



Swedish Veterinary Association

Guidelines for the clinical use of antibiotics in the treatment of dogs and cats

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REFERENCES AND SOURCES

Guidelines for antibiotic use in the treatment of dogs and cats were compiled on commission from the Board of the Swedish Veterinary Society. The General Assembly of the Swedish Veterinary Association then adopted these as their policy in October 2002.

Included in this work was the task to update the existing policy based on new knowledge or new insights whenever necessary. This document is the result of such an update

The intention is that this policy should be used as a guide when choosing management and treatment of dogs and cats. This can sometimes mean either to refrain from treatment altogether or alternatively to choose a treatment that does not include antibiotics. The main aim is that the chosen treatments are as effective as possible and that any undesirable side effects are kept to a minimum.

The policy can be used both by clinically active veterinarians as well as for educational purposes.

Concerning the definitions that are used in the document, it is advised that you refer to the Swedish Veterinary Association's (SVF) general antibiotic policy dating from 1998.

The document is divided into five main parts:

- 1) Antibiotic policy
- 2) The perioperative use of antibiotics
- 3) Guidelines for treatment based on disease-oriented treatment
- 4) General information concerning antibiotic alternatives
- 5) Available antibiotics.

Thanks are due to all employers who have supported us by designating time for work on this policy to the members of the working group. Thank you also to all colleagues who have contributed with both comments and facts.

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1) ANTIBIOTIC POLICY

In many cases, antibiotics¹ are life-saving medicines both within human and veterinary medicine. One of the largest threats against public and animal health is, however, the increase in antibiotic resistance. Antibiotic-resistant bacteria can be transferred between animals and humans and thus, in the case of the veterinary use of antibiotics, the benefits must be weighed-up against the possible effects on public health.

Resistance development can be counteracted by the responsible use of antibiotics, good hygiene and active disease control. Active advice to animal owners on, for example, hygiene and vaccination also plays an important part.

The objective of this document has been to produce a guide that can be used when deciding upon a course of treatment and it is written for current Swedish conditions and practices. Sometimes the “right choice” can be to refrain from antibiotic therapy altogether and instead to simply wait and see, or alternatively choose another treatment.

According to the Swedish Veterinary Association’s/Swedish Veterinary Society’s general antibiotic policy², antibiotic treatment is normally only motivated if both of the criteria described below are fulfilled:

- There is a bacterial infection (or when there is sufficient cause to suspect that an actual bacterial infection is present)
- If the infection, in all likelihood, will not resolve without the support of antibiotic therapy.

If there are equivalent methods of treatment by which antibiotics are not used, these should be the chosen courses of therapy. It is of fundamental importance that antibiotics should only be used when absolutely necessary and that the occurrence of infections should be counteracted, whenever possible, by means of preventative measures.

Antibiotic treatment prescribed “just in case” in the absence of a confirmed diagnosis or alternatively the strong suspicion that, pending the results of the examination or investigation, there is a bacterial infection is never acceptable. Prophylactic antibiotic treatment can in few specific situations be motivated in connection with specific surgical procedures, where the risk for bacterial infection is high or where an infection can drastically worsen the prognosis. The prophylactic use of antibiotics should never be implemented to compensate for poor hygiene.

The lifelong antibiotic treatment of chronic or continually recurring conditions is not compatible with good veterinary practice. The same applies to prolonged treatments with a low dose (less than the therapeutic dose) or so-called pulse dosing.

When possible, the actual infectious agent should be demonstrated by means of laboratory examination. This is especially important in cases of therapy failure, relapse and on other

¹ Throughout this text, the term antibiotics is used to denote both microbially derived compounds with inhibitory or lethal effects on bacteria (antibiotics in the strict sense) as well as synthetic or semi-synthetic substances with similar properties (chemotherapeutics).

² See www.svf.se

occasions when antibiotic resistance can be suspected. Samples should always be taken from infections that arise postoperatively.

The risk of antibiotic resistance should always be taken into consideration when choosing an antibiotic. This means that the antibiotic and the route of administration should be chosen so that the animal's normal flora is affected as little as possible (so-called narrow-spectrum antibiotics). With this in mind, local treatment when correctly implemented can, in fact, be preferable provided that its effect is thought to be sufficient. Any effect on the normal flora can also be minimised if the course of treatment is kept as short as possible and is then discontinued if the indication is no longer thought to be applicable.

In the interest of public health, antibiotics such as mupirocin and substances from classes such as the carbapenems, oxazolidones and glycopeptides should not be prescribed at all. Third or fourth generation cephalosporins should only be used in situations where their use is considered of the utmost importance to the animal's welfare and where there is a sound basis to suspect that alternative treatments will not have the desired effect. In such cases, it is wise to call on relevant specialist competence before prescribing treatment and the reasoning behind the choice of therapy should then be noted down in the animal's record.

It is Good Veterinary Practice to follow the general principles on which this document is founded.

2) THE PERIOPERATIVE USE OF ANTIBIOTICS

By using the expression, the perioperative use of antibiotics, reference is made to antibiotics that are administered before, during and after a surgical procedure that are either directly aimed at identified pathogens or otherwise aimed at pathogens that are assumed to be present. Antibiotics, as a means of prophylaxis, are administered preoperatively in order to prevent the emergence of postoperative infections whereas antibiotics prescribed for therapeutic purposes are given pre-, intra-, and postoperatively with the aim being to cure an already established infection. Sometimes the boundary between prophylaxis and therapy is somewhat fluid as in the case of an open complex fracture.

Antibiotics may never be used as a substitute for good asepsis but should only, with clear indications, be a complement to this.

One difficulty when drawing up of guidelines for the perioperative use of antibiotics is that the majority of the veterinary medical literature written on the subject, for example in textbooks, originates from the USA or the rest of Europe, where there is a totally different view on such treatment. The question there is most often "not if" but rather "in which form" an antibiotic should be administered. Sweden has advanced further and applies vital restrictions where the administration of antibiotics are concerned. Studies of human medical literature have given a certain amount of guidance but the conclusions that have been drawn there, concerning antibiotic prophylaxis and other measures that can be taken to reduce the risk of postoperative infections, are not always directly applicable to the animal world.

