In the name of Allah

Practical antimicrobial therapeutics

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Practical antimicrobial therapeutics

- Page(153-173)
- The success of antimicrobial therapy depends upon maintaining, at the site of infection, a drug concentration that will result, directly or indirectly, in the death or control of the infectious organism with minimal deleterious effect to the host.
- In order to achieve this aim the antimicrobial agent must have activity against the organism at its site of infection and it must be administered in such a way as to maintain an effective inhibitory or lethal concentration.

- Cost
- Tissue residue problems and withdrawal periods
- Animal welfare
- Antimicrobial resistance

- In the theoretically ideal situation, the following steps would be taken before selecting an antimicrobial agent for therapy.

➢ First, the site of infection would be located and the identity of the infecting organism established by culture

➢ Second, the minimal inhibitory concentration (MIC) of each antimicrobial agent for the infecting organism would be identified.

➢ Third, an initial selection would be made based on the sensitivity of the organism and the knowledge of the capacity of the individual antimicrobial agents to penetrate to the site of infection and to achieve and exceed these concentrations at nontoxic dose rates.

- Fourth, the dose rates, route of administration and frequency of administration required to achieve these concentrations for each of the selected antibiotics, in the particular animal species being treated, would then be considered.
- Finally, selection of a particular drug would be based on a consideration of the potential toxicity to the host, on the likely relative efficiency of each drug, on the cost and ease of administration and, in food animals, on costs associated with the relative withholding periods.
- recommended dose

IDENTIFICATION OF THE INFECTION BY CLINICAL EXAMINATION

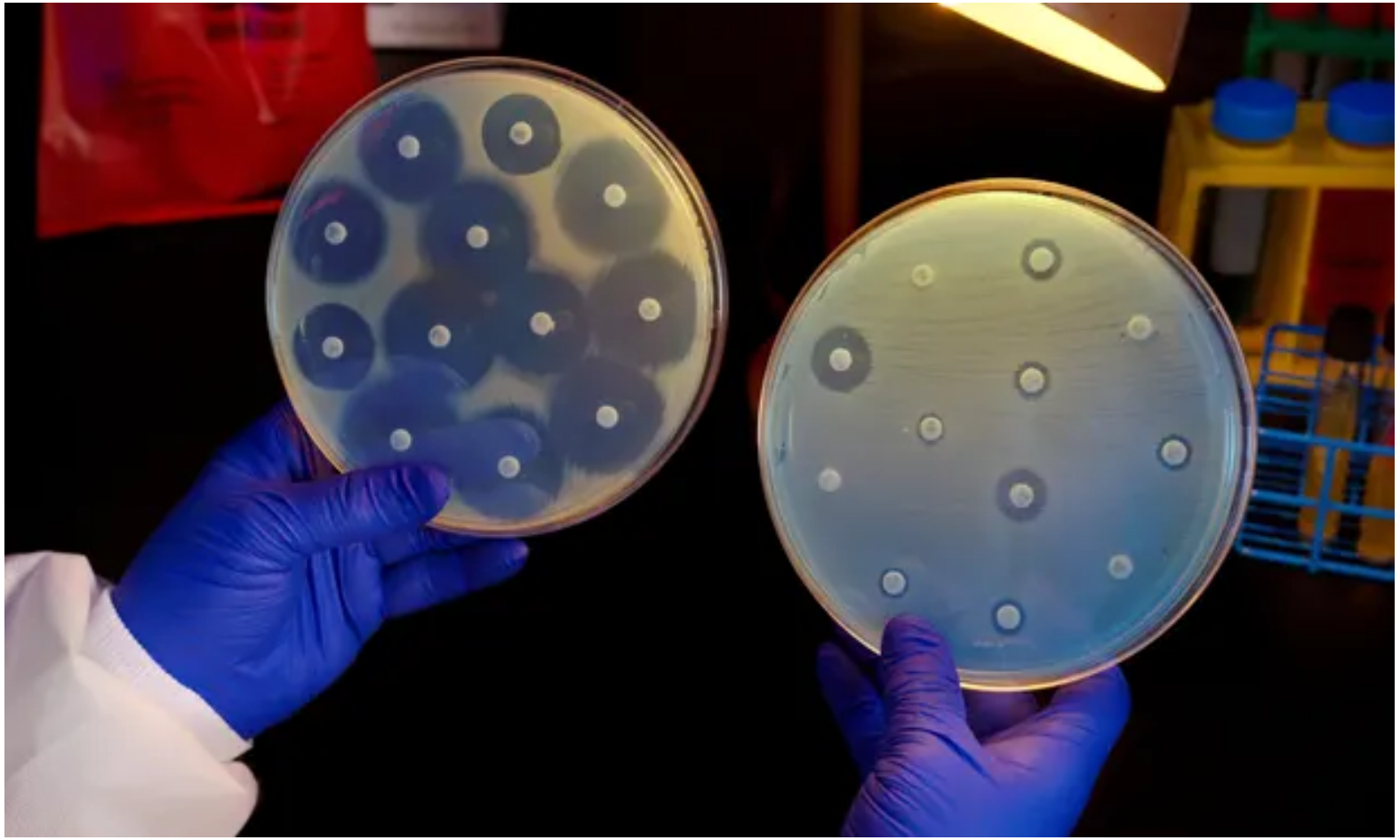
- accurate clinical diagnosis
- Differential diagnosis and with the relative prevalence of each condition in their area.
- peracute mastitis in recently calved cows is most commonly associated with infection by *staphylococci* but can also be associated with coliform organisms or, more rarely, *Actinomyces (Corynebacterium) pyogenes* or *Pasteurella multocida*

- **TAKING SAMPLES FOR DIAGNOSIS**
- ANTIMICROBIAL SENSITIVITY TESTS

- **ANTIBIOTIC RESISTANCE**

➢There is a higher prevalence of antibiotic-resistant *E. coli* in the normal intestinal flora of young animals than adults.

➢There is a particular risk to farmers, farm workers and veterinarians from exposure to contamination in the farm environment and a risk from transfer of resistant bacteria through farm food and via environmental contamination from farm effluents



Practical usage of antimicrobial drugs

- Theoretically, there is no set dose for any antimicrobial agent. The concentration of an antimicrobial drug required for effective activity against different microorganisms varies and these requirements could be met by varying the dose rate of the drug. However, this is an impractical situation and in practice one works from the **recommended dose**.

- The recommended dose is one that will give blood and tissue levels that will be effective against very susceptible organisms, with minimal side effects to the host. In this respect the recommended dose should be considered as a minimum dose.

- The label dose is the dose stated on the label of the drug and is the legal dose that can be used for that product. The label states the required withdrawal periods for avoidance of tissue or milk residues.
- The recommended doses given in the sections on individual diseases are based on our expectations of therapeutic efficiency, and may exceed the label dose recommendations for certain drugs.

- Label dose levels and dose intervals for many of the antimicrobial agents used in large animals are frequently too low and too long.
- The ultimate proof for dose levels and dose intervals of an antimicrobial is by clinical trials of its efficacy in the treatment of infectious disease.

- they will suggest changes in the dose levels and intervals for several of the antimicrobial drugs in use, which may result in more efficacious therapy and lead to label doses that have a broader spectrum of activity against disease.

Box 6-1 Pros and cons of empirical therapy versus culture and susceptibility-based antibiotic therapy

Empirical choice	Susceptibility-based choice
Advantages	**Advantages**
• Quicker	• Very likely to have the right antibiotic
• Cheaper	• More likely to have correct dosing regimen
Disadvantages	• Save time and money if wrong antibiotics are chosen empirically
• More likely to have the wrong antibiotics (up to 50% of cases)	**Disadvantages**
• More likely to have the wrong dosing regimen	• Takes 24–48 h
• Potential waste of time	• Cost
• Potential waste of money	• One to two member(s) of each class tested (assumption of similar results with other members)
• Potential for resistance (50% of isolates resistant to antibiotics commonly used empirically)	• Laboratory protocol might not perfectly represent reality

ROUTES OF ADMINISTRATION

- **INTRAVENOUS INJECTION**
- Intravenously administered antibiotics attain high and immediate blood and tissue levels.
- Septicemia, The concentrations obtained are much higher than those obtained with equivalent doses of the same drug given intramuscularly or orally, and consequently greater diffusion concentrations are achieved at sites of infection. For this reason this route of administration may also be used in an attempt to increase the drug concentration in areas where the antibiotic normally achieves only low concentrations, and where areas of necrosis increase the length of the diffusion pathway.
- Intravenous administration may also be indicated in chronic infections such as corynebacterial pneumonia in foals, where high diffusion concentrations are required in order to penetrate the abscess areas and the capsular material of the organism.

- An initial intravenous loading dose may combat the development of stepwise resistant mutants. Because of the initial higher blood and tissue levels, the intravenous route may also be used for the treatment of infections that are only moderately sensitive to the antibacterial drug being used. This is because effective concentrations may be achieved by repeated intravenous dosing which would not be achieved by equivalent doses given intramuscularly or orally.

- For practical reasons the intravenous route of administration is used for low concentration, high-volume antimicrobial agents such as sulfamethazine and oxytetracycline. It is also preferred to the intramuscular route in race horses where there is a need to avoid muscular soreness.
- The need to avoid muscle damage in beef cattle close to marketing may also dictate intravenous administration.

- Administration by this route is not without its dangers. Acute toxic reactions either to the drug or to its vehicle are more common when intravenous administration is used. Drugs specifically formulated for intravenous use should be used, or the manufacturer's recommendations on the advisability of the use of this route for any preparation should be followed. Severely toxemic terminal cases may die immediately following injection, and in the owner's mind death may be attributed to the therapy.

- Injections should be given slowly and not as a bolus. Therapy by repeated intravenous administration is generally restricted to hospital situations and can be expensive because of the added cost of the intravenous preparations. In field situations an initial intravenous loading dose followed by sustaining intramuscularly administered doses is frequently indicated in the treatment of infectious diseases and is sound therapeutic policy.

- The jugular vein is used in all species except the pig, where the inaccessibility of superficial veins other than the ear veins makes the jugular route of administration generally impractical. Perivascular reactions and intravascular thrombosis are a hazard with this route, especially following the administration of irritant drugs such as sulfonamides and tetracyclines.

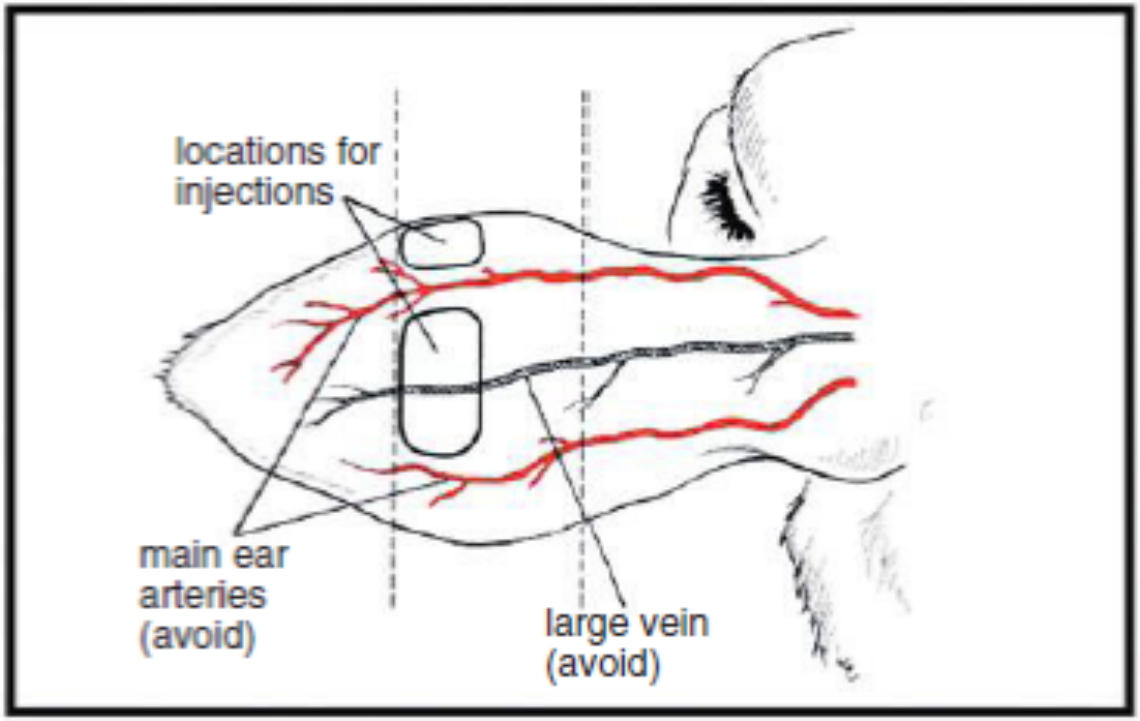
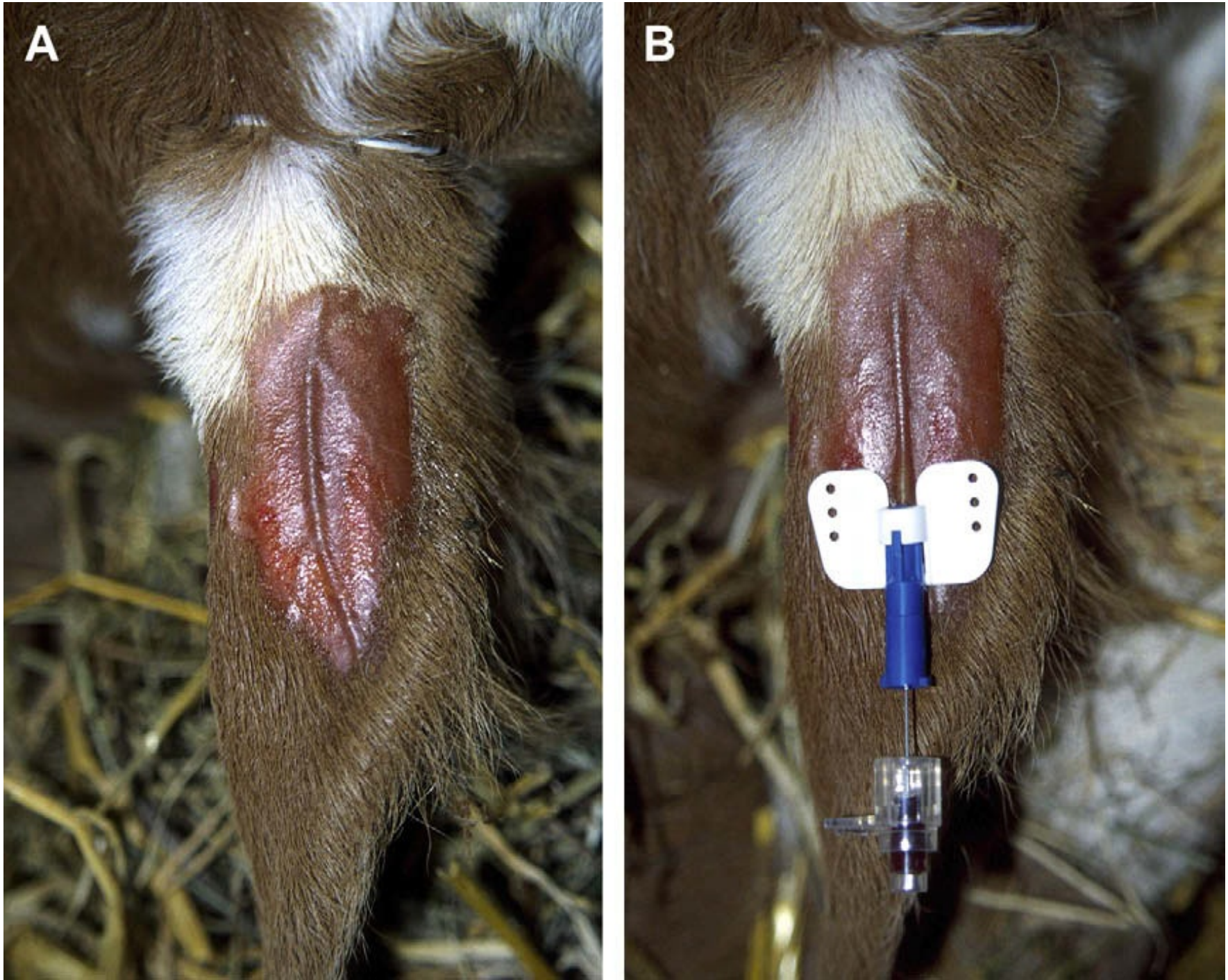


