VPC 402- VETERINARY CHEMOTHERAPY

GUIDELINES TO THE PRINCIPLES OF ANTIMICROBIAL THERAPY

Instructional objectives

- Definitions in Chemotherapy
- Phases of development of Chemotherapy
- Classification of antimicrobial agents

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.

HISTORICAL DEVELOPMENT OF CHEMOTHERAPY (VPC 302 REVIEW)

- Ever since it was realized that a large number of diseases that afflict animals and man were caused by bacteria, scientists have been looking for substances that would kill the bacteria but leave the infected subject unharmed.
- The evolution of chemotherapy can be traced through 3 distinct periods; a pre-Ehrlich era before 1891; the period of Paul Ehrlich (1854-1915), and the period after 1935 highlighted by the discovery of sulphonamides and antibiotics.
- **Pre-Ehrlich era:** The Chinese were aware, over 3,500 years ago, of the therapeutic properties of moldy curd of soybean. They applied this material as standard treatment for carbuncles, boils and similar infections.
- The powdered bark of cinchona has been used since 1630 to treat malaria.
- In 1877, Louis Pasteur and Joubert first described the concept of antibiosis. They noted that the anthrax bacilli grew rapidly when inoculated into sterile urine, but failed to multiply and soon died if one of the 'common' bacteria of the air was introduced into the urine culture at the same time.
- **Ehrlich era:** Towards the end of the 19^{th} century, a German bacteriologist, Paul Ehrlich (1854-1915), observed that certain vital dyes like methylene blue specifically killed and stained certain bacterial cells. He reasoned that chemical substances might be produced that could unite with and destroy parasitic agents of diseases without injuring the host cells. He aptly called these chemical substances 'magic bullets'. In 1891, he demonstrated the efficacy of methylene blue in the treatment of human malaria.
- The first real step forward was the preparation of arsphenamine, an organic arsenical by Ehrlich and co-workers in 1900. This substance was of value in treating syphilis and trypanosomosis. Ehrlich is regarded as the father of modern antimicrobial chemotherapy; he was awarded a Noble prize in 1908 with a Russian bacteriologist, Elli Metchnikoff.
- Little progress was made in the next thirty years. But there were many antiseptics and disinfectants introduced that could eradicate infections when applied topically; their systemic use was precluded by their toxic reactions or tissue injury.
- **Post Ehrlich era:** In 1929, Alexander Fleming of St Mary's Hospital, London, whilst studying variants of *Staphylococcus* found one of his culture plates contaminated with a fungus (later identified as *Penicillum notatum*); the fungus destroyed surrounding bacterial colonies. His efforts to extract the bacteriolytic substances failed.

- In 1935, Gerhard Domaqk reported that the red azo dye, prontosil protected mice against infection by certain bacteria. Bovet, Nitti and Trefoues proved that prontosil owed its therapeutic efficacy to its conversion in the body to sulphanilamide. This was a milestone in the history of chemotherapy.
- In 1940, Chain, Falk and Florey of Oxford succeeded in producing significant quantities of the first penicillins from culture of *Penicillin notatum*.
- In 1944, after more than 10,000 microorganisms had been screened, Waksman and his colleagues reported the isolation of streptomycin from *Streptomycin griseus*, found in a diagnostic culture from a chicken's throat. Waksman also first defined the term 'antibiotic' as a chemical substance produced by microorganisms (bacteria, fungi, and actinomycetes) having the property of destroying other micro-organisms or inhibiting their growth in high dilution.

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, which are structurally similar and dissimilar agents such as bacitracin, vancomycin, and the imidazole antifungal agents e.g ketoconazole and clotrimazole.

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) and fluoroquinolones (eg, ciprofloxacin) which inhibit DNA gyrase.

Interference with microbial metabolism: eg sulphonamides, trimethoprim. These agents are antimetabolites, which block specific metabolic steps that are essential to microbial growth and multiplication.

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

- When exerting their effect, antibacterial agents are usually described as being 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, tetracyclines, nitrofurans, lincosamides and sulphonamides.
- In theory at least, a bactericidal effect is preferable when a rapid action is needed, when the normal host defense mechanisms are impaired (as in serious staphylococcal infections), or when attempting to avoid a residue of dormant organisms leading to 'carrier or persistor' state.

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.
- A broad-spectrum antibacterial agent is one that is capable of inhibiting a wide variety of microorganisms, including usually both G+ve and G-ve bacteria, possibly rickettsia, large virus (Chlamydia), and even protozoa. Chloramphenicol, tetracyclines, and ampicillin are examples of broad-spectrum antibiotics.
- A narrow-spectrum antimicrobial agent is one in which the antibacterial effect is restricted to a relatively small number of organisms. Penicillin, which is active mainly against G+ve organisms, polymyxin B, which is active only against G-ve organisms, and

isoniazid, which is active only against mycobacteria are examples of narrow-spectrum antibiotics.