GENERAL PRINCIPLES FOR THE USE OF PROPHYLAXIS AGAINST INFECTIONS

A whole series of measures must be taken pre-, intra- and postoperatively with regards to the handling of the patient, hygiene routines for both the premises and equipment, as well as surgical asepsis and technique in order to reduce the risk for the generation of postoperative wound infections

THE SURGICAL DEPARTMENT

A separate operating room that is only used in order to carry out operative procedures should be the norm and it should be separate from the preparation room. Dental treatments, above all the removal of tartar by means of ultrasound, should not be carried out on the same premises. The surgical department premises and equipment should be kept clean and disinfected according to rigidly laid out routines.

Good ventilation is important in order to ensure that there are a reduced number of bacteria-carrying particles in the air. In the case of human surgery, it is recommended that the air in a conventional operating room be changed 16-20 times per hour.

PREPARING THE PATIENT

The treatment of an existing preoperative infection in the patient should, whenever possible, be concluded before the operation.

Human medical studies have shown that hospital care preceding an operation leads to the patient becoming colonised with hospital bacterial flora and that this flora can contain resistant bacterial strains. Consequently, the length of stay preceding the operation should be as short as possible and, whenever possible, the patient should be admitted the same day.

The evening before elective surgery, the patient should be bathed using chlorhexidine shampoo in order to reduce the number of skin bacteria and consequently minimise the risk of wound infection. Chlorhexidine preparations should be allowed to take effect in accordance with the instructions on the packaging. Preoperative whole-body bathing with chlorhexidine soap has not been demonstrated to reduce significantly the risk of wound infection in humans, but it can be supposed that the skin of small animal patients has a considerably more extensive bacterial flora than human skin. This is partly due to the fact that animals are not usually bathed so often, and partly because their dense coat and coarser skin structure makes mechanical cleaning difficult.

Disposable plastic gloves should be worn by staff carrying out the shaving, pre-wash and sterile wash, so as to avoid any infectious transmission between patients or between the premises and its equipment and the patient.

Any *shaving* of the operational area should be done immediately prior to the operation itself and not the day before as it has been demonstrated that the small ulcerations that arise as a result of shaving can become colonised with bacteria. Such colonisation increases the risk of wound infection. The clipper blades should be disinfected between every patient.

Prewash: After shaving, the skin should be cleaned properly with a suitable cleansing and disinfecting soap or shampoo containing chlorhexidine. This must be allowed to take effect for at least five minutes before being wiped off.

A waterproof surface provided by, for example, disposable so-called draw sheets should be used on the preparation table during the patient preparation, on the operating table, and during the awakening of the patient, so as to avoid the transmission of infectious agents from surfaces or from one patient to another.

Sterile wash: The skin is washed using sterile technique and an alcohol solution which has been designed for preoperative skin disinfection.

The surgical area should be draped so as to protect from any contamination from adjacent body parts. A draping material which acts as a bacteria- and leak-proof barrier should be chosen. Disposable, reinforced plastic surgical drapes are superior to textile material.

Disposable adhesive plastic film should be used on the skin over and around the surgical area in order to further reduce the risk for contamination. The plastic film can be of a type impregnated with disinfectants such as iodine compounds. It has been demonstrated in studies based on human hospital care, that incision drapes do not actually reduce the frequency of wound infections; however, it can be supposed that the higher number of hair follicles and the coarser skin structure found in animals can result in the actual skin disinfection process being less thorough. It should consequently be of value to separate the incision area from surrounding skin.

THE OPERATION

BEFORE THE OPERATION

The clinic should have strict routines concerning the changing of clothes before entering the operation department, preoperative hand washing, surgical attire, and the working rules for the operating room. The number of individuals in the operating room should be as few as possible and all unnecessary crossing of the operation room by staff should be avoided.

The surgical instrument sets and individual instruments should be sterilised by autoclave. The autoclave itself should be tested regularly in order to ensure full bactericidal function.

The preoperative disinfection of the hands should be carried out according to the following:
Clean the nails and cuticles. Wash the hands and forearms with soap solution.
Dry the skin. Disinfect the same areas with an alcohol solution containing moisturising additives which is specially designed for preoperative hand disinfection. The disinfecting alcohol solution should be allowed to act for at least three minutes and should be left to dry into the skin.

DURING THE OPERATION

The aim during the surgical procedure should be to utilise an atraumatic surgical technique in order to avoid the devitalisation of tissue. This requires, amongst other things, a careful handling of the tissues, the avoidance of any lengthy mechanical pressure especially in ischemic tissue from, for example, retractors and, furthermore, particular accuracy with haemostasis and tissue approximation. It is also important not to deposit foreign body

materials such as sutures into the surgical wound unnecessarily, and that the choice of such material is made with care in order to minimise the risk for postoperative wound infections.

In order to prevent any drying-out of viable tissue whilst the operation is being performed, and to assist the removal of blood and tissue remains before suturing the wound, the surgical wound should be rinsed with preheated sodium chloride or Ringer's solution

Hypothermia and hypovolemia impair the peripheral circulation and with that the patient's ability to fight against infection. The patient should be administered with fluid in the form of an intravenous drip in order to ensure optimal peripheral circulation. Hypothermia always arises in connection with anaesthesia and surgical procedures if special measures are not taken. Body temperature should be monitored and cooling counteracted by means of heat application; for example, by utilising warm infusions, a circulating-water mattress, a warm air blanket and/or covering the patient with a heat-reflective material.

POSTOPERATIVE CARE

The patient's status, including body temperature, should be continuously monitored postoperatively. A mild increase in temperature one to three days after the operation should not, on its own, be interpreted as a sign of postoperative infection.

The patient should be given adequate fluid and nutritional therapy. Care should be taken that wounds and any drains or bandages should be changed so as to ensure that they are always clean. Any contamination of the skin or operational wounds from floor surfaces must be avoided. The actual ward's premises and equipment should be kept clean and disinfected in accordance with well-established routines.

GENERAL GUIDELINES FOR THE USE OF ANTIBIOTIC TREATMENT IN CONNECTION WITH SURGICAL PROCEDURES.