Fig. 6-1 Diagram of the approximate locations of the major arteries of the posterior ear and the recommended needle insertion locations. Administration of Excede Sterile Suspension into ear arteries is likely to be fatal. Excede can also be administered SC at the base of the ear in a rostral direction toward the eye on the same side of the head as the ear, or administered SC at the base of the ear in a ventral direction. (Courtesy of Zoetis, Inc., https://www.zoetisus.com/products/pages/excede_beef/TechnicalResources.aspx Excede® (Ceftiofur Crystalline Free Acid) Sterile Suspension.)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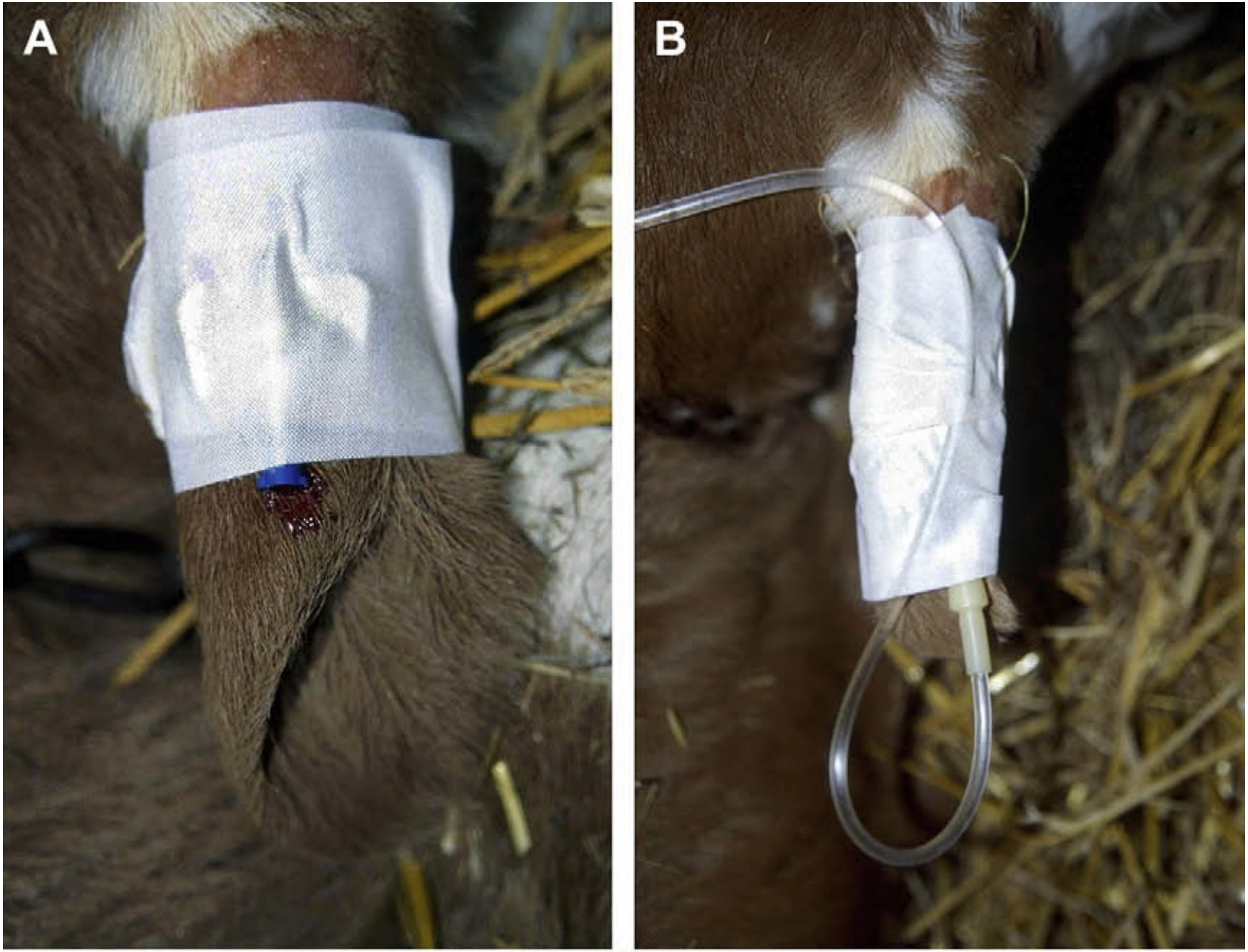
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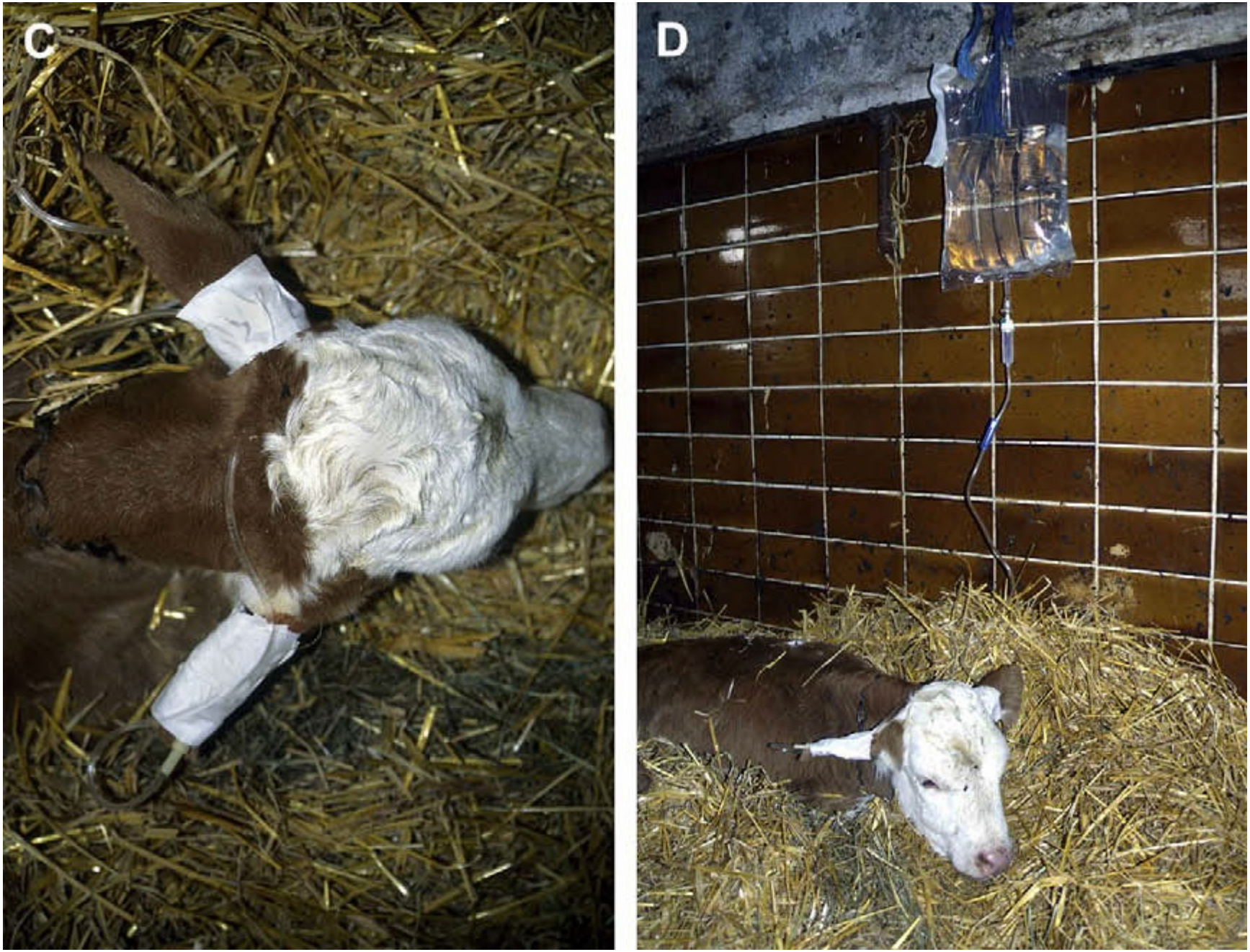
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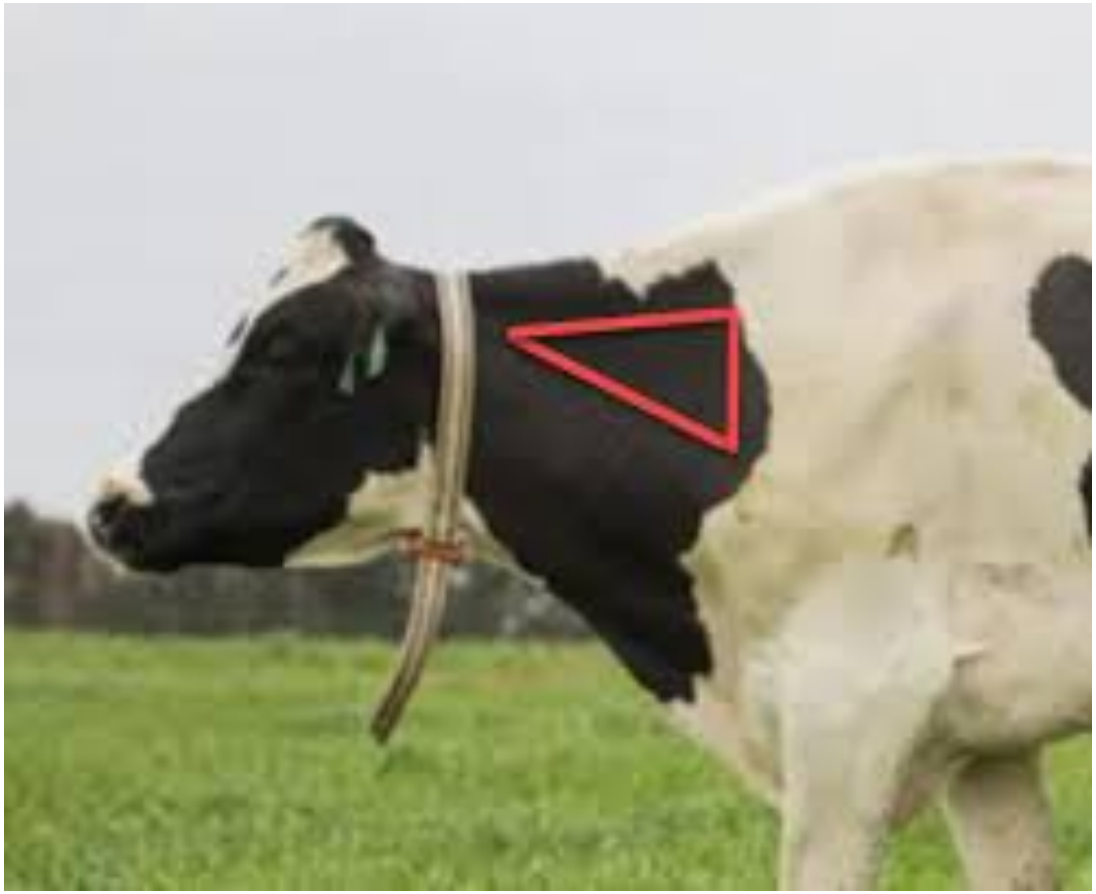
INTRAMUSCULAR INJECTION