- Streptomycin has a medium or extended-spectrum because it acts against G+ve and some G-ve bacteria.

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 use of combinations of antimicrobial drugs to treat or prevent infections is widespread. This may be beneficial in very specific circumstances on the basis that the mixture is either more potent, less toxic or has a wider spectrum of activity than a single agent used alone.
- A single, narrow-spectrum antibiotic is usually more desirable than a less specific, broad-spectrum agent.
- This strategy reduces the possibility of super-infection, decreases the emergence of resistant organisms, and minimizes toxicity.
- 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.

If two antimicrobial drugs are to be used together they must be carefully selected. A general guide is that antimicrobial agents fall into two groups:

Group 1: These have narrow and extended-spectrum bactericidal activity and include penicillins, cephalosporins, aminoglysides, bacitracin, polymyxins, quinolones, nitrofurans and metronidazole. These agents have synergistic effect if used together in certain combinations. For example, the use of penicillin G and streptomycin in mastitis and peritonitis in which the combination is more effective than either of the drugs used separately. Also the combination of β-lactam antibiotics (eg amoxicillin, ticarcillin or ampicillin) with β-lactamase inhibitors (eg, clavulanic acid, sulbactam or tazobactam), are now commonly found in fixed ratio combinations. Bacitracin, polymyxin B and neomycin are very effective when used together by topical application in skin or external ear infections.

Group 2: Members include the broad-spectrum bacteriostatic agents such as tetracyclines, macrolides, chloramphenicol, lincosamides, sulphonamides and trimethoprim. Members of the Group are seldom used together; but a combination of sulphonamides and trimethoprim (eg, co-trimazine) produces a synergistic effect.

A number of antibiotics (eg, penicillins) act only when organisms are growing. Thus, concomitant administration of a second bacteriostatic agent (e.g chloramphenicol) may interfere with the action of the first drug that is bactericidal.

COMPLICATIONS OF ANTIMICROBIAL THERAPY

Important advances made in antimicrobial drug therapy have been complicated, or offset to a large extent, by the emergence of drug-resistant microbes in animals and man, emergence of super-infection, and the appearance of toxic reactions including drug allergy and iatrogenic illnesses.

Bacterial resistance

Bacteria are said to be resistant if their growth is not halted by maximal level of an antibiotic that is tolerated by the host. Some bacteria are inherently resistant to certain antibiotics. For example, streptococci have a natural permeability barrier (a lipopolysaccharide cell wall layer) to aminoglycosides. But this can be partly overcome by co-administration of a cell wall inhibitor, eg penicillin. Often, however, resistance is acquired by mutation or by transfer of plasmids or other mobile genetic materials. Bacteria become resistant by incorporating a resistance (or R-) factor into their genes to render the antibiotic ineffective. This can pass quickly to other bacterial, carried on small pieces of genetic materials called plasmids. The resistant genes can sometimes be packaged in DNA units called transposons that allow them to jump from one DNA site to another. In multiple resistance to several antibiotics, resistance can also be transferred from one species to another. The mechanisms of bacterial resistance include:

Enzyme production: Bacteria may produce enzymes (via constitutive or inducible processes) that inactivate the drug eg staphylococci resistant to penicillin G produce a α-lactamase enzyme that destroys the drug. Gram-negative bacteria resistant to aminoglycosides produce adenylating, phosphorylating, or acetylating enzymes that inactivate the drugs.

Decreased cell wall permeability: Cell wall permeability to the drug may be decreased, limiting uptake by the organism, or the organism may develop an efflux system that pumps out the drug. For example, tetracyclines accumulate in susceptible bacteria but resistant ones do not transport tetracyclines.

Altered receptor site: Erythromycin-resistant organisms have an altered receptor or binding site on the 50s subunit of the bacterial ribosome, resulting from methylation of a 23s ribosomal RNA.

Enzyme adaptation: In some sulphonamide-susceptible bacteria, dihydropteroate synthetase has a much higher affinity for sulphonamide than for para-aminobenzoic acid. In sulphonamide-resistant mutants, the opposite is the case.

Alternative pathways: Microbes may develop alternate metabolic or synthetic pathways to bypass the effects of the antimicrobial agent. For example, sulphonamide-resistant bacteria do not require extra-cellular para-aminobenzoic acid but, like mammalian cells, utilize preformed folic acid.

Cross-resistance

This occurs commonly between agents that are closely related chemically, or that share a mechanism of action or attachment to a binding site. It is seen commonly with the tetracyclines and with members of the aminoglycoside groups.