THE CLASSIFICATION OF SURGICAL WOUNDS

All surgical wounds are essentially contaminated to a greater or lesser extent and the risk of a postoperative wound infection depends, amongst other things, upon the degree of contamination in the actual surgical area. A classification of surgical wounds divided into four groups was put forward in the 1960s. This categorisation has assisted our evaluation of the risks of wound infection and, as a consequence, the necessity for prophylactic or therapeutic antibiotic treatment. The average proportion of all surgical wounds that become infected is estimated at approximately 5%.

- (a) *Clean wounds* constitute more than half the total number of wounds in the sphere of small animal surgery. They are classified as atraumatic wounds within a non-infected soft tissue and unbroken aseptic environment and where there is an absence of luminal organ entry. Prophylactic antibiotic treatment is not indicated.
- (b) *Clean-contaminated wounds* occur following procedures where luminal organs are entered but where any leakage of luminal contents is minimal. Only minor discontinuation of the aseptic environment occurs. The use of prophylactic antibiotic

treatment can be justifiable if the operation is estimated to last more than one and a half to two hours.

- (c) *Contaminated wounds* include new traumatic wounds and open fractures that are less than four to six hours old, as well as operations where the gastrointestinal tract, biliary tract, lung lobes and urogenitalia are entered, and where there is simultaneous infection in any of these organs and/or the occurrence of considerable luminal leakage from any of the above. Large discontinuation of the aseptic environment can occur. The surgical area is not supposed to be infected from the outset. Prophylactic antibiotic treatment can be indicated if the risk of infection is deemed to be considerable. In certain cases, this is seen rather as early initiated therapy as opposed to prophylaxis as, for example, in the case of an open fracture. Long-standing clinical experience shows that antibiotic treatment is not normally indicated in connection with pyometra surgery. Fresh wounds that are treated according to standard surgical procedures are often not an indication for antibiotic treatment.
- (d) *Dirty wounds* presuppose that the surgical area is already infected at the time of operation. This applies, for example, to older bite wounds with considerable soft tissue trauma, severe and violent traumatic open fractures, or peritonitis caused by leaking and infected viscera. In such cases antibiotic treatment is administered.

BACTERIOLOGY

Bacteria can enter the wound during or following a surgical procedure. The bacteria that can cause surgical infections can originate from different sources:

- The patient's own normal flora found on the skin or mucous membranes.
- Patient located nidus, for example in the urinary or respiratory tracts followed by haematogenous dissemination to the wound area.
- Bacteria from hospital premises, instruments, equipment or personnel.

The bacteria that usually cause postoperative wound infections in the sphere of small animal surgery are the *Staphylococcus spp.*, where both surface and deep wound infections are concerned, and *Escherichia coli*, *Pasteurella spp.* (primarily cat) and *Bacteroides spp.* (anaerobic) in the case of deeper wound infections.

INDICATIONS FOR ANTIBIOTIC PROPHYLAXIS

The indications for antibiotic prophylaxis in the sphere of small animal surgery are few. Antibiotics are only prescribed in connection with procedures where there is a high risk of surgical complications or where the consequences of an infection can be catastrophic, such as in the case of hip joint prosthetic surgery. Operations that are expected to be lengthy or surgical procedures performed on high-risk patients are also situations where antibiotic prophylaxis can be indicated.

The use of surgical implants, such as plates, screws or pins in the case of fractures, corrective surgery, TPLO or TTA, are not in themselves indications for prophylactic antibiotic treatment. Antibiotic prophylaxis should also not be prescribed in connection with arthroscopy, laparoscopy or thoracoscopy. As stated in the above text, pyometra and clean wounds are to be treated in accordance with standard surgical principles and are not in themselves indications for antibiotic prophylaxis.

Dental treatments, such as tartar removal, oral sanitation or tooth resection, should not be performed at the same time as other surgical procedures due to the risk of haematogenous dissemination of bacteria from the oral cavity to the surgical area.

Some examples of operations and/or conditions in the sphere of small animal surgery where antibiotic prophylaxis can be motivated are listed below:

- Extensive operations in the gastrointestinal tract such as resections
- Bile duct surgery with a pre-existing infection in the biliary tracts
- Extirpation of a lung lobe with a pre-existing infection in the airways
- Cemented hip joint and other joint replacements
- A complicated fracture operation with extensive soft tissue trauma
- An operation on a high-risk and immunocompromised patient or on a patient with a generalized skin infection.

THE ADMINISTRATION AND CHOICE OF MEDICINE IN THE CASE OF ANTIBIOTIC PROPHYLAXIS

ANTIMICROBIAL SPECTRUM

There is absolutely no reason to make an attempt to eliminate all potentially pathogenic bacteria. The medicine that is chosen to serve as a prophylactic antibiotic should have as narrow spectrum as possible, have a high penetration into the tissue in question and be directed against the actual bacteria that are expected to be found within the operational area.

PHARMACOKINETICS AND PHARMACODYNAMICS

The aim when using antibiotics for prophylactic purposes is to act as a support for the patient's own defence forces during the operation so that any possible contamination is not then able to develop into an infection. The product that is to be used should be administered at suitable intervals and in such a dose that adequate concentrations, i.e. greater than MIC, are maintained in the blood, tissue and tissue fluids during the operation and for a short time thereafter.

DOSE AND METHOD OF ADMINISTRATION

Antibiotic prophylaxis should be administered at least 30 but not more than 60 minutes prior to incision. This usually means that the medicine is administered with the induction of anaesthesia. Intravenous administration is the preferred method as intramuscular or subcutaneous administration results in more uncertain serum concentrations. Per oral administration should not be used. When the half-life is known, the treatment should be repeated after approximately two half-lives ($T_{1/2}$). Numerous human medical studies have demonstrated that the risk for infection is not reduced if antibiotic prophylaxis is first started after the operation has been completed.

DURATION OF PROPHYLAXIS

The optimal length for antibiotic prophylactic treatment has not been determined but everything indicates that treatment should be discontinued at the same time as the operation is terminated. Many investigations based on humans illustrate that there is no further prophylactic effect if treatment is continued following the operation's conclusion, but that extended treatment increases both the risk of side effects and the development of bacterial resistance. Lengthy antibiotic administration does not, therefore, further reduce the risk of infection but rather enlarges the risk of complications.