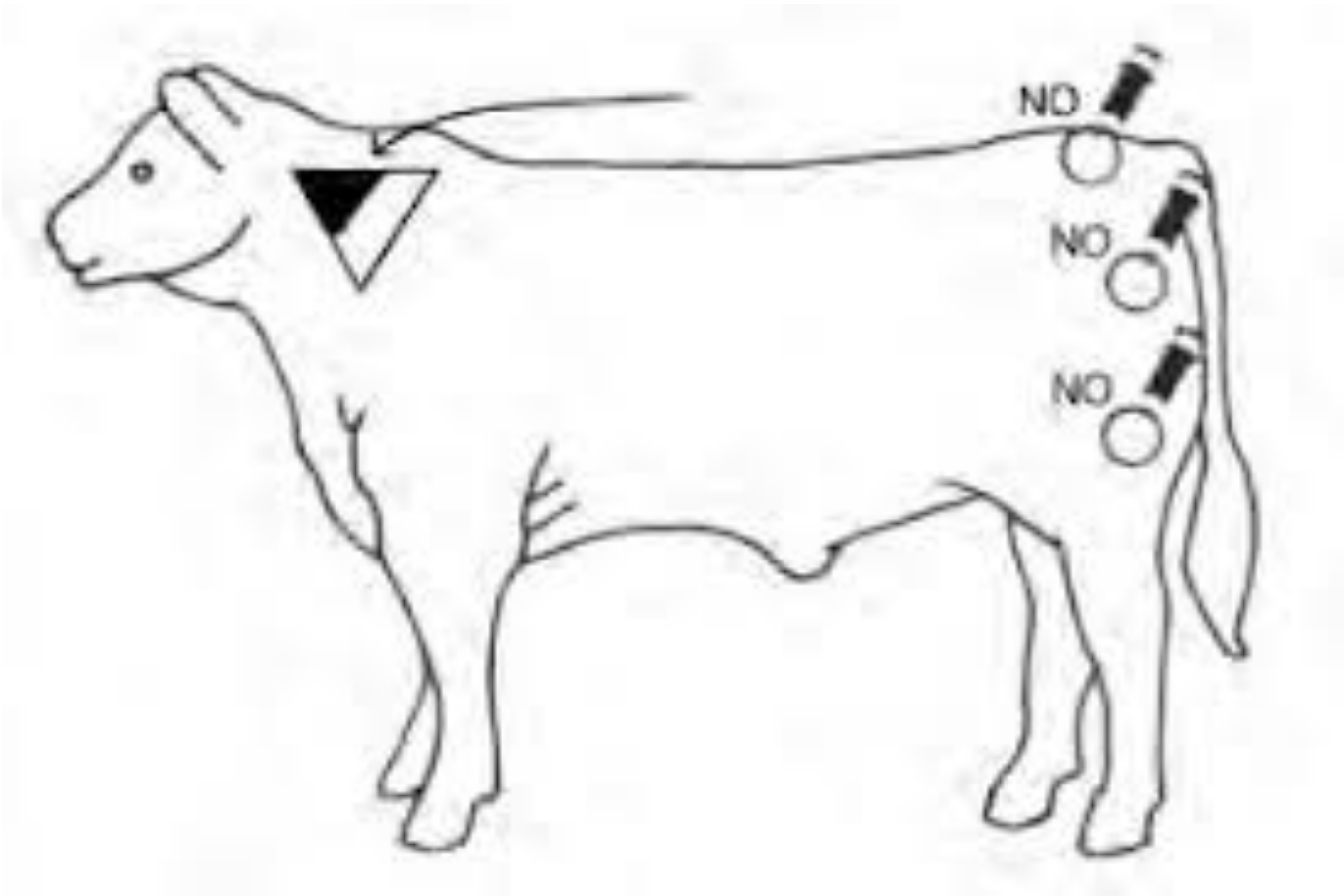
- Intramuscular injection is the most commonly used method for antimicrobial administration in large animals. Where possible this route should be avoided in meat-producing animals, especially with irritant preparations.
- Lesions can be detected at slaughter 12 months after the intramuscular injection of long-acting tetracyclines.

- If the drug must be given intramuscularly in a meat-producing animal it should be given in the muscles of the neck, as scar tissue and blemish are more likely to be detected at this site in the cutting process after slaughter and they can be trimmed. With certain antibiotics, drug residues may persist at these sites for long periods, and the label recommendation for withdrawal or withholding time should be followed.

- Irritant drugs should be used with care in horses, or avoided, as this species more commonly develops severe reactions at the site of injection. The development of such reactions is usually an indication to change to alternative therapy. Oil-based vehicles frequently produce severe reactions at the site of injection in horses and should not be used.

- There is evidence, for some antibiotics at least, that the site of intramuscular administration can influence the rate of absorption, the bioavailability and the subsequent pharmacokinetics of the administered antibiotic. In both cattle and horses, injection in the neck gives more favorable pharmacokinetic parameters than does injection into the gluteal or shoulder muscles.
- Injection into the dewlap gives the poorest bioavailability

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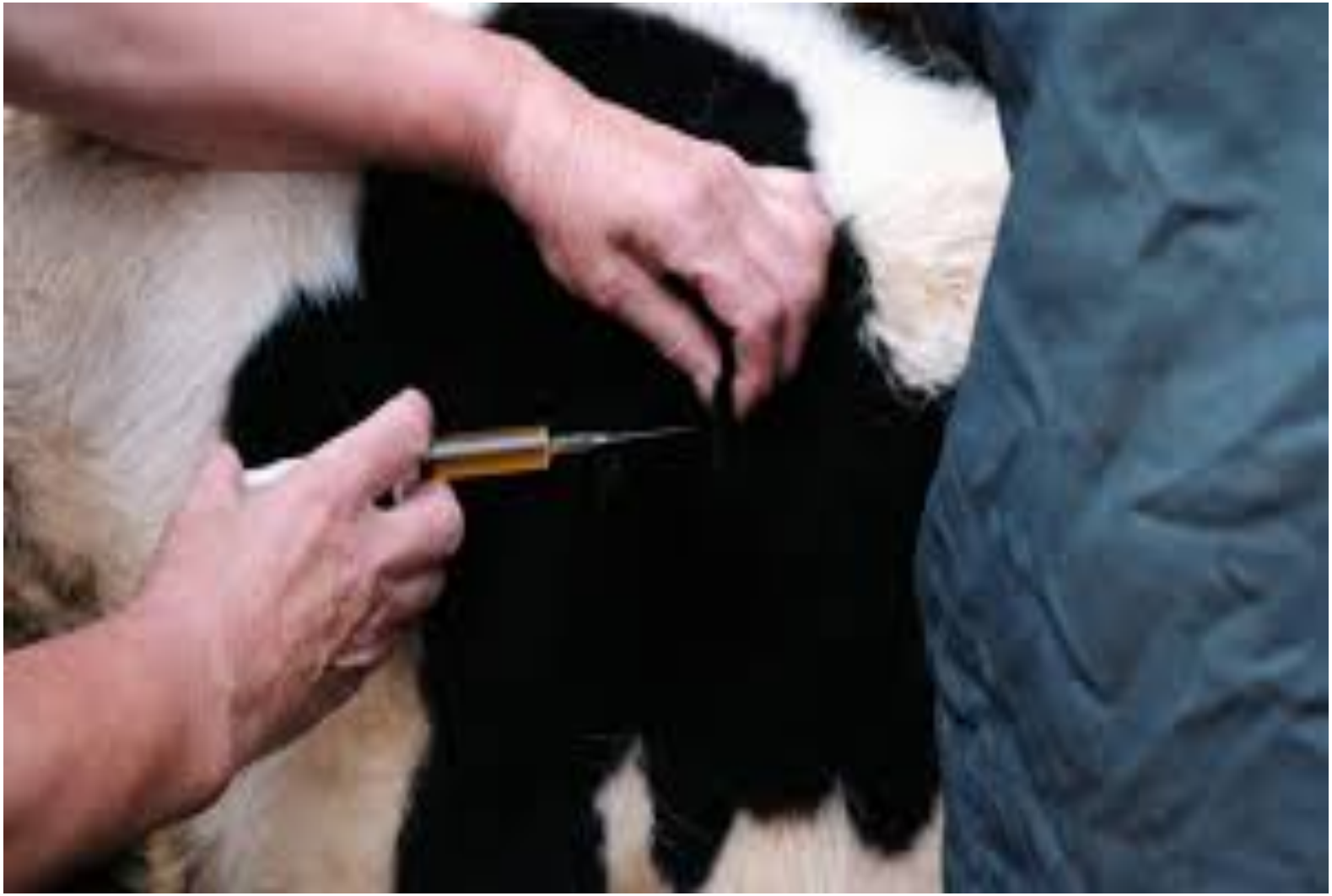
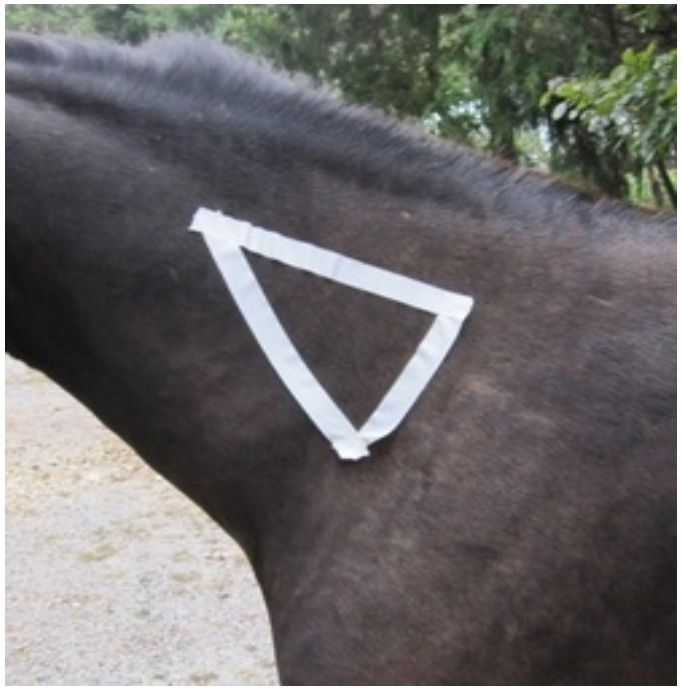
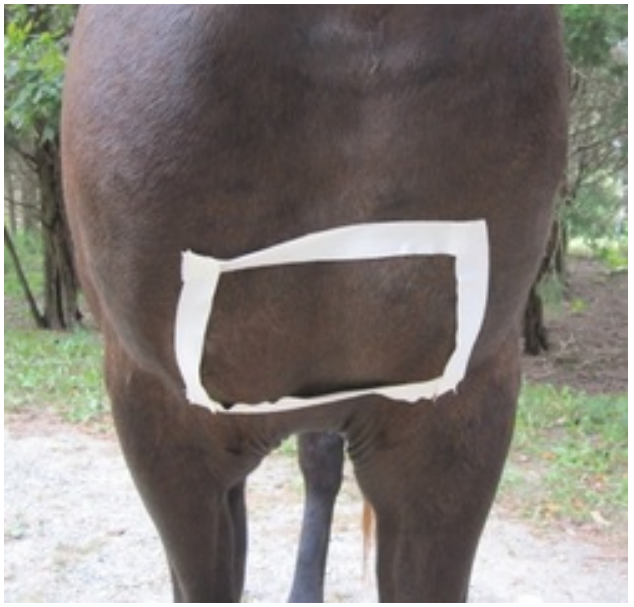
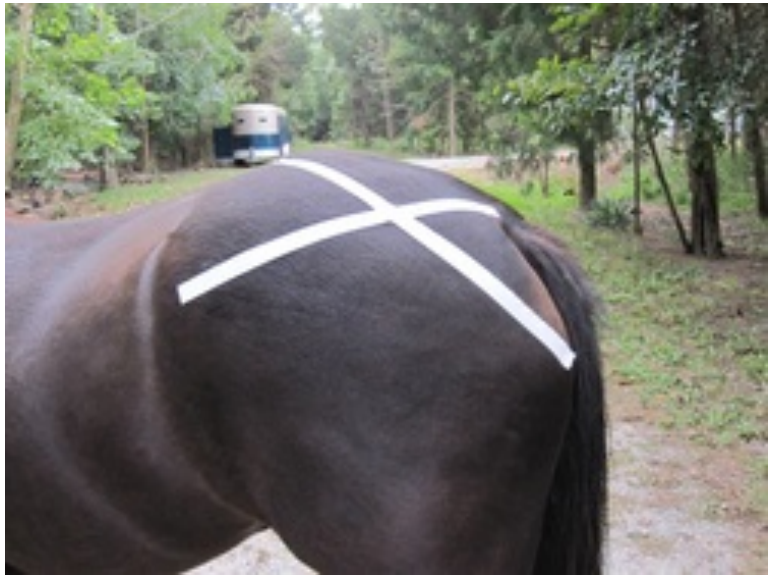
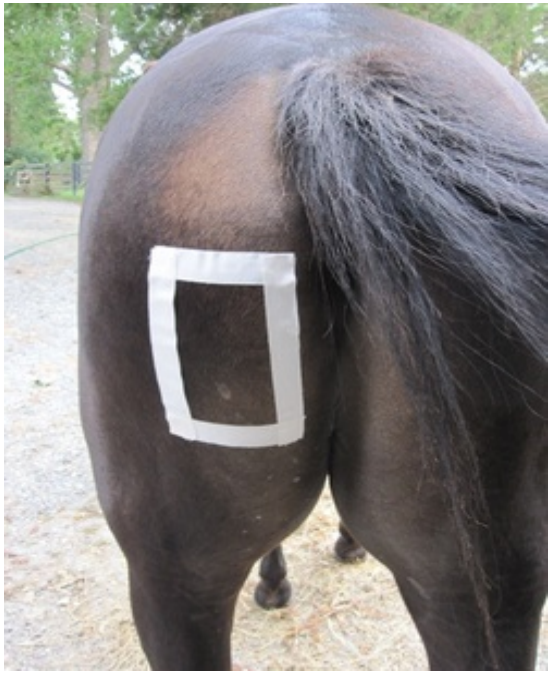