Super-infection

When any antimicrobial agent is used (particularly broad-spectrum antibiotics, or antimicrobial combinations), there is usually suppression of part of the normal bacterial flora of the patient which is susceptible to the drug. Often this causes no ill effects, but sometimes a drug-resistant organism, freed from competition, proliferates to an extent which allows an infection to be established. The principal organisms responsible for super-infection, in which the normal microbial flora of the gut, upper respiratory or genitourinary tract are altered, are fungi (*Candida*), yeast, or resistant bacteria (*Staphylococci, Pseudomonads, Proteus*), which are difficult to treat. Super-infection is the cause of much of the diarrhea and otitis externa encountered with prolonged administration of broad-spectrum antibiotics such as tetracyclines.

Antimicrobial prophylaxis

Prophylactic use of antimicrobial agents in certain clinical situations may be successful provided that the identity of the invading organism can be reasonably surmised. For example, antimicrobial agents are used to protect healthy animals against invasion by specific organisms to which they have been exposed (eg. diarrhoea in a litter of pigs); to prevent secondary bacterial infection in viral diseases, and in surgery in infected tissues. Antibacterial prophylaxis is used to reduce the risk of infection in animals with various types of chronic illness, or on chronic corticosteroid therapy and at times of stress (eg, calves and cattle arriving from or being shipped long distances to market), and to prevent the spread of disease from area of localized infection, eg, gas gangrene.

Extra-label use of antimicrobial agents

Antimicrobial agents are commonly used in veterinary practice, either to prevent or treat disease, or in food animals to promote growth and feed conversion efficiency. In Nigeria, veterinary drugs are sold and purchased in the open market, over the counter, and without prescription. Therefore, there are other extra-label uses of antimicrobial agents, ie, uses other than specified by the product labeling, such as in food preservation (eg, subtilin in canned food; chlortetracycline in ice and dipping solution for fish preservation, and streptomycin to preserve meat). A combination of penicillin, streptomycin and polymyxin B has been added to bull semen

in artificial insemination to prevent bacterial contamination and improve fertility. The extra-label use of drugs constitutes a major problem for regulators and the consuming public, and contributes to drug residue and resistance problems.

Antimicrobial dosage

One of the major causes of therapeutic failure associated with the use of antimicrobial drugs is when improper dosing regimens (eg, wrong dose, wrong route of administration, inappropriate dosing interval) are maintained. Most antimicrobial agents are administered for at least 3 days (typically 5-7 days) or until evidence of infection (eg, fever, leucocytosis) has been absent for at least 2 days. In serious infection, high doses are administered every 8 hours or more frequently. Depot preparations are long acting; they attain relatively low plasma-drug concentrations and are not suitable for treatment of acute severe infection.

Route of administration

The route of administration of antimicrobial agents depends upon the severity of the disease and ease of administration. In severe infections it is advantageous to give the initial dose by the intravenous route. In companion animals, subcutaneous injection may be preferred to the more painful intramuscular route. Although oral medication given with food is often convenient, it may considerably reduce the amount of drug absorbed. For example, ampicillin is poorly absorbed in dogs if administered following a meal. Milk, iron salts, and antacids all interfere with the absorption of tetracyclines from the gastrointestinal tract.

Adverse effects

Most of the antimicrobial drugs in current use have low order of toxicity. Nevertheless, they are capable of producing a wide range of toxic effects by affecting cellular processes in the host directly. For example, aminoglycosides can cause ototoxicity by interfering with the membrane function in the hair cells of the organ of Corti. Also penicillins, despite their almost absolute selective microbial toxicity can cause serious hypersensitivity problems in small animals, horses and man, ranging from urticaria (hives) to anaphylactic shock. Bloat, diarrhoea, inflammatory reactions at injection sites and abortion are observed following the use of antimicrobials in food animals. Kidney and liver damage are particularly important in small animals. In some cases, one species may show a particular susceptibility. This is true of the cat in which the toxic effects of streptomycin and chloramphenicol are more severe than in other species. The presence of antibiotic residues in meat, milk, or eggs poses potential human health hazards. Allergic skin

condition, nausea, vomiting, anaphylactic shock and even death have resulted from the ingestion of such residues.

ANTIBACTERIAL AGENTS – PENICILLINS, CEPHALOSPORINS, AMINOGLYCOSIDES AND TETRACYCLINES

- Antibacterial agents are among the most commonly used and misused of all drugs.
- Antibiotics are chemical substances produced by living organisms (fungi, bacteria and actinomycetes) that will kill other microorganisms or inhibit their growth and multiplication. Common usage often extend the term Antibiotics to include synthetic antimicrobial agents e.g sulfonamides and quinolones.

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. His efforts to extract the bacteriolytic substance failed. In 1940, Chain, Florey and their colleagues at Oxford succeeded in producing significant quantities of the first natural penicillins from cultures of *Penicillium notatum*. 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.

Penicillins are extremely effective antibiotics, and very widely used. They are among the least toxic drugs known; their major adverse effect is hypersensitivity reaction.