DIFFERENT MEDICINES THAT CAN BE USED AS ANTIBIOTIC PROPHYLAXIS DURING ORTHOPEDIC AND SOFT TISSUE SURGERY:

Penicillins: It is of primary importance to administer the medicine often enough so as to maintain the concentration. The dose, however, within reasonable limits, is of less importance.

- Benzylpenicillin sodium: A dose of 9-12 mg/kg (15 000-20 000 IE/kg). The half-life is 40 minutes and the injection can be repeated every 60 minutes throughout the operation.
- Ampicillin: A dose of 20-40 mg/kg administered intravenously. The half-life is approximately 45-80 minutes. A further dose is administered after two hours if the operation exceeds its estimated duration.
- Amoxicillin: A dose of 15 mg/kg body weight. It is administered subcutaneously approximately two hours before surgery.
- Cloxacillin: Can be regarded as a purely anti-staphylococcal antibiotic. The most suitable dose is uncertain, 25 or higher mg/kg is given in literature on the subject.

Cephalosporins: Cephalothin is an injectable first-generation cephalosporin. The substance is not authorised for veterinary or human medical use in Sweden, but can be prescribed as a so-called "licence product". Dose 20-30 mg/kg administered intravenously. The half-life is short (less than one hour), and the injection should be repeated every 60 - 90 minutes until the operation has been concluded.

THE TREATMENT OF POSTOPERATIVE INFECTIONS: BACTERIOLOGICAL DIAGNOSTICS

A bacterial culture with the determination of species and bacterial susceptibility should always be completed before any antibiotic therapy is prescribed. The motivation for this is the increasing frequency of resistant strains. If one chooses, for various reasons, to commence treatment of a postoperative infection based simply on clinical indications, a bacterial culture is nevertheless valuable if only to be able to switch, at a later date, to a preparation that can fight more effectively against the bacteria in question and that is then chosen in accordance with the determination of any bacterial susceptibility.

It must be observed that the existence of a small gap between the superficial wound edges during the postoperative period, caused by the fact that the patient, for example, has been able to access and lick the wound, does not in the majority of cases mean that the patient has a wound infection that requires antibiotic treatment. If a bacteriological sample is taken from such a wound surface, it will inevitably demonstrate the presence of bacteria. Antibiotic treatment is, however, not indicated and topical treatment in accordance with the accepted principles of wound management will suffice.

CHOOSING AN ANTIBIOTIC, DOSE, TREATMENT DURATION AND METHOD OF ADMINISTRATION:

The choice of product is steered by what we know to be the probable pathogens attacking the organ system in question and/or the result of a bacteriological culture. The different antibiotic groups' antimicrobial spectra should serve as a guide when choosing the product. Dose and duration of treatment are stated in FASS VET, FASS and national as well as international reference works. With regards to the duration of treatment, it can generally be said that the

course of treatment should continue until there are no longer signs of infection. In some cases, the pharmaceutical manufacturer recommends that the course of treatment should continue for a certain period of time after the patient is free from clinical signs of infection.

The chosen method of administration depends on factors such as the patient's gastrointestinal function, the ability to give a certain dosage form to a particular species and the financial cost of the treatment.

LOCAL REGULATIONS ON PERIOPERATIVE ANTIBIOTIC USE

Every clinic or hospital should have regularly updated written instructions outlining the policy for perioperative antibiotic use. These instructions should cover the indications, the choice of product, dosage, the means of administration, and the routines for bacteriological culture including antimicrobial susceptibility tests where prophylactic treatment and the treatment of postoperative infections are concerned.

3) GUIDELINES FOR TREATMENT

SKIN

Bacterial skin infections very commonly occur in dogs. Approximately one quarter of all dogs with dermatological conditions have a bacterial infection, usually secondary due to an underlying condition. Given that at least 20% of the patients visiting a small animal clinic have dermatological problems, these dogs consequently constitute a large group (1).

In cats, however, the number of bacterial skin infections, except abscesses, are comparatively few.

Bacterial skin infections can be divided up into wound infections, phlegmones, abscesses and pyodermas.

PHLEGMONES AND ABSCESES, TRAUMATIC WOUND INFECTIONS

(For information regarding postoperative wounds, see the section on "The Perioperative Use of Antibiotics")

ETIOLOGY, GENERAL INFORMATION

Traumatic wounds, phlegmones and abscesses arise in dogs and cats mostly as a result of sharp and blunt trauma, burns and bites.

BACTERIOLOGY

A mixed anaerobic flora with elements of aerobes such as *Streptococcus* spp., *Pasteurella* spp. (mostly in cats) and *Corynebacterium* spp. (mostly in cats) are usually found in connection with wounds, phlegmones and abscesses that are a result of bites (2). Wounds that are otherwise caused by sharp/blunt trauma or burns etc have a primarily staphylococcal and/or coli dominated bacterial flora yet they often become secondarily infected with oral flora as a result of the animal licking the wound. Also mycobacteriae need to be considered.

Differentials to bacterial infections are deep fungal infections, viral induced lesions (for example herpes in cats), and sterile immune-mediated processes (for example pancreatitis)

DIAGNOSIS

Medical history and clinical findings. Cytological specimen from the wound area or its secretions can demonstrate presence of a bacterial infection. Concerning bacteriological culture, see the specific sections in the text below. Histopathology of biopsies can also be helpful.

MANAGEMENT AND TREATMENT

The most important procedures in the treatment of different wounds, phlegmones and abscesses are mechanical cleansing in the form of flushing the wound (avoid hydrogen peroxide because of its tissue toxicity), the debridement of necrotic tissue, and drainage and suturing in accordance with standard surgical procedures.

Antibiotic treatment is not always necessary as, for example, in cases of well-defined abscesses in an otherwise healthy animal. Treatment with antimicrobial agents can be indicated to treat the conditions listed below, and a bacterial culture with the determination of bacterial resistance is then also required:

- The animal has a poor general condition as a result of the infection
- Cases where surgical procedures alone are not sufficient in order to induce total wound healing, e.g. in the event of a badly-demarcated phlegmonous condition.
- The tissue damage is very extensive and/or affects large areas of the animal.
- The injury affects a structure particularly susceptible to infection, for example, a joint
- The injury is heavily contaminated

Examples of substances for the standard treatment of wound infections, phlegmones and abscesses are benzylpenicillin, phenoxymethylpenicillin, ampicillin or amoxicillin; the choice of antibiotic agent has to be based on the species of the patient, alongside an assessment of the degree of bacterial contamination in accordance with the above. Oral cephalosporins or clindamycin can be prescribed in cases where staphylococci are considered likely or are verified to be responsible for the infection. If the patient, for some reason, does not respond to either of these treatments, new bacteriological cultures should be taken to determine the susceptibility pattern of the organism. Treatment with long-acting antibiotic injections of broad spectrum beta-lactam antibiotics (cephalosporins) is not indicated. In case of mycobacterial infection special treatment protocols, not covered in this document, need to be followed.

