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. They are the first alternative to penicillins in penicillin-intolerant patients for treating infections caused by G+ve aerobes. They are used in all species for the treatment of bone and soft tissue infections (eg oral cephalexin for staphylococcal dermatitis) and are frequently employed for antibiotic prophylaxis.

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. They possess enhanced activity against G-ve bacilli, including *Pseudomonas, Proteus*, and most other enteric organisms. They are resistant to β-lactamases (cephalosporinases) and penetrate the blood-brain barrier. Ceftriaxone and cefotaxime are first-line drugs in the treatment of meningitis; ceftiofur is approved for use in bovine respiratory disease principally caused by *Pasteurella* spp, and in urinary tract infections in dogs.

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.

Cephamycins are produced by *Streptomyces* organisms, and they are closely related to the cephalosporins. Some totally synthetic drugs (eg, moxalactam) resemble cephalosporins.

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.

Oxacephems

Oxacephems (eg, moxalactam or latamoxef) were first reported in 1974 where the sulfur in position 1 of the dihydrothiazine ring of cephalosporins was replaced by oxygen without loss of biologic activity.

Spectrum of activity: Moxalactam inhibits G+ve, G-ve, and anaerobic bacteria. It is extremely active against *Haemophilus* and *Neisseria gonorrhoea* including their β-lactamase-producing isolates.

Pharmacokinetics: Moxalactam is given parenterally. The half-life is about 2 hours. It is widely distributed to body fluids and has been found in bile, pleural fluid, interstitial fluid, and aqueous humour. Moxalactam undergoes only slight metabolism and most of it is excreted in the urine.

Carbapenems

Carbapenems (eg, imipenem, meropenem) are synthetic, β -lactam antibiotics that differ from the penicillins in that the sulphur atom of the thiazolidine ring has been externalized and replaced by a carbon atom.

Imipenem has a very broad spectrum of antimicrobial activity, being active against many aerobic and anaerobic G+ve and G-ve organisms. It resists hydrolysis by β -lactamases, but is inactivated by dehydropeptidase enzymes in renal tubules, to products that are potentially toxic to renal tubules. Consequently, imipenem is combined with cilastatin (as primaxin), a specific inhibitor

of renal dehydropeptidase, that prevents both inactivation and toxicity. Imipenem is used to treat septicaemia, especially of renal origin, intra-abdominal infection, nosocomial pneumonia, and urinary tract infections. Imipenem is administered intravenously and penetrates well into body tissues; it crosses the blood-brain barrier when the meninges are inflamed. **Its efficacy in veterinary medicine has not been established.** Adverse effects include allergic reactions and possible neurotoxicity (convulsions).

Meropenem is similar to imipenem but is stable to renal dehydropeptidase and can therefore be given without cilastatin. It penetrates into the CSF and is not associated with convulsions.

Monobactams

Monobactams are synthetic analogues of a compound produced by a bacterium, *Chromobacterium violaceum*. The group has an unusual activity- being active only against G-ve aerobic rods, including *Pseudomonas, Enterobacteriaceae, Neisseria meningitidis*, and *Haemophilus* species; it has no action against G+ve bacteria or anaerobes.

Aztreonam is the first member of this class. It is a simple monocyclic β-lactam, in which the β-lactam ring is not fused to another ring. It is resistant to most β-lactamases. The use of aztreonam in veterinary medicine has not been established. The drug is relatively nontoxic, but it may cause phlebitis, skin rashes, and hepatitis.

AMINOGLYCOSIDES

Following the demonstration of the clinical efficacy of penicillin, streptomycin was obtained in 1944 by Waksman and his colleagues from *Streptomyces griseus*, cultured from a heavily manured field, and also from a chicken's throat.

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. Aminoglycosides that are derived from *Streptomyces* have 'mycin' suffixes, whereas those from *Micromonospora* end in 'micin'. The closely related aminocyclitols (eg spectinomycin, apramycin) have the amino sugars on the cyclitol rather than on the sugar ring.

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.

Streptomycin and dihydrostreptomycin are the oldest members of this class of antibiotics. Their use has declined with the advent of broader spectrum aminoglycosides, such as gentamicin and amikacin. A unique disadvantage of streptomycin is the ease with which all bacteria, especially *E. coli*, develop resistance to it by genetic mutation. For this reason, if a patient fails to respond favourably within 2 or 3 days of streptomycin therapy it should be discontinued. Alternatively, if treatment is to extend beyond 5 days, streptomycin is usually employed in combination with other antibacterial agents. In veterinary practice, it is combined with penicillin, in which the synergism between the two drugs may be of great importance in selected cases such as *E. coli* peritonitis, mastitis, metritis, cystitis and septicemias in all species, leptospirosis, *Corynebacterium equi* infection in horses, and vibriosis.

Dose

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

Neomycin is principally used topically for skin, eye and ear infections, and some cases of bovine mastitis. For topical application, it is often combined with polymyxin, bacitracin or an anti-inflammatory steroid (eg, betamethasone); fungicides (eg, benzoic acid, salicylic acid) are occasionally included in the topical preparation. It is administered orally to treat enteric infections such as calf scours, often combined with poorly absorbed sulphonamides (eg, phthalylsulphathiazole).

Dose

All species	100mg/kg/day PO, divided into 2 or 4 equal doses.

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.

Bacitracin is a narrow-spectrum antibiotic active against G+ve cocci and spirochaetes. It inhibits bacteria cell wall synthesis and is bactericidal. Bacitracin is commonly combined with polymyxin B or neomycin that act upon G-ve bacteria, and with corticosteroid to treat topical infections. Various forms of bacitracin (bacitracin-zinc, bacitracin methylene disalicylate) have

been added, at concentrations of 1-100gm per tonne, to the rations of calves, lambs, pigs, broiler chicks and turkey poults, to promote growth and feed conversion efficiency.

Polymyxins interact with phospholipids in the bacterial cell membrane to produce a detergent-like effect and membrane disruption. It is rapidly bactericidal and has a selective action on *Pseudomonas aeruginosa*. In addition, polymyxin B has been added to bull's semen along with penicillin and streptomycin to eliminate contaminating bacteria. It has also been combined with oxytetracycline for intramammary infusion in mastitis. Polymyxin B is administered orally to cattle and swine for the treatment of G-ve enteric infections while given IM at approximately 2mg/kg/day in severe urinary tract infections.

Colisten (polymyxin E) is obtained from *Aerobacillius colistinus*. It is particularly useful in urinary tract infection and otitis media due to *Pseudomonas aeruginosa*, but gentamicin combined with ticarcillin is preferred in clinical usage. Colisten is available as a sulphomethate sodium salt for IM injection at the dose rate of 2.5-5 mg/kg, 3 times daily. Colisten sulphate is the preparation for oral administration.

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.

The parent drug and/or metabolites are secreted into bile, and undergo enterohepatic circulation. Concentrations in the bile are ten times higher than in serum. Renal excretion by glomerular filtration is the major route of elimination for most tetracyclines, but small amounts are excreted into faeces via bile.

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

Tetracycline:

Dog, cat	50 mg/kg PO, daily

Long-acting oxytetracycline:

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

As feed additive: In Nigeria, oxytetracycline is commonly incorporated in poultry feed for various purposes of growth promotion, increased feed conversion efficiency, and in the prevention and treatment of a wide range of enteric and respiratory infections of poultry. Dosage is usually 200-300gm per ton of feed. Tetracycline feed-supplement is given to ruminating calves for 7-14 days to control pneumonia due to *Pasteurella*. Growing pigs are also given tetracycline feed-supplement to prevent chronic rhinitis caused by *Haemophilus parasuis*.

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.