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). The carboxyl group attached to the thiazolidine ring is the site of salt formation

(sodium, potassium, procaine, etc). Cleavage of the β -lactam ring destroys antibacterial activity; some resistant bacteria produce β -lactamases (penicillinases). Amidase cleavage of the amide bond side chain yields 6-aminopenicilanic acid (6-APA) nucleus, which is used in producing semisynthetic penicillins.

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. They have similar antibacterial spectrum to penicillin G, but are less active. They should not be used for severe infections because their absorption can be unpredictable, and plasma-drug concentrations variable. They are also not used for the treatment of bacteraemia because of their higher minimum lethal concentration (MLC).

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. Their use is restricted to the treatment of infections caused by penicillin-resistant staphylococci. Cloxacillin is commonly incorporated into intra-mammary and ophthalmic preparations. Flucloxacillin is better absorbed and is available for oral administration. The use of methicllin and nafcillin is now confined to laboratory sensitivity tests.

β-Lactamase inhibitors

β -lactamases are a family of enzymes produced by many penicillin-resistant organisms (eg, staphylococci, gonococci, and most gram-negative rods). These enzymes inactivate β-lactam antibiotics by opening the β-lactam ring. 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. β-lactamse inhibitors are formulated with penicillins to act as 'suicide' inhibitors. Clavulanic acid is produced by *Streptomyces clavligerus*. It is combined with amoxicillin as co-amoxiclav (clavulanate-potentiated amoxicillin), or with ticarcillin as timentin. Sulbactam-ampicillin and tazobactam-piperacillin (as tazocin) combinations are also available. Potentiated penicillins are used in dogs

and cats to treat skin, respiratory and enteric infections caused by β-lactamase producing organisms.

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. They are acid-stable, but not penicillinase-stable. Ampicillin is well absorbed after oral administration. It is excreted into both bile and urine; the concentration in the bile may be forty times higher than the level in the plasma. This is of use in the treatment of cholecystitis. Ampicillin has wide usage in veterinary medicine, but many bacteria quickly develop resistance to it. Amoxycillin, a para-hydroxy analogue of ampicillin, is twice as well absorbed when given orally to dogs, giving higher and longer sustained blood, tissue, bile and urine levels. Its half-life is 17 hours, whereas that of ampicillin is 12 hours. Amoxycillin also has greater resistance to gastric acid. It has been used to treat urinary tract infections and streptococcal infections of the upper respiratory tract and skin.

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. Pivmecillinam is an oral agent; it is hydrolysed in vivo to the active form mecillinam (which is poorly absorbed by mouth). It has been used to treat urinary tract infection. Diarrhea and abdominal pain may occur.

Antipseudomonal penicillins

Carboxy penicillins

Carboxypencllins (carbenicillin, ticarcillin) in general have the same antibacterial spectrum as ampicillin (and are susceptible to β-lactamses), but have the additional capacity to destroy *Pseudomonas* and *Proteus* spp. They are used alone or in combination with the aminoglycosides; gentamicin or tobramycin to cure serious *Pseudomonas* infections. Carboxypenicillins inactivate aminoglycosides if both drugs are administered in the same syringe or intravenous infusion system. Carbenicillin has largely been replaced by ticarcillin that is four times more potent in

Pseudomonas infection. Ticarcillin is presented in combination with clavulanic acid (as timentin).

Ureidopenicillins

Ureidopenicillins (azlocillin, mezlocillin, piperacillin) are adapted from the ampicillin molecule, with a side-chain derived from urea. Their major advantage over the carboxypencillins is expanded spectrum of activity against gram-negative organisms including *Pseudomonas, Enterobacter* and *Klebsiella* spp. The high cost of ureidopenicillins limits their use to the treatment of severe gram-negative infections of dogs and cats. For pseudomonas septicaemia, an ureidopenicillin plus an aminoglycoside provides a synergistic effect.

Therapeutic uses of penicillins: The penicillins are commonly used to treat or prevent local or systemic infections caused by susceptible bacteria. 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

Intramammary infusion:

Sodium cloxacillin	200 mg/quarter
Benzathine cloxacillin	500 mg/quarter

Infusion of benzathine cloxacillin into the under is effective in the prevention and control of bovine mastitis, the only use for which it is recommended in animals.

Ampicillin

Dog, cat	10-20 mg/kg PO, 2-4 times per day
Cow	5-10 mg/kg IM, IV, SC, 2-3 times per day

Amoxycillin

Dog, cat	11mg/kg PO, 2 times per day
Cow, other animals	4-7 mg/kg IM, 1-2 times per day

Ticarcillin

All species	15-110 mg/kg IM, IV, 3-6 times per day

Amoxycillin + Potassium clavulanate (co-amoxiclar)

All animals	10-20 mg/kg (amoxicillin) and 2.5-5 mg/kg (clavulanate) PO, 2 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.