The duration of treatment depends on the type and age of the injury but, as a general rule, treatment should continue until signs of infection are no longer present. In most cases of uncomplicated wounds, phlegmones and abscesses, this means that the antibiotic drug is generally prescribed for a duration of five to seven days.

PYODERMAS

GENERAL ETIOLOGY

A pyoderma is a bacterial infection in the skin and this is one of the most frequent dermatoses found in dogs (3,4). An infection arises when the bacteria break through the skin's protective barrier.

Pyodermas should always be considered as secondary to other underlying factors. The aim when managing pyodermas is to eliminate the actual bacterial agent as well as to identify and correct the underlying problem that has caused the defect in the skin's protective barrier and consequently made bacterial invasion possible.

Traumatic injury to the skin's protective barrier, ectoparasites, allergic inflammation, seborrheic diseases, hormonal imbalances or immune-mediated diseases are all examples of possible underlying conditions.

BACTERIOLOGY

Staphylococcus pseudintermedius (previously known as *S. intermedius*) is by far the most common micro-organism involved (3-8). This bacteria belongs to the skin's resident bacterial flora and is also to be found on the mucosa of the lips, nose and in the perianal region soon after birth (9).

S. aureus, *S. hyicus*, *S. schleiferi*, *Proteus* spp., *Pseudomonas aeruginosa* or *E. coli* are all other, more rarely isolated, bacteria causative of pyodermas.

Pyodermas can be categorised according to the depth of infection, which also is of relevance for the subsequent treatment.

- A surface pyoderma is an inflammation caused by bacterial colonisation of the epidermal outer layers (Stratum corneum)
- A superficial pyoderma is a bacterial infection in the epidermis and in the upper regions of the hair follicles.
- A deep pyoderma is an infection that extends down into the dermis or subcutaneous layers

DIAGNOSIS

EXAMPLES OF DIFFERENT DIAGNOSTIC TOOLS USED IN THE EVENT OF A PYODERMA

- **Medical History:** The importance of an accurate medical history when investigating a skin problem can never be overstated. Is the animal pruritic? What came first, the skin lesion or the itching? Does any contact animals show evidence of skin problems? Does the owner have skin lesions? How long has the problem been present? Type of feed?
- **Clinical examination:** A thorough physical examination of the whole animal. Search for other clinical signs which can be a clue as to the underlying cause.
- **Direct microscopy examination** of samples taken by means of skin scraping, hair plucks or material collected by flea combing or a clear acetate tape test, in order to demonstrate the presence of ectoparasites.
- **Cytological examination** can reveal the presence of bacteria and/or yeast organisms in specimens collected from intact pustules, via direct smears from the skin surface, by fine needle aspirates or tape stripping. If a pustule is present, insert a needle and transfer the material on to a glass slide. Direct smears are made by gently pressing the slide towards a moist skin lesion. A dull scalpel blade or a cotton swab can also be used to collect skin surface material before rolling, or spreading it out on the slide. For deeper lesions a fine needle aspirate can be more useful. Leave the glass slide to air dry before staining it, using a rapid staining method (Hemacolor or Diff-Quick). Tape strips can be dyed by applying a drop of the blue (thiazine) on the slide, then attach the tape. The specimen is ready to examine in oil immersion field under the microscope.

- **Culture and susceptibility testing** should always be performed in case of recurrent pyodermas, from deep pyodermas and from pyodermas where cytology has revealed rods intracellularly in neutrophils and/or macrophages or when treatment fails. The sample should ideally be taken from an intact pustule. Biopsies can be used for microbiological examination in the case of deep pyodermas. Place the biopsy in a few drops of sterile saline solution before it is sent away for cultivation, or alternatively dip the culture swab into the biopsy aperture.
- **Serological examination** for the presence of antibodies against sarcoptes – if there is clinical suspicion that the animal is suffering from sarcoptic mange but the parasite has not been detected via direct microscopic examination of skin scrapings.
- A skin biopsy **for histological examination** can give a clue as to the etiology behind the skin problem. A biopsy should be taken once the pyoderma has been resolved.

MANAGEMENT AND TREATMENT

In the event of a suspected pyoderma, a cytological sample should be taken in order to verify bacterial infection and to eliminate the possibility of a yeast infection (*Malassezia pachydermatis*). Cytological examination determines the presence of cocci if the infection is staphylococcal but, if the determination reveals the presence of rod-shaped bacteria, a bacterial culture including determination of antimicrobial susceptibility should be done.

Topical treatment with an antibacterial shampoo and/or antibacterial sprays sometimes suffices to induce the pyoderma resolution and these agents can also be utilised in order to shorten the duration of antibiotic treatment (10). Shampoos and sprays that contain chlorhexidine, benzoyl peroxide, boric acid and vinegar or ethyl lactate have a good antibacterial effect.

If antibiotic treatment is deemed necessary, then the following should be taken into consideration: the antibiotic product that is chosen should be safe for the patient, be effective against the offending organism and have a good penetration and distribution to the skin. Primarily, an antibiotic should be prescribed that is licensed for the species in question. Oral formulations are preferable as the animal does not then need to be hospitalised but can instead be cared for at home. It is also important to be certain that the owner is able to carry out the ordination. For example dosing three times daily can be a problem and another drug might better be chosen instead.

Injections with so-called long-acting antibiotics (cephalosporins) should not normally be used to treat pyodermas. Exceptions are situations where 1) Clindamycin is not active and 2) it is not possible to medicate the patient orally (e.g. due to gastrointestinal disturbances or because the owner is not able to administer the medicine to the patient per os). It is important to be aware of the fact that beta-lactam antibiotics are drugs that can induce serious antibiotic-related side effects, for example toxic epidermal necrolysis (TEN). In the event of a patient developing side effects following the administration of a long-acting antibiotic, it is not possible to stop the effects of the drug quickly by merely terminating its administration. This consequently constitutes a safety risk.