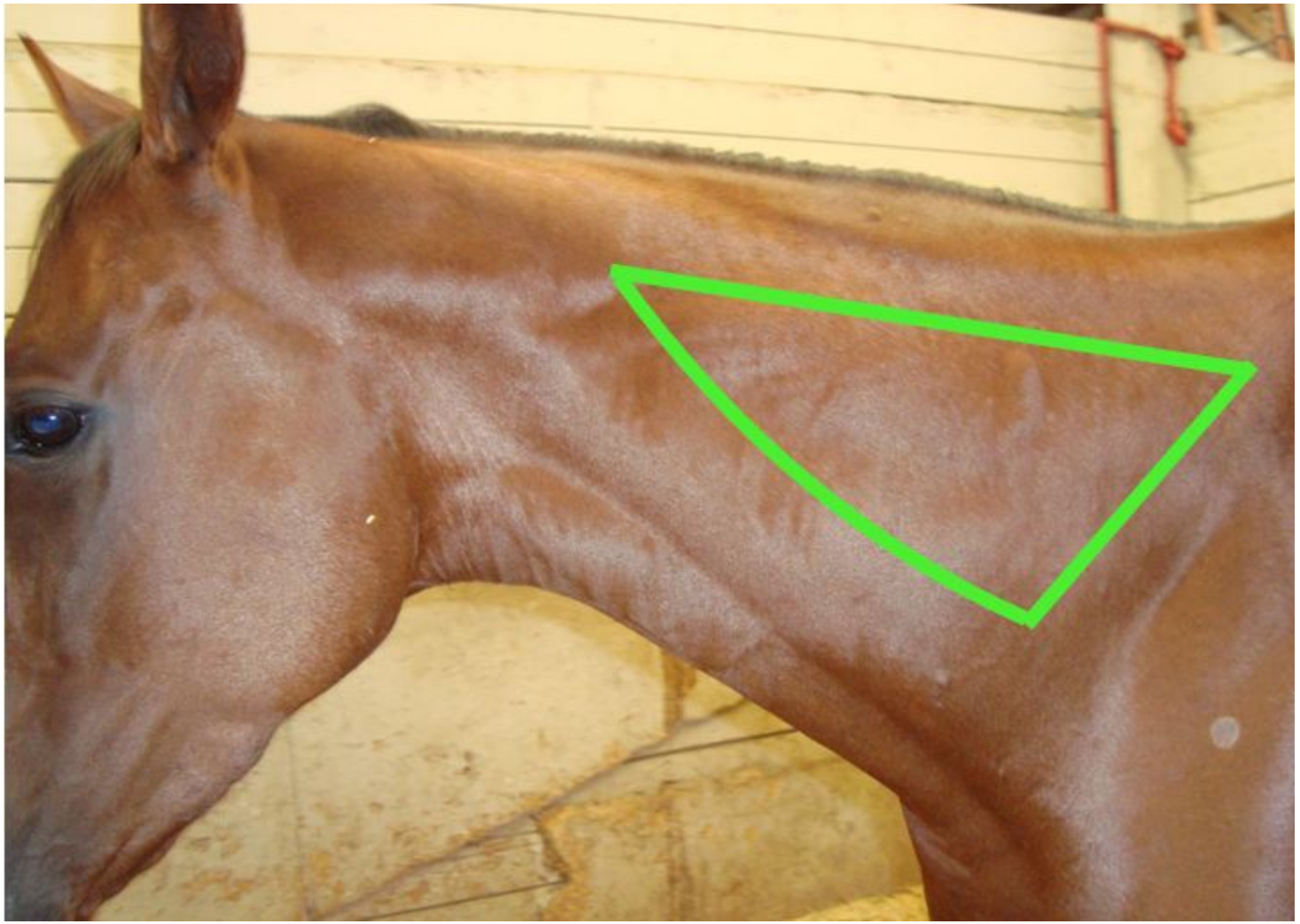
- Injection into the side of the neck of horses is considered to be malpractice in some countries. When irritant preparations must be given to horses it is wise to inject them into the muscle of the chest between the forelegs, as reactions in this area have less tendency to spread and are more accessible to drainage and treatment.

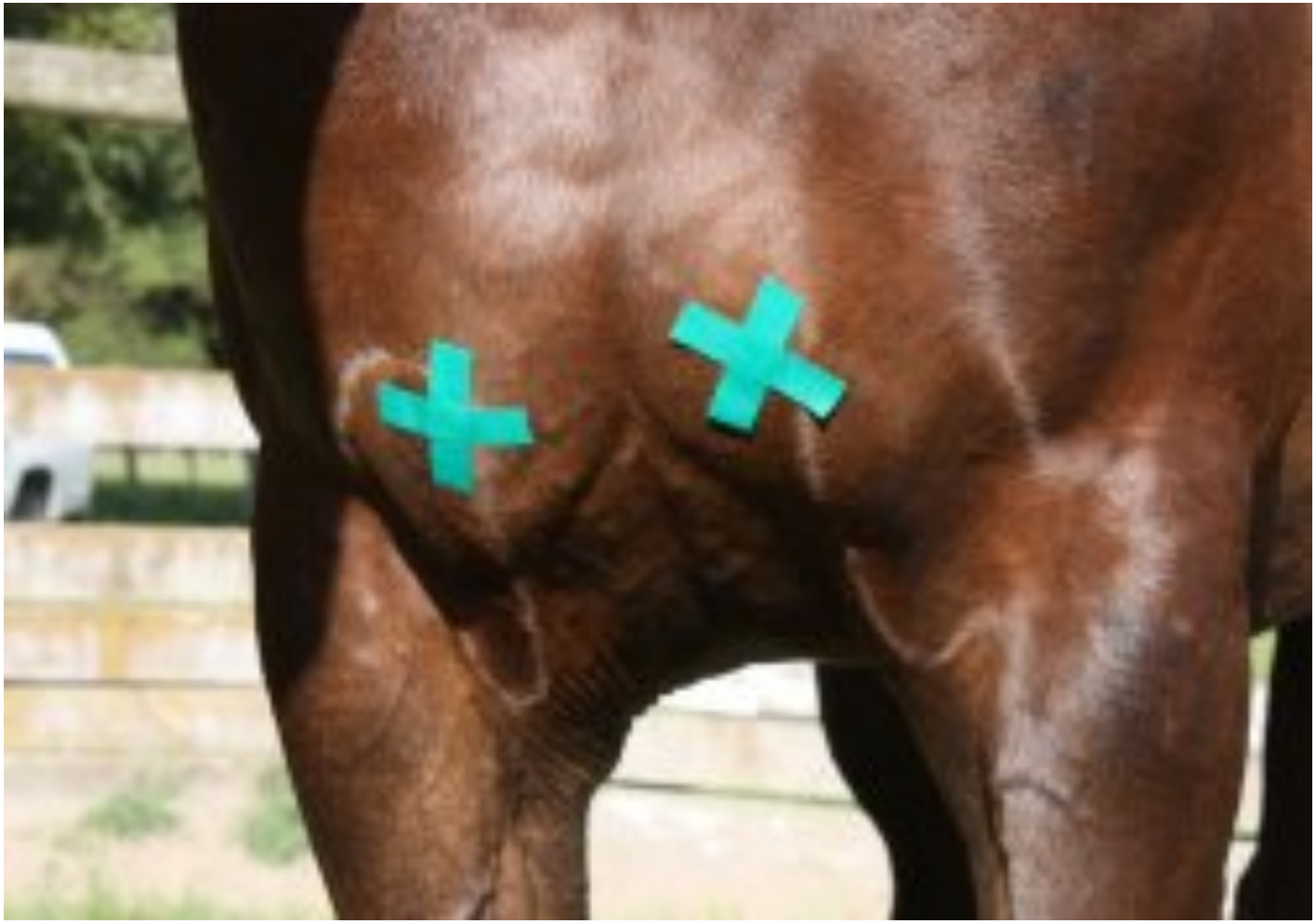












- At all sites, care should be taken to ensure that the injection is not inadvertently given intravascularly, by applying negative pressure to the syringe prior to injection. In adult animals no more than 10 mL should be given at any injection site. Large injection volumes can result in the formation of encapsulated antibiotic filled cysts in muscle.

- With most antimicrobial drugs, excepting the repository forms and drugs of an irritant nature, peak blood concentrations are obtained within 30-120 minutes of injection. However, the bioavailability of drugs given by intramuscular injection is markedly influenced by their formulation and irritant nature. This is especially marked with oxytetracycline preparations

INTRAPERITONEAL INJECTION

- Intraperitoneal injection is occasionally used for antimicrobial administration, especially in cattle close to market size, and where intravenous administration for various reasons may be impractical.

- In cattle the injection is given in the right flank midway between the last rib and the tuber coxae and at least 10 cm ventral to the lateral processes of the lumbar vertebrae so as to avoid retroperitoneal and perirenal deposition of the drug. An aseptic injection technique should be used. Animals with peritonitis are also occasionally additionally treated by this route of injection. In horses with peritonitis the peritoneal cavity can be drained through a cannula inserted in the ventral midline as used for abdominal paracentesis, and the antimicrobial agent is injected via this route. Intraperitoneal injection may also be used for the parenteral administration of the tetracycline group in acutely toxemic animals or in animals with severe respiratory distress where intravenous injection may result in collapse and even death.

SUBCUTANEOUS INJECTION

- Subcutaneous injection has not been commonly used in large-animal practice but concerns regarding lesions in meat following intramuscular injections is leading to a greater use of this route.
- Providing the drug is not deposited in a fat depot, this route provides a reasonable alternative to intramuscular injection. With irritant preparations there is a danger of excessive reaction and the occurrence of sterile abscesses.

ORAL ADMINISTRATION

- Oral administration of antimicrobial agents is generally restricted to preruminant animals, young foals and pigs. The blood and tissue levels achieved following oral administration are considerably less than those achieved by an equivalent dose of the same antimicrobial agent given parenterally, and for this reason the oral dose rate is generally 2-5 times greater than the parenteral dose. Oral drugs are less reliable because absorption characteristics may vary with the volume of ingesta, the presence or absence of gastric and intestinal stasis or hypermotility and the nature of the ingesta, which variably bind the orally administered drug. For example, oxytetracycline and trimethoprim have a much lower bioavailability to calves when administered in milk, rather than in water, because of the high degree of binding to milk.

- There is some evidence that the oral administration of antibiotics to calves in glucoseglycine- electrolyte solutions is associated with more favorable absorption characteristics.
- The aminoglycoside and polymyxin groups of antimicrobial agents are not absorbed from the alimentary tract and benzylpenicillin is largely destroyed within the stomach.

- The oral route is the one of choice for the treatment of enteric infections. Experimental studies have shown that the oral administration of antibiotics to healthy neonatal calves may induce villous atrophy within the intestine and a malabsorption diarrhea. This occurred particularly with neomycin and to a lesser extent with tetracycline and ampicillin. Although this does not negate the use of antibiotics for specific therapy of enteritis in young calves (when this is indicated), it does suggest that prophylactic use of oral antibiotics has a risk in young calves

- Prolonged oral medication at therapeutic levels may result in superinfection in all animal species. Commonly a yeast, staphylococcus or *Pseudomonas aeruginosa* is involved. It occurs most commonly in calves given courses of differing antimicrobial agents. It is more common following medication involving tetracyclines and usually a treatment period of at least 2 weeks is required for its development.

- Antimicrobial drugs are seldom given orally to ruminant animals. Exceptions are the use of sulfonamides, especially as sustaining medication following initial parenteral treatment, and low-level antibiotic therapy to feedlot animals to reduce the incidence of liver abscess and respiratory disease. Blood levels following oral administration in ruminants are variable and frequently not achieved until 12-18 hours after dosing. Also, many antibacterials are destroyed or inactivated within the rumen. Orally administered antimicrobials cause a significant disruption of the ruminal flora and by itself this may result in a syndrome of ruminal stasis, anorexia and depression. If antibacterial agents are given orally to ruminants, the course should be followed by reestablishment of the ruminal flora by cud transfer.

Dietary medication

- This is generally used for long-term disease control. In many countries, the amount of an antimicrobial that can be added to a feed is restricted to the approved label level and the veterinarian has no legal right to alter this concentration. The drug is usually added at the feed mill.

OTHER ROUTES

- These include intra-articular, intrapleural and subconjunctival injection.
- Non-irritant preparations should be used with strict aseptic technique. In most cases these treatments should be supported by parenteral treatment.
- Intramammary infusion
- Intratracheal administration of antibiotics has its advocates for the treatment of pneumonia in cattle. In theory, this could result in higher levels of antibiotics at the site of infection, although with many pneumonias diffusion through the affected lung must be minimal

- The antibiotics are administered in sterile physiological saline equivalent to 2.0 mL/kg body weight. An extensive study has shown variation in absorption and persistence between antibiotics administered by this route, when compared to parenteral administration, but has concluded that there is no potentially useful advantage to its use

- The local administration of antibiotics may not always be the preferred route despite historical precedence. For example, in the treatment of the genital tract, it has been shown that parenteral administration of antibiotics achieves tissue concentrations of drug in all areas of the genital tract, whereas intrauterine infusion results in comparable concentrations only in the endometrium and uterine secretions. Local and/or parenteral administration may be indicated in different cases of genital tract infection.

DRUG DISTRIBUTION

- **ABSORPTION**
- Antibiotics of the aminoglycoside group and polymyxins are not absorbed from the alimentary tract and if circulating levels of these antibiotics are required they must be given by parenteral injection. Where both intestinal and systemic levels are required, as may be the case in neonatal colibacillosis, these drugs should be given both orally and parenterally. Benzylpenicillin and methicillin are destroyed by acid pH and significant blood levels are not achieved following oral administration but blood levels are achieved with ampicillin and amoxicillin. Certain sulfonamides (phthalylsulfathiazole, phthalylsulfacetamide, sulfaguanidine and succinyl sulfathiazole) are not absorbed from the alimentary tract. The remaining antibiotics and sulfonamides are absorbed following oral administration in preruminant calves and lambs and in pigs and horses. However, in general, blood and tissue levels obtained are considerably lower than those achieved with equivalent doses given parenterally. Whey feeding (calcium) will inhibit the absorption of tetracylines in pigs.

DISTRIBUTION

- Factors governing the distribution of antimicrobial agents in the body fluids are complex, and distribution should be considered as involving a multicompartmental system with all body compartments being in contact directly or indirectly with the blood. The occurrence of exchange, and its rate, between the blood and the various tissue compartments is governed by the factors that influence the diffusion of solutes, such as the concentration of the drug and the volume of blood flow through the tissues and the volume of the tissue. It is also considerably influenced by the extent of protein binding of the drug in blood and in the tissues, the ionization constant of the drug, pH differences in the compartments, and the lipid solubility of the drug.
- Drug distribution is also influenced by age and the disease state of the animal.

- In most diseases infection occurs in the extravascular tissue compartments and it is the concentration of the unbound drug at these sites that determines the efficacy of therapy. The majority of antibiotics diffuse relatively freely in extracellular fluids but sulfonamides, the chloramphenicol group, tetracyclines, fluoroquinolones and macrolides have a distribution that more closely approximates total body water, and they can enter cells. There are several so-called barriers to antimicrobial diffusion and these include the brain and cerebrospinal fluid, serous cavities, joints and synovial fluid, the eye and the placenta and fetus.
- In general sulfonamides, the tetracyclines and chloramphenicol have some ability to penetrate these barriers in the normal state, whereas penicillin may not.
- Erythromycin has the ability to penetrate intracellulariy and across most barriers but will not produce effective levels in the brain or cerebrospinal fluid.

