against Toxocara and Trichuris. In ruminants, bephenium has specific action in Nematodirus infestations (which are not of importance in Nigeria).

Bephenium is poorly absorbed by the host and has low toxicity, causing only vomiting in some (about 19 percent) of the dog treated. **Thenium closylate,** an analogue of bephenium is used strictly in dogs to control hookworms. It is 98 percent effective against adult and immature stages of *A. caninum and U. stenocephala*. It is moderately effective against ascarids. The combination is used in weaned puppies and dogs infested with both hookworms and roundworms. Thenium and bephenium are administered orally in from the gut because of their quaternary structure.

Microfilaricides

Ivermectin and **milbemycin** are the only two drugs that may be safely and effectively used as extralabel microfilareicides. They are larvicidal and kill the larvae. As a microfilaricide, *ivermectin* therapy entails one dose (50 ug/kg), administered orally or subcutaneously. It may cause toxicity in certain blood-lines, for example, rough-haired collies, and is contraindicated in this breed. One dose of *milbemycin* (0.5 mg/kg) is administered orally; the dose may be repeated in 2 weeks. The drug can be safely used in collies. When used as larvicide, **ivermectin** is administered orally at dosage of 6-12 µ g/kg once monthly.

Larvicides

Diethylcarbamazine is a synthetic methylpiperazine derivatine. Its chief value is as a prophylactic treatment of heartworm (*Dirofilaria immitis)* infection. It kills the L_3 larvae, thereby eliminating stages L_3 - L_5 of the heartworm life cycle. It also has as effect on the muscular activity of the microfilariae and adult worm so that they are dislodged and killed more slowly. It reduces the worm burden in ascariasis and strongyloidosis of small animals, but efficacy is low. After an oral dose, plasma levels peak at 3 hours and fall to zero in 48 hours. The therapeutic level of diethylcarbamazine has to be maintained by daily dosing. About 10-30 percent of the dose is dose is excreted as an unchanged drug in urine; the rest is excreted as metabolites.

Drugs for the treatment of cestodes

Praziquantel

Praziquantel and its analogue **episiprantel** are synthetic isoquinoline-pyrazine derivates. Both drugs have high efficacy against cestodes and are effective in the treatment of schistosome infections of all species and most other treametodes. However, their activity against *Fasciola hepatica* or hydatid cyst in humans is erratic.

Pharmacokinetics-

In dogs, praziquantel is readily absorbed orally. Peak plasma levels occur in one-half to one hour. About 80 percent of the drug is bound to plasma proteins. It undergoes extensive first-pass metabolism in the liver to many inactive products, which limits its bioavailability. Praziquantel is distributed throughout the body, including the CNS, where it attains therapeutic concentrations, making it useful in human neurocysticercosis. It is excreted primarily in the urine. The elimination half-life is 3hours in dogs.

Dose

Dog, Cat	5mg/kg PO; 3.5-7.5 mg/kg SC or IM
Horse	10 mg/kg PO

Others are epsiprantel, bunamidine and niclosamide.

Drugs for the treatment of trematodes

Some benzimidazoles (albendazole, netobimin, triclabendazole); salicylanilides (brotianide, clioxanide, closantel, niclosamide, oxyclozanide, rafoxanide); substituted phenols (bithionol, disophenol, hexachlorophene, niclofolan, nitroxynill); the aromatic amide diamphenethide, and the sulphonamide clorsulon are effective flukicides, but none has a wide therapeutic index.

Vaccination against certain helminthes

Active immunization can be induced to lungworm and hookworm infection. A special type of live vaccine (**irradiated third stage larvae of *dictyocaulus viviparous***) is available for protecting calves against infection by the lungworm. This vaccine consists of two does of 100 irradiated third stage at an interval of one month. A similar vaccine (irradiated infective larvae of *Ancylostoma canium and Uncinaria stenocephala*) has also been devised to protect puppies and dogs against hookworm.

ANTINEOPLASTIC DRUGS

Factors affecting chemotherapy

- The length of time that a tumor is exposed to an effective dose of drug.
- The development of specific resistance to a drug by the tumor
- MTD (maximum tolerated dose)
- Metronomic method (Low dose over a relative long period)
- Constant monitoring of patient
- The combinations effective to the particular situation
- Proper diagnostic tool used to diagnose the phase of tumor for appropriate and rational use of drugs.

Patient status.

Classification:

- **Cytotoxic agents** includes alkylating agents (nitrogen mustards and alklysulfonates); anti metabolites (folate, purines and pyrimidine antagonist); Microtubule inhibitors (Vica alkaloids, taxnes, epipodophyllotoxins navelbine), and cytotoxic antibiotics.
- **Enzymes**; interferons; monoclonal antibodies.
- **Steroid hormones** and their antibiotics.
- **Miscellaneous agents** that do not fit the above categories (e.g. hydroxyl urea, procarbazine, mitotane, cisplatin carboplatin). Protein fragments (angiostatin and endostatin) used in therapy of mice tumors. They interfere with blood supply to tumor cell this leads to reduction in size of tumor regression.