In Sweden *S. pseudintermedius* is often, in up to about 80% of cases, a beta-lactamase producing bacteria (5,11,12) (11) and is consequently most often penicillin-resistant. Suitable antibiotics are therefore clindamycin and the cephalosporins. Amoxicillin combined with clavulanic acid has, alongside the cephalosporins, had good effect against beta-lactamase producing staphylococci in vitro. The use of fluoroquinolones, following bacterial culture

with the determination of bacterial resistance, should be restricted to the treatment of deep pyodermas in patients where cephalosporins are not suitable (for example, in a patient with hypersensitivity towards beta-lactam antibiotics).

The duration of treatment depends on how deeply into the skin layers the infection extends. It is of the utmost importance that, with the help of a follow-up veterinarian consultation, it is confirmed that the infection has completely healed before treatment is terminated.

Recurring pyodermas should always be investigated in order to ascertain the underlying cause and they should be shampooed or sprayed with antibacterial agents regularly in order to prevent or lengthen the period between recurrences. Cases of relapse despite investigation and antibacterial bathing should be referred to a veterinarian with specialist competency in the field of dermatology.

Continuous long-term treatments or so-called pulse treatments (a course of treatment where the medicine is prescribed for a certain number of days a week over a lengthy period of time) with antibiotics in order to reduce the risk of relapse should not be prescribed.

Methicillin-resistant strains of *S. pseudintermedius* or *S. aureus* do occur. This should always be taken into consideration when treating cases of pyoderma in dogs and strict hygiene measurements should consequently be a matter of course. Culture samples with the determination of bacterial resistance should be taken from 1) pyodermas that do not respond to treatment 2) recurring pyodermas and 3) from deep pyodermas.

SURFACE PYODERMAS

For example, skin fold pyodermas (intertrigo), and moist eczema (hot spot, pyotraumatic dermatitis).

ETIOLOGY

Skin fold pyodemas can be caused by genetically and anatomically occurring deep skin folds that can be found on the nose and on the base of the tail of, for example, Pugs and Bulldogs. Skin folds can also be acquired and occur, for example, round the vulva or between the udders of overweight bitches. Moist eczema arises as a result of a local inflammation in the skin that has become colonised with bacteria. Itching as a result of, for example, ectoparasites, otitis, anal sac bursitis, poorly rinsed-out shampoo or allergies can lead to the condition.

DIAGNOSIS

Medical history, clinical signs and demonstration of bacteria, with or without presence of degenerated neutrophils by means of cytological determination.

MANAGEMENT AND TREATMENT

TOPICAL TREATMENT

In the event of moist eczema (hot spot, pyotraumatic dermatitis): Shave the actual area and a circumferential marginal zone. Since moist eczema can be a painful condition, it is most often suitable to use some form of sedation with analgesia before shaving. Inspect the marginal zone. The discovery of papules, pustules or nodules in the marginal zone are

indications of folliculitis (superficial pyoderma) or a deep pyoderma and the infection should consequently be treated (see below).

- Mechanical cleaning with antibacterial washing agents (for example, benzoyl peroxide, chlorhexidine, boric acid/vinegar or ethyl lactate).
- Treatment with a drying/astringent agent, e.g. polidocrylon. This should not be used on a dog in the absence of sedation with analgesia.
- Topical treatment with an antiseptic ointment containing hydrogen peroxide, with or without a topical glucocorticoid (for example, hydrocortisone aceponate cutaneous spray).
- Difficult cases require topical treatment with a cream or gel containing antibiotics and glucocorticoid.
- Protect against recurring self-trauma (collar, body stocking).
- Pain relief with NSAIDs during the first days.

In the event of intertrigo (skin fold pyoderma):

- Wash with an antibacterial solution (for example benzoyl peroxide, chlorhexidine, boric acid/vinegar solution or ethyl lactate).
- Topical treatment with an antiseptic ointment containing hydrogen peroxide.
- Difficult cases require topical treatment with a cream or gel containing antibiotics and glucocorticoid.
- Prevent against relapse with the help of regular antibacterial washing agents or antibacterial wet wipes.

GENERAL INFORMATION

Systemic treatment with antibiotics is not indicated.

The skin folds should be cleaned regularly in order to prevent pyodermas. Plastic surgery can be required in special cases and weight loss in the animal is indicated in some patients.

SUPERFICIAL PYODERMAS

Examples: Folliculitis, impetigo

DIAGNOSIS

Medical history, appearance. Clinical discovery of papules, pustules, crusts, collarettes and multifocal, spontaneous alopecia. Cytological examination demonstrates the presence of bacteria (often intracellular) and degenerating neutrophil leukocytes.

MANAGEMENT AND TREATMENT

TOPICAL TREATMENT

Antiseptic shampoo or spray (containing benzoyl peroxide, chlorhexidine, boric acid / vinegar solution or ethyl lactate). The animal is shampooed or sprayed at least twice a week initially. The shampoo should have a contact time of about 10 minutes before rinsing. The dog should be re-checked after two weeks. If the animal has not responded to treatment or if the pyodermal lesions are extensive, see the section on standard treatment.

STANDARD TREATMENT

Non-recurrent (first-time cases) superficial pyodermas: If topical treatment does not suffice, the treatment is supplemented with an antibiotic agent.

Treatment with an antibiotic agent should continue for at least one week after the skin lesion has healed. This usually results in a course of treatment lasting at least three weeks. The animal should be re-checked by a veterinarian before treatment is discontinued.

The suitable antibiotic for non-recurrent (first-time cases) pyodermas is clindamycin.

Recurrent superficial pyodermas: The choice of antibiotic should be made in accordance with the result of the culture and susceptibility testing. Should clindamycin be active against the offending bacteria, it should be prescribed over and above a cephalosporin.

It is of the utmost importance that any underlying conditions (for example, ectoparasites, seborrhoea, hormonal disturbances, allergies etc.) are investigated and treated.