- Members of the aminoglycoside group of antibiotics generally achieve effective levels in synovial fluid and the pleural and peritoneal fluid but not in the brain or eye. The importance of these barriers, especially those of serous cavities and synovia, in the presence of inflammation is open to doubt and effective therapy can often be achieved by the use of antibiotics that do not in normal situations reach these areas unless they are inflamed.
- An exception to this rule is infections involving the eyes where, in order to achieve effective levels, high circulating levels of the antimicrobial agent are required and intravenous injection to achieve this is usually necessary.
- Lipophilic drugs diffuse into tears and parenterally administered erythromycin, oxytetracycline and gentamicin, for example, may achieve bacteriostatic concentrations in tears.

- In many areas, especially joints and the peritoneal, pleural and pericardial cavities, high levels of the required antimicrobial agent can be achieved by local administration.
- Almost all antimicrobial agents are excreted via the kidney, and the urine usually contains high levels of them. This feature is not of great significance in large animals, where urinary tract infections are comparatively rare, but violative residue levels can persist in the kidney for long periods with drugs such as the aminoglycosides.
- Penicillins and tetracyclines have a significant enterohepatic cycle, and erythromycin also may obtain significant levels in bile.

DURATION OF TREATMENT

- For certain infectious diseases there is an established regimen of therapy that is known from clinical experience to be therapeutically effective. Where such regimens are known they are stated in the treatment section for the individual diseases in the Special Medicine section. As a rule of thumb in undifferentiated diseases, therapy should be continued for at least a 3-5-day period, or longer if there is evidence of chronic infectious disease with localization. An alternative rule of thumb is that treatment should be continued for at least 1 day beyond the return of body temperature to normal, especially if bacteriostatic antibiotics are being used.
- Chronic pyogenic processes may require treatment for a 2-4-week period or even longer.

DRUG COMBINATIONS

- Combinations of antimicrobial drugs are frequently used in veterinary practice.
- Combinations of antimicrobial agents are used either to achieve a synergistic effect in the case of a single infection, or to achieve a broad spectrum of activity in the case of infections involving more than one agent. Combinations may also be of value in combating the emergence of resistant mutants during therapy. The combination of two drugs may result in indifference, where the effect is either that of the single most effective drug or is equal to the sum of the effects of the two individual drugs, or it may result in synergism or antagonism.

- There are, however, no hard and fast rules for combinations that will result in any of these effects. Knowledge of these effects results largely from laboratory animal studies and from some human therapeutic trials. From these trials it is evident that the occurrence of synergism is very much dependent on the type of infectious organism, and to some extent the site of infection, and, whereas two drugs may show a synergistic effect with one type of infection, the effect may be indifferent or even occasionally antagonistic with other infective agents. Antagonism is equally not easily predictable but the drugs that most commonly result in antagonistic effect when combined with others are the tetracycline group, chloramphenicol and the macrolide groups.

- A traditional approach has been that combinations of bactericidal drugs will generally result in an indifferent effect or in synergism; combinations of bacteriostatic drugs generally give an indifferent effect, whereas combinations of a bactericidal with a bacteriostatic drug may result in antagonism (Table 4.1). This approach is, however, too general for validity as interactions are specific to individual infections and are dose-dependent.
- In farm animals, synergistic activity between penicillin and streptomycin has been demonstrated in the therapy of mycotic dermatitis and footrot in sheep.

- The synergism between aminoglycoside and beta-lactam antimicrobials is widely used in the approach to the therapy of sepsis in neonates. Carbenicillin and gentamicin in combination can be of value in therapy against *P. aeruginosa, Klebsiella and Proteus spp., and tylosin* and oxytetracycline can be of value in treating infection with *Mannheimia and Pasteurella spp. Trimethoprim and* sulfonamide combinations are of special value in treating several infectious diseases in large animals.
- Rifampin and erythromycin show in-vitro synergism against *Rhodococcus equi, as does a* combination of gentamicin and penicillin.

- Drug combinations are also used for broad-spectrum therapy. An accurate diagnosis with consequent recognition of the likely infectious organism allows specific antibacterial therapy and obviates the need for broad-spectrum antibacterial therapy. However, there are clinical situations where broad-spectrum therapy, including the possibility of combined drug therapy, is indicated. These include such problems as the acute septicemia, where a number of different organisms, with differing antibacterial sensitivities, can produce identical clinical disease, and those infections associated with organisms that have a varying sensitivity depending upon the isolate. The requirement for immediate treatment without knowledge of the bacterial sensitivity dictates the use of antimicrobial drugs designed to obtain a broad spectrum of activity.

- The availability of broad-spectrum drugs such as ampicillin or amoxicillin and trimethoprim-potentiated sulfonamides has lessened the need to use drug combinations but the latter may still be necessary in certain situations and are fully indicated. Although antagonism has not been demonstrated in clinical veterinary situations it is wise to avoid bacteriostatic and bactericidal drug combinations.

- Fixed-dose combinations are available commercially for some antibiotics but they are not recommended for use and are gradually being withdrawn from the market or being declared not legal for use in food-producing animals. Fixed dose combinations suffer from the deficiency that the dose level of anyone of the drugs in the combination is dictated by the level of the other. Also, the excretion rates of the two drugs may be markedly different. The most common of these, fixed-dose penicillin/ streptomycin combinations, suffer from this deficiency.

- Where combinations of antibacterial drugs are used they should be given individually and at their respective recommended doses and repeats. Some antibiotics are physically incompatible when mixed together. The incompatibility may rest with the drugs or their vehicles and may be visible, as with crystalline benzylpenicillin and neomycin, or it may be inapparent, as with gentamicin and carbenicillin. The two drugs should be given separately at separate sites. Incompatibilities can also occur with antibiotics and intravenous fluid solutions - especially those containing protein hydrolysates. Antibiotics may influence the activity of other drugs. In particular, chloramphenicol and tetracyclines inhibit liver microsomal metabolism and may significantly increase the half-life of drugs metabolized by this mechanism, such as digitalis or barbiturates, with resultant potential toxicity.

ADDITIONAL FACTORS DETERMINING SELECTION OF AGENTS

- COST
- EASE OF ADMINISTRATION
- TOXICITY

BACTERICIDAL OR BACTERIOSTATIC ANTIMICROBIALS

- Antibiotics are either primarily bactericidal or primarily bacteriostatic in their activity.
- Some of the bactericidal group are bacteriostatic at low concentration. Both classes rely on intact and effective body defense mechanisms for full effect. Although in terms of clinical response little if any difference can be detected between the two groups in most diseases, in certain situations it is probably advisable to choose a bactericidal antibiotic for therapy. This is especially true when dealing with acute septicemic infection where there is frequently a significant leukopenia, and quick maximal bactericidal effect is required. There is also the need to prevent subsequent localization.

- Bactericidal antimicrobials are also indicated for antibacterial treatment of secondary infection in granulocytopenic syndromes such as bracken fern poisoning or chronic furazolidone poisoning in calves. Bactericidal antibiotics are also preferable in the treatment of heavily capsulated organisms, such as *Klebsiella* spp. and R. *equi, which show antiphagocytic* activity.
- Infections in which significant intracellular parasitism occurs are a problem. The majority of antimicrobials that diffuse relatively freely into cells are bacteriostatic in activity and, although the disease may be controlled by their use, infection may still persist in a latent carrier state.

Box 6-2 Mode of action of antimicrobial drugs

Bactericidal antimicrobials

- β-Lactams
  - Penicillin
  - Cephalosporins
- Semisynthetic penicillins
  - Ampicillin
  - Amoxicillin
  - Cloxacillin
  - Methicillin
  - Carbenicillin
- Aminoglycosides
  - Streptomycin
  - Neomycin
  - Gentamicin
  - Paromomycin
  - Tobramycin
- Glycopeptides
  - Vancomycin
- Rifampin
- Bacitracin
- Polymyxins
- Fluoroquinolones

Bacteriostatic antimicrobials

- All sulfonamides
- Trimethoprim
- Methotrexate
- Pyrimethamine
- Tetracyclines
- Macrolides
  - Erythromycin
  - Oleandomycin
  - Spiramycin
  - Tylosin
  - Carbomycin
- Lincomycin
- Chloramphenicol
- Florfenicol

ANTIMICROBIALS PROHIBITED FROM USE IN ANIMALS INTENDED FOR FOOD IN THE UNITED STATES

- Chloramphenicol
- Dimetridazole
- Ipronidazole
- Other nitroimidazoles
- Furazolidone, nitrofurazone, other nitrofurans
- Sulfonamide drugs in lactating dairy cattle (except approved use of sulfadimethoxine, sulfabromomethazine, and sulfamethoxypyridazine)
- Fluoroquinolones
- Glycopeptides (e.g., vancomycin)

DRUG DETERIORATION

- Many antibacterials lose their activity rapidly when kept under adverse conditions. Quality control in terms of purity, efficacy and freedom from toxicity costs money but for these reasons it is preferable to purchase from known reputable companies and follow their recommendations with respect to storage and expiration periods. The use of cheap antibacterial preparations, often purchased in bulk and simply packaged, and distributed with little consideration for factors influencing drug stability, often results in poor therapeutic results. Crystalline or dry preparations that require reconstitution to a solution before parenteral administration are frequently presented this way because their activity degenerates rapidly once they are in solution. Therefore, once they have been prepared they should be used immediately, or the manufacturer's recommendations should be followed regarding storage. Attention should be paid to the length of activity expected following reconstitution.
- Temperature and exposure to sunlight can be important factors in antibiotic stability and become especially important in farm ambulatory practice: car cold boxes should be used to store antibiotic preparations and other sensitive drugs.

UNFAVORABLE RESPONSE TO THERAPY

- In clinical cases that do not respond to antimicrobial therapy the initial consideration should be that the wrong antimicrobial agent has been chosen for therapy. This is especially true of infectious conditions of undetermined etiology where the drug has been chosen on the basis of an educated guess. In these circumstances adequate time should be given for an evaluation of the efficacy of the treatment before a change is made. In general a 3-day period of treatment is allowed for this evaluation provided there is no marked deterioration in the clinical state or further elevation of temperature during this period. If there is no response to initial therapy then, in the case of conditions of undetermined etiology, it is generally best to change to an entirely different class of antimicrobial agent. However, the possibility of viral or noninfectious etiology should always be considered in these cases and the case and diagnosis should be reviewed before any change is made.

- In any situation where there is a poor response to therapy the usual causes of this failure should be considered in any further adjustments to therapy or future therapy of similar cases. The first and most obvious of these is that the organism is either insensitive to the drug or that it is not susceptible to the level of the drug that is being used for therapy.
- There are two possible approaches. The first is to increase the dose rate and dose frequency and/or to change the route of administration so that higher and possibly effective levels will be achieved, bearing in mind the possible toxic consequences.
- The second, and safer, approach is to change the antimicrobial agent being used. This problem can be avoided if the organism and its potential sensitivity can be identified, either by clinical examination or by appropriate sampling with culture and sensitivity testing.

- Another common cause of poor response is that the infection is situated in an area to which the drug is poorly accessible. If this is associated with an area behind a barrier to the entry of the antibiotic, such as the joints or the eye, it may be necessary to resort to higher dose rates and frequency, or intravenous administration of the drug, or to ancillary local treatment into this area. Alternatively, another drug with superior penetrability may be used.

- Organisms must be actively metabolizing in order for antimicrobial agents to exert their effect. This feature can result in poor response to therapy or relapse following discontinuation of therapy in chronic infections such as endocarditis or where there is excessive necrotic or fibrotic tissue associated with the infection. In these instances, dormant organisms and the long diffusion tracks make effective cure difficult and high antimicrobial levels sustained over longer periods are required. In purulent conditions surgical drainage, where possible, is an essential adjunct to antimicrobial therapy. The importance of ancillary and supportive therapy to counteract the effects of shock, toxemia and dehydration that may be associated with infection cannot be overemphasized and frequently such therapy may markedly influence the outcome of a case. It is obvious, for example, that 3 mL of antibiotic will do little to counter the effects of a 4 L fluid deficit in a scouring calf.

DRUG WITHDRAWAL REQUIREMENTS AND RESIDUE AVOIDANCE

- Antibiotic contamination of food products can be a public health risk, although proven risk for toxicity or allergy from antibiotics in humans is minuscule. An example would be allergic reactions to antibiotic residues - particularly penicillin. There are also commercial considerations where residues of antibiotics in milk can cause considerable problems in the manufacture of milk products. Effects on starter cultures for cheese and yoghurt can be particularly deleterious and can result in downgrading or total loss of large quantities of manufacturing milk.

- A withdrawal period is the time during which the animal must be held free of the drug before it can be marketed. In the case of milk, the term withholding period is commonly used and defines the period during which milk cannot be sent for human consumption following the treatment of the animal with a drug. A tolerance for the pharmacologically active ingredient in tissues is set by regulatory authorities for each drug. The tolerance level is the level below which tissue concentrations must fall before they are considered safe for human consumption, and there is a large margin of safety.

- The required withdrawal and withholding periods will vary between antimicrobial agents and also with the same antimicrobial agent depending upon the amount of drug given; factors such as age and the disease state of the animal are also important. Unfortunately, the required withdrawal and withholding periods to ensure freedom of food products from violative drug residues are not known for the variety of dose concentrations and dose intervals of the various antimicrobials that could be used in clinical practice - nor are they likely to be known in the near future. In many countries this has led to regulations that limit the quantity of antibiotics in drug products.
- Label instructions explaining product usage and drug withdrawal times are required. These label instructions include what is generally called the label dose.

The label dose and extralabel use

- The label dose (and dose interval) is a dose of an antimicrobial for which the specific withdrawal and withholding periods have been established, and these are stated in conjunction with the label dose. The label dose is the officially approved or legal dose rate for that drug. When an antimicrobial is used, it is incumbent upon the practitioner to notify the owner that the animal cannot be marketed (or milk sent for human consumption) before the accompanying withdrawal (or withholding) period has expired. The practitioner may be legally liable if a violation occurs and this notification has not been given.

- In the USA the label dose of a drug also includes use only in the species of animal for which the drug is labeled, the class of animal (lactating versus non lactating dairy cow), the disease conditions indicated by the label, the route of injection, the amount of drug to be injected at one site and the number of repeat treatments that can be given. These label directions, and the need to follow them, are directed primarily at lay users of these drugs and lay users may not use the drug in a non label fashion. The label directions should also be followed by the veterinarian whenever possible.