ANTI-VIRAL DRUGS

- There are draw-backs when using an antiviral agent or drugs, the major draw-backs are;

  a) Highly specific selective toxicity is difficult. These drugs could cause injury to the host.

  b) A substantial amount of multiplication of the virus would have taken place before symptoms manifest.

c) Control of viral infections is expensive.

Mechanisms of preventing viral infections.

- Coating the viruses cell surfaces receptors (polypeptide) that are needed to attach to the host cells.
- The coated viruses are rendered more susceptible to phagocytosis.

Diseases that could be prevented are: *Measles, hepatitis, rabies, poliomyelitis.*

There are hyper-immune globulins specific against particular viruses (eg. Maxagloban P derived from canine serum is used in dogs and other susceptible species against canine distemper, canine viral hepatitis and parvovirus.

Side Effects

- Danger of hypersensitivity reactions serum sickness.

CLASSIFICATION:

- Adamantanamines- amantadine, rimantadine.
- Guanidine and hydroxybenzylimidazole
- Ribavirin
- Pyrimidine nucleosides – Idoxuridine, Irifluridine, Cytarabine**,** 5-fluorouracil and 5-bromouracil
- Purine nucleosides – Vidarabine
- Guanosine analogue- acyclovir, ganciclovir, famiciclovir, cidofovir.
- Nucleoside reverse transcriptase inhibitors - Zidovudine
- Retroviral protease inhibitors - Ritronavir, saquinavir, indivinir, nelfinar and amprenavir.
- Non –nucloside reverse transcriptase inhibitors - Nevirapine, elavirdine, efavirenz
- Host immune modulators : interferons

ANTIFUNGAL DRUGS

Fungal infections (mycoses) are classified into two types: topical (superficial), which affects the skin and mucous membranes, and systemic which affect areas as the blood, lungs, or C.N.S. Patients with fungal infection are treated with oral, topical, or parenteral drugs that are suitable for these infections used in veterinary medicine are as following

1) Polyene macrolides e.g amphotericin B, nystatin

2) Imidazole derivatives e.g ketaconazole (the prototype), miconazole, clotrimazole, fluconazole, itraconazole, enilconazole, and terconazole.

3) Antimetabolites e.g 5-flucytosine

4) Superficial agents e.g griseofulvin

FUNGAL DISEASES OF VETERINARY IMPORTANCE

Dimorphic fungal infections:- Includes

a) Blastomycosis

B) Cryptococcosis

C) Histoplasmosis and

d) Coccidioidomycosis

Superficial forms_are on the skin and they *cause dermatophytosis, candidiasis and trichophytosis.*

ANTIPROTOZOAN AGENTS

ANTI TRYPANOSOMAL DRUGS:

- **Diamidines** – Examples are Dininazene aceturate, Phenamidine, Stilbamidine and Pentamidine.
- **Phenanthridines** - Examples are phenidium, dimidium, homidium and isometamidium.

- **Quinapyramine Compounds -** Examples are quinapyramine chloride, quinapyramine sulphate and suramin.
- **Organic arsenicals -** An example of organic arsenicals is melarsomin, or melarsoprol.

OTHER TRYPANOSOMAL DRUGS

- Antimony and potassium tartrate used I.V at 3.5mg/kg in horse and cattle and 1-3mg/kg for dogs.
- Stibophen.
- Trypan red
- Trypan blue.

ANTIPIROPLASMAL COMPOUNDS

The clinically important proplasms are anaplasmosis, babesiosis, cowdriosis, theileriosis, ehrlichriosis, hepatozoonosis and in avian spirochaetosis.

- They are amicarbalide isethionate, buparvquone, halfuginone, menoctone, parvaquone tetracycline, imidocarb, quinuronium sulphate.

ANTIHISTOMONIASIS

- Aminonitrothiazole
- Nithiazide

TREATMENT OF GIARDIASIS

- The main drugs used for treatment of giardiasis are follows: Metronidazole, dimetridazole, pronidazole, tinidazole, nimorazole these are know as 5 – nitroimidazoles

ANTICOCCIDIAL DRUGS

The major drugs used are classified as

- Sulphonamides

- Quinazolines
- Quinolones
- Symmetrical triazinones
- Thiamine antagonists

OTHER ANTICOCCIDIALS

Pyridines

Examples: clopidol

Ionophores (polyether antibiotics)

Examples are

- Monensin
- Lasalocid