Treatment with an antibiotic agent should continue for at least one week after the skin lesion has macroscopically healed. This usually results in a course of treatment lasting at least three weeks. The animal should be re-checked by a veterinarian before treatment is discontinued.

DEEP PYODERMAS

Examples: Cellulitis, phlegmone, furuncles, draining fistulas.

DIAGNOSIS

Appearance, clinical signs with pustules, nodules and draining fistulas. *Always* examine the animal for any underlying conditions that are responsible, e.g. dermodicosis, allergies, hormonal disturbances etc.. Cytological examination determines the presence of bacteria (often in low numbers and intracellular), degenerating neutrophil leukocytes and often even macrophages, plasma cells and eosinophils.

MANAGEMENT AND TREATMENT

TOPICAL TREATMENT

- Shave the affected area. Sedate the animal if necessary.
- Clean with an antiseptic shampoo (benzoyl peroxide is preferable for a deep penetration).
- Protect against recurring self-trauma.

SYSTEMIC TREATMENT

The choice of antibiotic should be made in accordance with the result of the culture and the susceptibility testing. Antibiotics with a bactericidal effect should, if possible, be chosen over and above bacteriostatic antibiotics.

Treatment with an antibacterial agent should continue for at least one to two weeks after the skin lesions have healed. This usually results in a course of treatment lasting at least three weeks, most often longer. The animal should be re-checked regularly by a veterinarian whereupon the patient is evaluated clinically.

These patients often require pain relief (NSAIDs) .

In the event of a relapse and so-called German Shepherd Dog Pyodermas, further investigation by a veterinarian with specialist competency in dermatology is recommended.

EARS

OTITIS EXTERNA

ETIOLOGY

The discussion of otitis externa below applies to the canine condition as feline otitis is usually caused by ear mites (*Otodectes*) or polyps/neoplasias in the ear/auditory canal.

Otitis externa is often an associated symptom connected with general skin disease, such as an allergy or seborrhoea. In the event of recurrent otitis conditions, the underlying cause should **always** be investigated and corrected. If the primary cause can not be addressed, the progression leads to chronic tissue changes which can become irreversible and refractory to medical treatment. Bulla tympanica can become involved in the process. When irreversible tissue changes are present, surgery, or even euthanasia, is the final alternative to manage the case.

BACTERIOLOGY

The microbiological agents involved in otitis externa are mostly *S. pseudintermedius*, *Pseudomonas aeruginosa*, *Proteus spp.*, *E. coli*, *Klebsiella spp.* and the fungal organism *Malassezia pachydermatis* (13).

DIAGNOSIS

Appearance, inspection of the ears, ear canals, and eardrums. Clinical symptoms are pain, itching, erythema (redness) in the auditory canal and the outer ear, as well as accumulation of exsudate in the auditory canal.

MANAGEMENT AND TREATMENT

Careful general, physical examination should always be performed. Sometimes effective sedation or possibly even a general anaesthetic is deemed necessary when diagnosing investigating and treating patients with otitis. Cytological examination should be carried out in order to determine any possible bacteria, neutrophil leukocytes and/or fungal organisms. The result of the cytological examination is a deciding factor when it comes to choosing the treatment.

Antibiotics should not be used to treat otitis conditions that are not actually infected with bacteria.

In cases of bacterial external otitis infection, systemic treatment with antibiotics is not indicated, unless there is involvement of bulla tympanica.

All otitis conditions should be followed up with both a clinical re-check and a new cytology examination. A microbiological culture and susceptibility testing should be performed if rod-shaped bacteria have been demonstrated or in the case of treatment failure aimed at the elimination of cocci.

When *Malassezia* (fungal organism) is demonstrated: clean thoroughly with a cerumen-dissolving agent. If daily cleaning over a ten-day period does not lead to a clinical response – use a local treatment with a cerumenolytic, pH-reducing substance with or without ketoconazole and or a corticosteroid.

When cocci and neutrophil leukocytes are demonstrated: in the event of a relapse or treatment failure, take a sample for culture and susceptibility testing. Clean thoroughly with a cerumen-dissolving agent followed by local treatment with eardrops containing antibiotic and corticosteroid.

When rods and neutrophil leukocytes are demonstrated: take a sample for culture and susceptibility testing. Thorough cleaning is important before beginning local treatment as pus can inactivate certain antibacterial agents (for example, polymyxin B or gentamicin). Treat afterwards with an appropriate antibiotic and glucocorticoid.

When Pseudomonas is demonstrated by culture: Use a Tris-EDTA based solution in combination with the local application of an antibiotic based on susceptibility testing (most often marbofloxacin, polymyxin B or gentamicin). Tris-EDTA is deposited in the auditory canal approximately 15 minutes before the local application of the antibiotic. Tris-EDTA inactivates the bacterial efflux pumps and consequently makes the bacteria more susceptible to the antibiotic (14-16). Repeated ear flushing under general anaesthesia are often required and should be continued regularly until remission is achieved.

UNCOMPLICATED (FIRST-TIME) OTITIS INFECTIONS

If necessary, clean thoroughly with a cerumenolytic agent.

Local treatment: The choice of local treatment is made in accordance with any findings on the cytological examination as mentioned above. If the otitis infection is acute and painful, give the patient a pain-relieving agent (NSAID) per os, so that the owner will be able to complete the treatment at home. The condition should be followed up by a re-check including a new cytology examination within 10-14 days. Treatment should be continued until the infection has cleared.

RELAPSING OTITIS INFECTIONS

All relapsing otitis infections *must* be investigated in order to ascertain the underlying cause. Common causes of relapsing otitis infections are foreign bodies, allergies, seborrhoeic diseases and neoplasias. Dogs with bilateral otitis infections, younger than six months old at onset, and without the presence of demonstrable ear parasites or a foreign body, should be investigated with a view to allergies/hypersensitivity and above all with regards to cutaneous food adverse reactions. In dogs with atopic dermatitis more than 80 % of the patients have recurrent otitis externa, which predisposes for secondary infectious otitis(17-19). Examples of keratinisation defects that can be the primary cause of recurring otitis infections are primary seborrhoea, sebaceous adenitis, ichthyosis, but also hypothyroidism and testicular neoplasia can lead to seborrhoea and subsequently otitis externa. If underlying conditions can not be identified or corrected referral to a dermatologist need to be considered.