Extralabel use

- There are times where extralabel use of drugs is necessary and veterinarians can do this where they have established a proper veterinarian-client-patient relationship .It is the intention that the label dose should be one that is therapeutically effective for that drug. However, this is not always the case, and the label dose should not be confused with the term 'recommended dose'. There are also circumstances where, although the label dose may be therapeutically efficient in many cases, it is not for the particular case in hand. In fact, optimal therapeutic dose regimes often require extralabel use of the drug. In these situations, antimicrobial drugs may need to be used at dose concentrations and dose intervals different from the label dose. Extralabel use of the drug may be therapeutically necessary for the successful treatment of the problem, but it is not officially approved and the establishment of the required withdrawal period is entirely incumbent upon the veterinarian. The withdrawal period in these circumstances cannot always be extrapolated from that for the label dose.

REQUIREMENTS FOR EXTRALABEL USE OF DRUGS IN THE UNITED STATES

- Extralabel use of drugs (ELDU) is permitted only by or under the supervision of a veterinarian.
- ELDU is allowed only for U.S. Food and Drug Administration (FDA)-approved animal and human drugs.
- A valid veterinarian–client–patient relationship is a prerequisite for all ELDU.
- ELDU must be for therapeutic purposes only (animal's health is suffering or threatened), not drugs for production use.
- Rules apply to dosage form drugs and drugs administered in water—ELDU in feed is prohibited.
- ELDU is not permitted if it results in a violative food residue or any residue that may present a risk to public health.
- FDA prohibition of a specific ELDU precludes such use.

WITHDRAWAL PERIODS

- Label dose withdrawal periods are determined from pharmacokinetic studies of excretion following administration of the label dose. However, the rate of drug elimination from the body can be influenced by drug dose and dose frequency.
- For example, the metabolism and excretion half-life of sulfonamides in cattle is dose-dependent. With repeated dosing of antibiotics such as tetracycline and the aminoglycosides, there is deposition of the antibiotic in certain tissues and following cessation of drug administration there is a slow release from these tissues and a long washout period.

TESTING FOR COMPLIANCE

- Most countries have a monitoring program to detect the occurrence of residues in meat.
- Violative drug residues occur predominantly in cull dairy cows and in bob veal calves.

CAUSES OF RESIDUE VIOLATIONS IN MILK

- In a retrospective study of reasons for the presence of violative antibiotic residues in milk failure to withhold milk for the full withdrawal period and accidental inclusion of treated milk in the shipment were the most common. Accidental inclusion of treated milk can occur when there is inadequate identification of treated cows. The veterinarian should work with the producer to establish a system that easily identifies cows whose milk is subject to a withholding period.
- Colored leg markers are one system and are immediately visible to the milker.

- Contamination of recorder jars and milking equipment with the high concentration of antibiotic secreted in milk in the first milking after treatment 'is a further reason for residue violations.
- Treated cows should be milked last in large dairies, or milked with separate equipment, and are preferably kept separate as a hospital string.

- Other reasons for residue violations include short dry periods, where dry cow therapy has been used but the cow has calved earlier than expected. The infusion of dry cow treatments into the udder of heifers prior to calving for the prevention of summer mastitis has also been followed by the presence of violative residues for as long as 26 days.

- A less common cause is the accidental milking of dry cows, where the latter are not kept as a separate group, and the withholding of milk from only treated quarters. The use of dry cow infusion preparations for treatments during lactation can occur by mistake if drugs intended for the treatment of lactating cows are not kept in a separate storage area from other drugs.
- The risk for residues is higher for farms that have higher frequency of antibiotic usage and for those that use part time labor. The use of records to document treatments and the day of exit from the withholding period is an important preventive measure.
- Sulfonamides, tetracyclines, penicillins, aminoglycosides, cephalosporin and chloramphenicol have been found in milk in the USA

COMMON CAUSES OF ANTIBIOTIC RESIDUES IN MILK

- Extended usage or excessive dosage
- Failure to observe withdrawal times
- Poor records of treatment
- Prolonged drug clearance
- Failure to identify treated animals
- Contaminated milking equipment
- Milker or producer mistakes
- Products not used according to label directions
- Lack of advice on withdrawal period
- Withholding milk from treated quarters only
- Early calving or short dry periods
- Purchase of treated cows
- Use of dry cow therapy for lactating cows
- Milking dry cows

CAUSES OF RESIDUE VIOLATIONS IN BEEF CATTLE

- Violative drug residues occur predominantly in cull dairy cows and in bob veal calves. In one study the primary reasons for violations for this group were:
- Failure to observe the withdrawal periods (61 %).
- Use of an unapproved drug (10%).
- The feeding to calves of milk or colostrum from a treated cow (9%).

- A greater risk for residues occurs in herds that feed larger volumes of colostrum, possibly reflecting contamination from dry cow therapy; waste milk, discarded from treated cows and fed to calves, is also a risk especially if extralabel doses of antimicrobials are used for udder infusions.
- Exceeding the label dose (6%).

- The major drugs involved with residues in meat are neomycin, streptomycin, penicillin, oxytetracycline, gentamicin and sulfamethazine, with intramuscular injection being the route of administration in 60% of the residue cases, oral administration in 28% and intramammary infusion in 9%. The use of orally administered antimicrobial boluses in calves that were subsequently slaughtered as bob veal calves is also a problem.

TYPE OF THERAPY

- In the USA veterinarians are responsible for a very minor proportion of detected residue violations. Possible causes of violations resulting from veterinary therapy include the selection of an inadequate withdrawal period following extralabel use of an antimicrobial and treatment modalities that may not be considered a risk. The local infusion of antibiotic solutions into the uterus of cows may result in circulating concentrations of antibiotic and residues in body tissues and in milk.

- This results from the absorption of the antibiotic through the endometrium and from the peritoneal cavity following passage through the fallopian tubes. Similarly, following infusion of antibiotic solutions into one quarter of the udder, low concentrations of the antibiotic can occur in milk secreted from the remaining quarters. Gentamicin is generally considered not to be absorbed from the mammary gland but more than 87% of an intramammary dose of gentamicin is absorbed from the *inflamed* udder

APPROVED DRUGS

- Whenever possible, approved antimicrobials should be used for therapy at label dose and a known withdrawal time in order to comply with regulatory requirements and to minimize the possibility of antibiotic residues in meat and milk. It may be necessary to use non approved antimicrobial drugs in certain circumstances and in minor species. The use of an approved antibiotic in a minor species for which it is not approved constitutes an extralabel use of the drug.
- The legality of the use of unapproved drugs, or of approved drugs in minor species for which they are not approved, is questionable. If such use is contemplated it is probably wise to have culture and sensitivity data indicating that the use of the unapproved drug is therapeutically necessary. Certain nonapproved antibiotics are totally banned for use in food producing animals in some countries (e.g. in the USA chloramphenicol, the nitroimidazoles, sulfamethazine in dairy cattle over 20 months of age, furazolidone and the use of fluoroquinolones in an extralabel fashion) and local regulations should be followed. The use of sulfamethazine in food-producing animals may be banned in some countries.

DURATION OF TREATMENT

- For certain infectious diseases there is an established regimen of therapy that is known from clinical experience to be therapeutically effective. Where such regimens are known they are stated in the treatment section for the individual diseases in subsequent chapters. As a rule of thumb in undifferentiated diseases, therapy should be continued for at least a 3- to 5-day period or longer if there is evidence of chronic infectious disease with localization. An alternative rule of thumb is that treatment should be continued for at least 1 day beyond the return of body temperature to normal, especially if bacteriostatic antibiotics are being used. Chronic pyogenic processes may require treatment for a 2- to 4-week period or even longer.

CLASSIFICATION OF ANTIMICROBIAL AGENTS: MECHANISMS OF ACTION AND MAJOR SIDE EFFECTS

AMINOGLYCOSIDES AND AMINOCYCLITOLS

- Aminoglycosides are a class of bactericidal antimicrobial compounds (e.g., amikacin, tobramycin, apramycin, streptomycin, gentamicin, neomycin, kanamycin, dihydrostreptomycin, spectinomycin) produced from strains of *Streptomyces spp*., *Micromonospora spp*., and *Bacillus spp*. They are the drugs of choice for the treatment of serious aerobic gram-negative infections in animals.

MECHANISM OF ACTION

- Aminoglycosides exert a bactericidal action by entering the bacterial cell and inhibiting protein synthesis.
- Aminoglycosides bind to one or more receptor proteins on the 30S subunit of bacterial ribosome. This binding interferes with protein synthesis via restricting polysome formation and causing disaggregation to monosomes, misreading mRNA, nonsense and frameshift mutations of proteins, and cell death.

TOXICITY

- Ototoxicity and nephrotoxicity are common side effects of aminoglycoside administration because cellular matrixes in these organs contain large amounts of phospholipids (anionic aminoglycoside receptors) compared with other tissues of the body. As a result, aminoglycosides should not be used with other ototoxic or nephrotoxic drugs (i.e., furosemide, amphotericin B).

- Ototoxicity results from progressive damage to cochlear cells (more common with amikacin and neomycin) and can result in deafness in dogs, as well as damage to vestibular cells (more common with streptomycin and gentamicin) and can cause ataxia in cats. Ototoxicity is largely irreversible but has rarely been documented in large animals administered aminoglycosides.

- Nephrotoxicity (occurring most commonly during prolonged therapy, longer than 10 days) is caused by the damage of the membranes of proximal tubular cells that have a high metabolic rate, resulting in a loss of brush border enzymes, proteinuria, decreased glomerular filtration rate, and azotemia. The mechanism of renal toxicity is not fully understood. Risk factors for nephrotoxicity include high doses, long duration of treatment, preexisting renal dysfunction or dehydration, concurrent administration of nephrotoxic drugs or diuretics, persistently elevated trough concentrations, and very young or old age.

- Renal toxicity is largely reversible because of regeneration of tubules after the drug is cleared. Metabolic acidosis and electrolyte disturbances (e.g., hyponatremia, hypokalemia) increase renal toxicity of aminoglycosides.
- High-protein diets increase the glomerular filtration rate and renal bloodflow, promoting aminoglycoside excretion and protecting against nephrotoxicity.

- Aminoglycosides cross the placental barrier and can produce nephrotoxicity and ototoxicity in a pregnant animal and its developing fetus. All aminoglycosides given rapidly IV cause bradycardia, decreased cardiac output, and lower blood pressure through an effect on calcium metabolism. Neuromuscular blockade is uncommon following administration of aminoglycosides and is caused by prejunctional blockage of acetylcholine release caused by impaired calcium release at myoneural junctions (muscle paralysis and apnea). The IV administration of calcium salt is used as a treatment for this toxicity. Because of this potential toxicity, it is best not to administer an aminoglycoside when neuromuscular blocker administration is considered.

- Spectinomycin is much less toxic than the aminoglycosides; as much as 400 mg/kg IV can be tolerated. There are few important side effects of spectinomycin administration including no ototoxicity or nephrotoxicity. However, pain at the injection site; dizziness, nausea, and insomnia; and urticaria, chills, and fever have been reported. Administration of lincomycin-spectinomycin oral preparations, by parenteral injection to cattle, has produced heavy losses associated with severe pulmonary edema.

β-LACTAM ANTIBIOTICS: PENICILLINS, CEPHALOSPORINS, AND β-LACTAMASE INHIBITORS

- β-Lactam antibiotics are bactericidal.
- There are many congeners in this group of drugs.

- There are four major groups of penicillins: narrow spectrum, broad spectrum (aminopenicillins), extended spectrum, and penicillinase resistant. Penicillin-β- lactamase inhibitor combinations (potentiated penicillins) include amoxicillin-clavulanate (orally, PO), ampicillin-sulbactam (IV), ticarcillin-clavulanate (IV), and piperacillintazobactam (IV).

Table 6-1 The four major categories of penicillin: Narrow spectrum, broad spectrum, penicillinase resistant, and extended spectrum

Narrow-spectrum penicillins	Aminopenicillins (broad spectrum)	Penicillinase-resistant penicillins (antistaphylococcal penicillins)	Extended-spectrum penicillins (antipseudomonal penicillins)
Crystalline penicillin G (IV) Penicillin V (PO) Aqueous penicillin G (IM)	Amoxicillin (PO) Ampicillin (IV or PO) Hetacillin	Methicillin (IV) Nafcillin (IV) Isoxazolyl penicillins (IV or PO) Cloxacillin Dicloxacillin Oxacillin Flucloxacillin	Ureidopenicillins Piperacillin (IV) Azlocillin (IV) Mezlocillin (IV) Carboxypenicillins Ticarcillin (IV) Carbenicillin (IV)

IV, intravenous; PO, orally; IM, intramuscular.

Mechanism of Action

- Penicillins and cephalosporins induce their mechanism of action by inhibiting bacterial cell wall synthesis by interfering with the final stage of peptidoglycan synthesis.
- Penicillin is most effective against actively dividing bacterial colonies and should not be used with bacteriostatic agents.

- The composition of cell wall differs between gram-positive and gram-negative bacteria.
- The gram-positive cell wall is between 50 and 100 molecules thick, whereas the gram negative cell wall is one to two molecules thick. The lipopolysaccharide outer membrane forms a barrier to water-soluble penicillins, but porins inserted in this layer permit entry to some extended-spectrum penicillins, depending on size, charge, and hydrophobicity of R groups. As a result, many gram-negative bacteria are resistant to penicillins.

Toxicity and Clinical Considerations

- Allergic reactions to penicillin and its metabolites (penicilloic acid) occur when penicillin acts as a hapten to evoke antibody reactions, including hypersensitivity skin eruptions, hemolytic anemia, and anaphylaxis. As a result, penicillin residues in food-producing animals constitute a public health risk.

- Superinfection can be a clinical problem during penicillin administration, reflecting the appearance of bacteriologic and clinical evidence of a new infection during the chemotherapy of a primary one. Penicillins can promote a single resistant microorganism to become dominant, invading the host and producing infection. Penicillins can alter normal intestinal flora and bowel function (anorexia, vomiting, and diarrhea) and can result in death in some species such as guinea pigs, hamsters, and rabbits.
- Central nervous system seizures and cardiac arrest can occur in humans with epileptogenic foci that receive large doses of penicillin G. To avoid the induction of fatal ventricular arrhythmias, care should be taken with the rate at which potassium penicillin G is injected IV because of the potassium content of the injection.

- Cephalosporins are β-lactam antimicrobials that have a mechanism of action similar to that of the penicillins (inhibition of bacterial cell wall synthesis). Different side chains exist in cephalosporins to create individual drugs (four generations of cephalosporins now exist). Unlike penicillins, cephalosporins contain a dihydrothiazine ring instead of a thiazolidine ring.

TOXICITY

- Cephalosporins cause fewer hypersensitivity reactions than penicillins. Cephalosporins should not be used in animals with a known sensitivity to penicillins (cross-reactivity). Cephalosporins are potentially nephrotoxic and, consequently, caution should be used when administered with other nephrotoxic drugs such as aminoglycosides (e.g., gentamicin, amikacin, neomycin) and amphotericin B. Cephalosporins in the urine can cause a false-positive reaction for glucosuria (copper- reduction technique) and proteinuria (sulfosalicylic turbidimetric test).

CHLORAMPHENICOL

- Chloramphenicol inhibits protein synthesis by binding to the 50S ribosomal subunit near the site of action of macrolides and lincosamides; antimicrobials in the latter two classes interfere with the binding of chloramphenicol and may therefore interfere with each other's actions if given concurrently. Chloramphenicol is usually bacteriostatic with a broad-spectrum activity (gram-positive, gram-negative, aerobic, and anaerobic bacteria).

MECHANISM OF ACTION

- Chloramphenicol binding to the 50S bacterial ribosomal subunit inhibits peptide bond formation and protein synthesis by interfering with peptidyl transferase enzyme activity. This may affect mammalian mitochondrial protein synthesis, because mammalian mitochondrial ribosomes have a strong resemblance to bacterial ribosomes.

TOXICITY

- Dose-dependent anemia can occur in animals (especially in cats) and humans and is reversible. The anemia is caused by inhibition of mitochondrial protein synthesis in bone marrow, as well as inhibition of iron uptake by erythrocytes, which slows the rate of maturation of erythrocytes in bone marrow. Dose-independent anemia (aplastic anemia) occurs in humans and is independent of treatment duration. The mechanism of toxicity is thought to involve nitroreduction of a para-nitro group, leading to the production of nitrosochloramphenicol and other toxic metabolites that trigger stem cell damage. Because of the occurrence of rare but fatal aplastic anemia in humans, the use of chloramphenicol in food-producing animals is banned by the Food and Drug Administration (FDA). As a result, humans should use gloves and eye protection when administering chloramphenicol and avoid repeated contact with or inhalation of the powder.

- Other side effects are uncommon but occur mainly in young animals because of impaired glucuronidation pathways. Depression, dehydration, reduced fluid intake, weight loss, emesis, diarrhea, and anorexia have been reported with high or prolonged dosages of chloramphenicol.
- Administration is not recommended in lactating animals because of excretion in milk and possible toxicity risk in offspring (liver is not fully functioning in neonates and fetus).

CHLORAMPHENICOL ANALOGS

- **Florfenicol** and **thiamphenicol** are chloramphenicol derivatives. They were synthesized because of the rare occurrence of chloramphenicol-induced aplastic anemia in people and also the ban on the use of chloramphenicol in food-producing animals. Attempts were made to synthesize chloramphenicol analogs to maintain broad-spectrum antimicrobial activity and eliminate the induction of aplastic anemia in people. The mechanism of the antimicrobial activity and antimicrobial spectrum are similar to that of chloramphenicol.

TOXICITY

- Signs of toxicity are varied and include diarrhea and hyperbilirubinemia in horses, diarrhea and decreased feed consumption and rumen activity in cattle, local tissue reaction following intramuscular and subcutaneous administration, and perianal inflammation and rectal eversion/ prolapse in swine. Fatal bone marrow suppression with overdose or prolonged florfenicol administration has been reported.

FLUOROQUINOLONES

- Fluoroquinolones are a class of synthetic antimicrobial compounds with broad-spectrum antimicrobial activity (enrofloxacin, orbifloxacin, difloxacin, ciprofloxacin, marbofloxacin, danofloxacin, etc.).

- Fluoroquinolones exhibit good activity against many gram negative bacteria (e.g., *E. coli, Enterobacter species, Klebsiella species, Pasteurella species, Proteus species, Salmonella* species). Some gram-positive bacteria are also susceptible to fluoroquinolones (primarily *Staphylococcus intermedius* and *S. aureus*, including β-lactamase producing gram-positive bacteria;

- Poor activity in general against anaerobes and fluoroquinolones should not be used to treat anaerobic infections.
- *Chlamydia, Rickettsia, Mycoplasma, Mycobacteria, Ehrlichia, Coxiella*, and *Ureaplasma sp*. can also be susceptible to fluoroquinolones.

- New-generation fluoroquinolones, such as grepafloxacin, trovafloxacin, and premafloxacin, have increased activity against gram positive cocci and anaerobic bacteria. They are bactericidal, potent, and are well tolerated by animals and can be administered with a variety of routes (orally, subcutaneously, intramuscularly, and intravenously).

MECHANISM OF ACTION

- Fluoroquinolones are bactericidal and exhibit good antibacterial activity, especially against gram-negative bacteria. They inhibit bacterial DNA gyrase or topoisomerase IV enzyme activity, which is necessary for the DNA supercoiling, because the replicating strands separate inhibiting bacterial DNA replication and transcription. Mammalian cells are resistant to the killing effects because topoisomerase II activity is only inhibited at much higher concentrations.

TOXICITY

- Fluoroquinolones are relatively safe with no allergic and teratogenic activity in animals.
- They do not alter the anaerobic flora of the gastrointestinal (GI) tract, but high doses might generate reversible GI tract disturbances (e.g., nausea, vomiting, diarrhea).
- Central nervous system toxicity (e.g., convulsion, seizure) caused by inhibition of the GABA neurotransmitter has been reported primarily in humans but has also been reported in horses.

- Arthropathy, characterized by formation of vesicles on the articular surface of the chondrocyte, has been reported to occur at recommended dosages in young dogs and foals, with other domestic animals appearing to be more resistant.

- This toxicity is thought to be caused by the ability of drugs to bind magnesium ions, which are necessary for the proper development of the cartilage matrix (loss of proteoglycan in the articular cartilage).
- No effect on pregnancy has been observed, but it is better to avoid using fluoroquinolones in pregnant animals unless no other antimicrobials are effective. Although enrofloxacin and orbifloxacin have been used in horses (in an unapproved manner), these drugs should not be used in young horses because of potential cartilage damage (enrofloxacin and orbifloxacin should not be administered to horses less than 3 years of age, except as a last resort for severe infections not treatable with other medications).
- Inhibition of the activity of hepatic microsomal enzymes can alter the metabolis of certain drugs such as theophylline. Crystalluria has been reported in humans (primarily with ciprofloxacin) but not in animals.

LINCOSAMIDES

- There are three antibiotics in the lincosamide group: lincomycin, pirlimycin and clindamycin.
- Like the macrolides, lincosamides are primarily used to treat gram-positive bacterial infections (including β-lactamase producing gram-positive bacteria, Staphylococcus spp., and Streptococcus spp.), in which there is resistance or intolerance to penicillins. Lincosamides are highly effective against anaerobes with poor activity against gram negative aerobes.

MECHANISM OF ACTION

- Lincosamides bind to the 50S ribosome in which they inhibit protein synthesis. Because this binding site is similar to that of chloramphenicol and the macrolides, concurrent use of these antimicrobials decreases overall efficacy; therefore combination therapy should be avoided.

TOXICITY

- Severe side effects in humans include pseudomembranous colitis, and this has also been reported in animals with fermenting GI tracts (horses, ponies, ruminants, hamsters, rabbits, guinea pigs, and chinchillas). Oral administration is contraindicated because of severe, often fatal, diarrhea. In cattle, oral administration of lincomycin at concentrations as low as 7.5 parts per million in feed has resulted in inappetence, diarrhea, ketosis, and decreased milk production. Intramuscular clindamycin injection is very painful. No serious side effects have been observed following intramammary injection of pirlimycin in dairy cows.

MACROLIDES

- Chloramphenicol inhibits protein synthesis by binding to the 50S ribosomal subunit near the site of action of macrolides and lincosamides; antimicrobials in the latter two classes interfere with the binding of chloramphenicol and may therefore interfere witheach other’s actions if given concurrently. Chloramphenicol is usually bacteriostatic with a broad-spectrum activity (gram-positive, gram-negative, aerobic, and anaerobic bacteria).

MECHANISM OF ACTION

- Macrolides bind to the 50S ribosomal subunit interfering with the binding of aminoacyl-tRNA-to 50S and block peptide bond formation. This inhibits the translocation of a newly synthesized peptidyl tRNA molecule from the acceptor site to the peptidyl site.

TOXICITY

- Macrolides are relatively safe, with toxicity most often reported in humans. Studies have been conducted documenting the prokinetic effects of erythromycin, spiramycin, tilmicosin, tulathromycin, and tylosin in cattle.

- There can be pain and irritation following intramuscular injection that is formulation dependent. Macrolides and lincosamides such as tylosin are associated with causing colitis and fatal diarrhea in horses, so their use is usually restricted to oral erythromycin for the treatment of *R. equi* infections in foals. Erythromycin has been associated with hyperthermia in foals; treated foals that are turned out on hot, sunny, humid days develop fever, tachypnea, and distress, which may result in fatal heat stroke. Diarrhea has been reported in horses and cattle.

- **Cardiovascular toxicity** has been reported in animals other than cattle, and has been particularly associated with tilmicosin.
- Deaths have been reported in humansrelated to accidental tilmicosin exposure.
- Tylosin and spiramycin may induce contact dermatitis in veterinarians. The intravenous administration of tylosin in cattle can cause shock, dyspnea, and depression.

SULFONAMIDES

- The sulfonamides are synthetic antimicrobial agents with a wide spectrum encompassing most gram-positive and many gram-negative organisms. Sulfonamides are the oldest group of antibiotics used therapeutically. These drugs were the first efficient treatment to be used systematically for the prevention and cure of bacterial infections. Sulfonamides are derived from the first sulfonamide, sulfanilamide. The long-term use of these drugs may have resulted in resistance that now limits their use. **To increase the efficacy of sulfonamides and convert them from bacteriostatic to bactericidal drugs (most of the time they function as bacteriostatic antimicrobials), they are sometimes combined with other compounds such as trimethoprim and ormetoprim (also pyrimethamine) to potentiate their antibacterial effects.**

MECHANISM OF ACTION

- Folic acid is an essential nutrient necessary for protein and nucleic acid synthesis (DNA and RNA). Folic acid is synthesized by bacteria from the substrate, para-amino-benzoic acid (PABA), and all cells require folic acid for growth. Folic acid (as a vitamin in food) diffuses or is transported into mammalian cells. However, folic acid cannot cross bacterial cell walls by diffusion or active transport. For this reason, bacteria must synthesize folic acid from PABA. Sulfonamides act by competing with PABA as a substrate for the enzyme dihydropteroate synthase, which incorporates PABA into dihydropteroic acid, the immediate precursor of folic acid.

- Sulfonamides are bacteriostatic. Trimethoprim, ormetoprim, and pyrimethamine are bacteriostatic, inhibiting dihydrofolate reductase activity necessary for purine and pyrimidine nucleotide synthesis. They also inhibit folic acid synthesis but at a different point in the metabolic pathway from sulfonamides.

TOXICITY AND CLINICAL CONSIDERATIONS

- Sulfonamides can cause toxicity of multiple organs, including the liver, but there is no difference among the various sulfonamides in the risk of toxicity. Use can be limited in a small number of patients because of hypersensitivity drug reactions (Type II and III hypersensitivity reactions). Idiosyncratic reactions, including immunemediated reactions such as drug fever, urticaria, skin rashes, anemia, leukopenia, thrombocytopenia, nonseptic polyarthritis, focal retinitis, and hepatitis, are reported in some species.

- Immune-mediated diseases of skin, kidney, liver, and eye (keratoconjunctivitis sicca) are not dose dependent and occur in response to any of the sulfonamides. Fortunately, these adverse reactions are rare when sulfonamides are used at recommended doses and for less than 2 weeks.

- High doses of sulfonamides (30 mg/kg twice a day) can alter thyroid function, especially in dogs, causing decreased levels of thyroxin and thyronine (hypothyroidism).
- Decreases are clinically significant after 3 weeks of administration and will return to normal by 3 weeks after the drug is discontinued.

- Renal crystalluria has been reported when administering high doses, and as a consequence it is important to ensure that the animal is well hydrated to avoid renal damage caused by precipitation of the sulfonamide (crystalluria). Because herbivores generally have alkaline urine, crystallization is not as much a concern in herbivores as in carnivores with their acidic urine.
- Congenital defects are possible in foals born to mares treated for equine protozoal myeloencephalitis during pregnancy.

Precautions and Contraindications

- As a general rule, sulfonamides should be used with caution or avoided in animals with liver disease, kidney disease, blood dyscrasia, or a history of hypersensitivity to sulfonamides.
- Although commonly administered orally to horses, potentiated sulfonamides are not for use in horses intended for food.
- Potentiated sulfonamides have been associated with inducing diarrhea in horses. The injectable formulations of potentiated sulfonamides are suspensions; rapid IV administration causes hypotension and collapse.

TETRACYCLINES

- Tetracyclines (tetracycline, chlortetracycline, oxytetracycline, doxycycline, minocycline, etc.) possess a broad-spectrum bacteriostatic activity against aerobic and anaerobic gram positive (not β-lactamase-producing grampositive bacteria) and gram-negative bacteria.
- They are also effective against microorganisms that are resistant to other antibiotics, such as several *Rickettsiae* (*Anaplasma*, *Ehrlichia* and *Haemobartonella*), *Spirochetes* (including Lyme disease), *Mycoplasma pneumoniae*, *Chlamydia spp*., and *Plasmodium spp*. Superinfections are rare with prolonged tetracycline administration.

MECHANISM OF ACTION

- Tetracyclines cross the outer bacterial cell membrane by diffusion through aqueous channels (porins). They enter the cytoplasm by a protein carrier system in gram-negative bacteria and by an energy-dependent process in gram-positive bacteria. Tetracyclines then bind to the 30S ribosomal subunit of bacteria; binding interferes with bacterial protein synthesis in growing or multiplying organisms. This binding prevents the attachment of the aminoacyl-tRNA to the acceptor site on the mRNA ribosomal complex.

TOXICITY

- Tetracyclines are considered relatively safe. The clinically most important toxicity occurs in animals administered high doses or animals administered with impaired renal function that are administered typical therapeutic doses (except for doxycycline and minocycline). In addition, expired tetracycline and oxytetracycline can decompose to form a nephrotoxic compound that results in Fanconi syndrome and glucosuria because reabsorption of glucose from the glomerular filtrate is impaired.

- Most tetracyclines, except oxytetracycline, are too irritating to be administered intramuscularly or subcutaneously (sterile abscess), and great care is applied in the formulation of intramuscular products to minimize tissue damage. As a result, tetracyclines are often administered intravenously or orally. Rapid IV administration can cause the animal to collapse; to avoid this, the tetracycline should be injected slowly over a period of several minutes or administered diluted in normal saline solution free of polyvalent cations (as they bind tetracyclines and result in precipitation). Collapse is attributed to transient cardiovascular dysfunction such as atrioventricular block, ventricular bradycardia, and hypotension. The IV use of doxycycline in horses is associated with deleterious side effects on the cardiovascular system, which may result in fatalities.

- Impaired bone development in fetus and young animals (tetracyclines pass the placental barrier readily and are administered for research purposes to monitor the rate of bone growth). As a result, tetracyclines should not be used in pregnant animals during the last half of gestation.

- Tooth mottling (discoloration of tooth enamel) also occurs if tetracyclines are administered during pregnancy (especially the last 2–3 weeks of pregnancy) and during the first postnatal month when tooth development is occurring. This effect is caused by chelation of tetracyclines to the calcium deposits in the developing teeth. Tetracyclines are antianabolic because they decrease protein synthesis at high concentrations.

MISCELLANEOUS ANTIBIOTICS

Bacitracin

- Bacitracin is a complex labile polypeptide produced by *Bacillus subtilis*. It inhibits peptidoglycan synthesis during the second step of bacterial cell wall synthesis by interfering with the activity of phosphorylase and is bactericidal.
- Bacitracin has activity against gram positive bacteria and is often combined with antibiotics that have gram-negative spectrum of activity (such as polymyxin B, neomycin, or both). Bacitracin is not absorbed orally; systemic usage is associated with the development of nephrotoxicity in addition to pain, induration, and petechiae at the site of injection. As a result, bacitracin is most commonly applied topically in ointments.

Dapsone

- Dapsone is a chemical class different from sulfonamides but its mechanism of action is similar to sulfonamides via inhibition of bacterial synthesis of dihydrofolic acid.
- There is no veterinary approved form of dapsone. It is potentially useful for the oral treatment of some protozoal infections in horses. Dapsone is carcinogenic and should be used with caution in pregnant and nursing animals. Toxic effects include hepatotoxicity, anemia, thrombocytopenia, neutropenia, and GI effects.

Metronidazole

- Metronidazole is a bactericidal agent that is also effective against protozoa that cause intestinal disease such as *Giardia* organisms, *Entamoeba histolytica, Trichomonas organisms,and Balantidium coli*. It is effective against most obligate anaerobes including *Bacteroides spp*., *Fusobacterium, Veillonella, Clostridium spp., Peptococcus,* and *Peptostreptococcus*. Metronidazole is primarily used as part of the treatment of anaerobic bacterial infections. It is taken up by anaerobic bacteria and protozoa and reduced to a cytotoxic metabolite that disrupts DNA synthesis, which results in bacterial cell death.

- There is no veterinary-approved form of metronidazole, and its use is prohibited in food-producing animals in many countries because laboratory studies have demonstrated mutagenicity and carcinotoxicity.
- Human formulations are used for treatment of enteric bacterial infections caused by anaerobic bacteria in horses such as *giardiasis* and *clostridiosis*. Metronidazole may be teratogenic; therefore the drug should be avoided if possible in pregnant animals, especially during the first few weeks of gestation, and also in nursing animals. Metronidazole should not be used in debilitated animals.

- The most severe adverse effect is dose related central nervous system toxicity including loss of balance, head tilt, nystagmus, disorientation, tremors, and seizures with high doses of metronidazole in horses.

Nitrofurans (e.g., Nitrofurantoin, Nitrofurazone, Furazolidone)

- Nitrofurans are derived from 5-nitrofuran, and more than 3500 nitrofurans have been synthesized. The use of nitrofurans in food producing animals is banned in many countries because of potential carcinogenic effects in laboratory animals. Nitrofurans are broad-spectrum antibiotics that are highly effective against gram-negative bacteria, with some activity against gram-positive bacteria. Furazolidone also has activity against protozoa, *Giardia, Trichomonas,* and *coccidia*.

- Nitrofurans are bacteriostatic and inhibit bacterial carbohydrate synthesis by interfering with the conversion of pyruvate to acetyl coenzyme A. They have been administered orally and topically, with oral bioavailability improved when administered with feed. Nitrofurans are no longer commonly used for the treatment of systemic infections because the effective MIC often approximates the toxic concentration. Nitrofurans are also rapidly eliminated so it is difficult to achieve and sustain therapeutic concentrations in tissues. Nitrofurans (primarily nitrofurantoin) are very occasionally used in horses for the treatment of lower urinary tract infections because they are highly concentrated in urine.
- The most common use of nitrofurans is in topical preparations for the eye, ear, mucous membrane, and skin.

Novobiocin

- Novobiocin is a dibasic acid derived from coumarin and is clinically used as a mono- (Na+) or dibasic (Ca2+) salt form. The mechanism of antibacterial activity is not known but is bactericidal. Novobiocin has activity against gram positive and gram-negative bacteria with higher efficacy against the gram-positive bacteria (most gram-negative bacteria are resistant), especially *S. aureus*. Other susceptible organisms include *Neisseria spp., Haemophilus spp., Brucella spp.*, and some strains of *Proteus spp*. Novobiocin is used occasionally as an alternative to penicillins against penicillin-resistant *Staphylococcus spp.*
- It has synergistic activity with tetracyclines, and combination novobiocin–tetracycline therapy has been used in an attempt to broaden the spectrum of activity and decrease the development of resistance. Toxic reactions to novobiocin include skin rashes, leukopenia, thrombocytopenia, agranulocytosis, anemia, nausea, vomiting, and diarrhea. Novobiocin is less toxic when used topically; its use in large animals is limited to topical application and intramammary administration in lactating dairy cattle.

Polymyxins

- Polymyxin A, B, C, D, E, and M represent a group of N-monoacetylated decapeptide antimicrobial agents produced by *Bacillus polymyxa*. Sulfate salt forms of polymyxin B (mixture of polymyxin B1 and B2) and E (also called Colistin) are used clinically. The usage is primarily limited to oral (Colistin) or topical (polymyxin B) use because of their systemic toxicity, although short-term IV administration of polymyxin B has been used as part of the initial treatment of endotoxemia in horses. Polymyxins are surface-active cationic detergents and are bactericidal by interfering with bacterial cell membrane phospholipids and disrupting their structure. Development of bacterial resistance is rare for susceptible bacteria.

- Polymyxins and Colistin are primarily used in topical skin, mucous membrane, eye, and ear preparations and intramammary formulations for lactating dairy cattle. Antimicrobial activity is markedly reduced in the presence of pus, in tissues containing acidic phospholipids, and in the presence of anionic detergents. Polymyxins have been used orally in cattle and swine for the treatment of gram negative enteric infections, but they have a narrow safety margin.
- Toxic effects include nephrotoxicity, respiratory paralysis (rapid IV injection), and central nervous system dysfunction including anorexia, pyrexia, and depression.

Rifampin

- Rifampin is a complex macrocyclic semisynthetic antibiotic derived from rifamycin B. It is highly active against gram-positive bacteria (*Staphylococcus spp.), Mycobacterium spp., Haemophilus spp., Neisseria spp., and Chlamydia spp.,* but has limited activity against gram-negative bacteria because of differences in the ability of the antibiotic to pass through the bacterial cell wall. Rifampin also has some antifungal and antiviral (poxviruses and adenoviruses) activity. In large animals, rifampin is most commonly administered orally in conjunction with other antibiotics to treat deep-seated abscesses such as liver abscesses in sheep caused by *Corynebacterium pseudotuberculosis* (caseous lymphadenitis) or pulmonary abscesses in foals caused by *R. equi*. Rifampin has also been used to treat individual valuable cattle with Johne's disease. Combined administration with another antibiotic is strongly advised because coadministration slows the development of resistance to rifampin

- Rifampin is bactericidal and inhibits the activity of DNA-dependent RNA polymerase, preventing the initiation of RNA synthesis by interfering with the activity of the β-subunit of DNA-dependent RNA polymerase.
- Rifampin metabolites may impart a red-orange color to the urine, feces, saliva, and tears.
- Rifampin is a potent inducer of hepatic microsomal enzymes (hepatotoxicity) and is also teratogenic, so the use in pregnant animals should be restricted. Rifampin
- administration accelerates the metabolism of chloramphenicol and corticosteroids (prednisone and dexamethasone).
- The most common toxic effect is hepatotoxicity, and animals on long-term administration should have a periodic serum biochemical analysis performed to monitor for signs of hepatic injury and dysfunction.

Vancomycin

- Vancomycin is a glycopeptide bactericidal antibiotic that inhibits peptidoglycan synthesis in the bacterial cell wall during replication.
- A variety of n-alkyl vancomycin forms have been synthesized with some forms being more active and with some having longer elimination half-lives than that of vancomycin. Vancomycin is primarily effective against gram-positive bacteria (in particular, *Staphylococcus spp*. and *streptococci)*, *enterococci* (*E. faecium* and *E. faecalis*), and *Neisseria spp*. It is also effective against gram-positive anaerobic cocci with no activity against anaerobic gram-negative bacteria.
- Its most important use in veterinary medicine is for the treatment of life threatening methicillin-resistant *S. aureus* infections.

- Extralabel usage of vancomycin in food producing animals is prohibited by the FDA.
- Vancomycin is not absorbed orally, intramuscular and subcutaneous injections are painful and irritating, and, consequently, vancomycin must be administered with slow IV infusion over at least 30 minutes as a dilute solution.
- Rapid IV administration has been associated with flushing of the skin, pruritus, tachycardia, severe hypotension, cardiac arrest, and other signs associated with histamine release.
- Nephrotoxicity and ototoxicity are possible. Newer formulations are safer but might be associated with histamine release following IV injection.

Virginiamycin

- Virginiamycin is a peptolide antibiotic consisting of a predominant M fraction ($C_{28}H_{35}N_3O_7$) and the lesser S fraction ($C_{43}H_{49}NO_{10}$). The S and M fractions have bacteriostatic and bactericidal activities when they are used separately and together, respectively. Virginiamycin is not known to have synergistic activity with other classes of antibiotics. Virginiamycin inhibits protein synthesis by binding to the 23S ribosomal subunit and blocking the translation process, with no effect on transcription.
- It is not commonly used to treat bacterial infections in domestic animals despite possessing a broad-spectrum antimicrobial activity.
- Most often it is used as a feed-additive formulation for growth promotion in animals such as swine, turkey, and broiler chickens

FURTHER READING

- Giguere S, Prescott JF, Dowling PM, eds. *Antimicrobial Therapy in Veterinary Medicine*. 5th ed. Ames, IA: Wiley-Blackwell; 2013.
- Hsu WH, ed. *Handbook of Veterinary Pharmacology and Therapeutics*. 1st ed. Ames, IA: Wiley-Blackwell; 2008.
- Oakes J, Seifert S. American association of poison control centers database characterization of human tilmicosin exposures, 2001-2005. *J Med Toxicol*. 2008;4:225-231.
- Plumb DC, ed. *Plumb's Veterinary Drug Handbook*. Ames, IA: Blackwell; 2015.
- Riviere JE, Papich MG, eds. *Veterinary Pharmacology and Therapeutics*. 9th ed. Ames, IA: Wiley-Blackwell; 2009.

European parliament approves curbs on use of antibiotics on farm animals

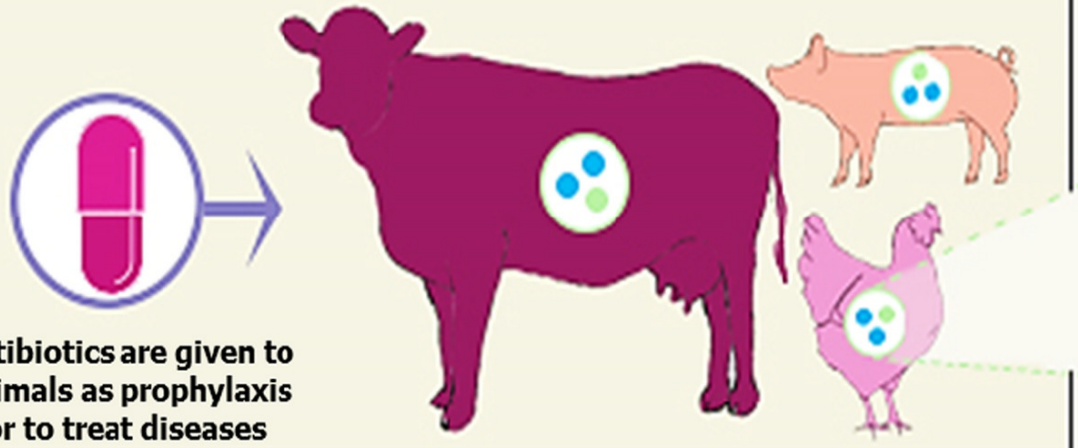
Move is aimed at halting the spread of ‘superbugs’ resistant to medical treatment

ANTIBIOTIC RESISTANCE

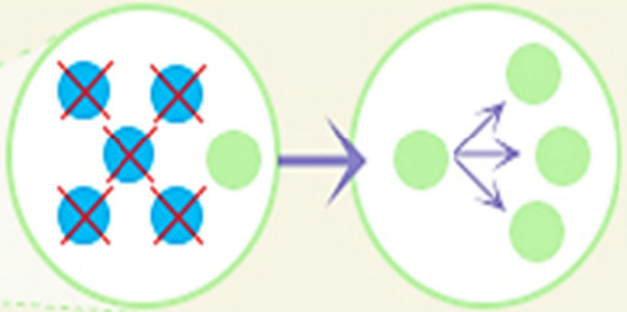
from farm to fork

RESISTANCE

Animal gut bacteria can acquire antibiotic resistance



Antibiotics are given to animals as prophylaxis or to treat diseases



Antibiotics aim to kill bacteria

Certain bacteria acquire resistance, survive and multiply

ANTIBIOTIC-RESISTANT BACTERIA can be passed on...

Animal food products

Contaminated water or soil

Contaminated surfaces

Contaminated faecal manure


2014