A swollen auditory canal results in an increased accumulation of wax, sebum, inflammatory secretion and debris within the ear canal. Recurrent or sub-optimal treatment of external otitis infections and the underlying cause can result in the development of secondary soft tissue changes, for example dermal oedema, gland hyperplasia, fibrosis and calcification. As hypertrophy of the soft tissue results in occlusion of the ear canal, the normal migration of cell debris and ear wax from deeper parts of the ear canal towards the opening and out is inhibited. Subsequent perforation of the eardrum then allows the deposition of inflammatory material and debris into the middle ear. Imaging techniques (CT-scan, radiographs) should be made if

there is suspicion of bullae involvement. Cytology and culture should then also be taken from the middle ear. Systemic treatment with corticosteroids can be necessary if the auditory canal has become occluded (stenotic) which can reduce the swelling, opening up the canal if tissue changes have not already become irreversible. Patients with an inflammation of the middle ear need to receive systemic antibiotic therapy in accordance with the determination of bacterial resistance.

Thorough inspection (otoscopy) should be carried out. If needed cleaning (flushing) under sedation or anaesthesia should be performed. A cytological sample and samples for culture should be taken. The choice of treatment is made in accordance with any findings in the cytological and culture results.

It is of critical importance that the underlying cause of recurrent otitis externa is rectified in order to prevent relapse and progress of chronic tissue changes. In the event of irreversible soft tissue changes, surgical intervention is required.

THE URINARY TRACT

GENERAL INFORMATION CONCERNING URINARY TRACT INFECTIONS

Urinary tract infections (UTI) are one of the most commonly occurring canine infectious disorders (1-2).

The feline urinary tract is rarely affected by bacterial infections. Research has shown that very few cats with signs from the lower urinary tract actually have any growth of bacteria in their urine (2-4). The reason behind this lower incidence in cats is thought to be a very effective local defence against bacterial infections within the feline urinary tract (5). One should always suspect an underlying cause if a bacterial urinary infection occurs in a cat. The predisposing factors for a feline UTI are, however, the same as in dogs.

An infection in the urinary tract can be found at one or more locations, for example, in the kidneys (pyelonephritis), in the bladder (cystitis), and in the prostate (prostatitis). The term "significant bacteriuria" is used to indicate that the concentration of bacteria in the urine is so high that an actual UTI is probable (2). An increased number of white blood cells (pyuria) can occur in the urine without the actual existence of a urinary tract infection, and many factors can be responsible for a rise in pH of which bacterial infection is just one. Struvite crystals are a normal finding in canine and feline urine. Consequently, none of these findings should serve as the basis for diagnosing an infection. Urinary Tract Infection as a diagnosis, should be given based on the results of a urine culture, especially in cases where the patient does not exhibit clear symptoms of cystitis (see below).

BACTERIAL FLORA AND PATHOGENESIS IN URINARY TRACT INFECTIONS

Swedish and foreign studies have shown that nine different species of bacteria are responsible for 95% of urinary tract infections in dogs and cats (2,6). Most frequently responsible were *E. coli* followed by staphylococci, *Proteus spp.*, *Klebsiella spp.*, and enterococci. Infections with Streptococci, *Pseudomonas spp.*, *Mycoplasma spp.*, and *Enterobacter sp.* were less common. Infection of the urinary tract normally occurs via the urethra and consists, to a large extent, of Gram-negative bacteria from the normal bacterial flora in the colon or the lower urogenitalia.

A single bacterial strain is normally responsible for a UTI in dogs and cats. Studies have shown, however, that coinfection with two or three strains of bacteria can occur (2, 7).

The presence of bacteria in the urine alone is not enough to result in the development of a UTI. For this to occur, the invading bacteria must be able to attach themselves to the urinary tract epithelium and multiply.

Diagnosis. The clinical signs of a UTI include haematuria, dysuria and an increased frequency of urination. Clinical examination of the urinary tract does not often reveal very much, which is why more extensive investigation is often required. During abdominal palpation, a contracted and tender bladder can occasionally be detected.

A urine analysis is of fundamental importance for the diagnosis of a UTI. In cases of infection, epithelial cells, red and white blood cells as well as bacteria are usually detected in the sediment. The presence of only white blood cells in the urine is not synonymous with a UTI as these can also be the result of non-bacterial inflammatory conditions. It must be noted that the fields for white blood cells and nitrite on the human urine test strips are not reliable when used to test dog and cat urine. The presence of white blood cells should only be diagnostic when detected during the examination of the urinary sediment under the microscope.

Cultivation. The only certain way to diagnose a UTI is by means of urine culture and, when the infection is complicated or recurrent, a determination of antimicrobial susceptibility should also be performed. Urine samples for cultivation should preferably be taken by cystocentesis. Voided urine samples and urine samples taken by means of catheterisation are, especially in the case of bitches, usually contaminated with white blood cells and bacteria from the vulva and urethra. The sample should be cultivated within 20 minutes of it being taken from the dog, as the bacteria in the sample can multiply several times (a false-positive diagnosis) or alternatively die out (a false-negative diagnosis) if left to stand for too long before cultivation is begun. If a voided urine sample is taken from a dog, the number of bacteria should exceed 100 000 colony forming units (cfu) per mL of urine in order for the diagnosis UTI to be given with any degree of certainty, i.e. one can regard the bacteriuria as "significant" (see the introduction to this chapter). A lower number of bacteria per mL of urine in a spontaneous urine sample can represent its contamination with bacteria from the urethra's normal bacterial flora, the vagina or from the coat/the skin around the vulva. Some authors argue that even the growth of > 100 000 cfu/mL can represent a contaminated sample and advise against the culture of voided urine samples under any circumstances (2). Concerning the cultivation of urine taken by means of cystocentesis, a growth of > 1000 cfu/mL is regarded as significant. In a sample taken from a cat, the number of bacteria can be lower and nevertheless represent a true infection. It is recommended that urine samples be taken with cystocentesis wherever possible in order to reduce the difficulty connected with the interpretation of sample results.

Other methods. X-ray and ultra-sound examination are good methods with which to identify underlying causes responsible for recurrent urinary tract infections. Blood test results are normally normal in the case of an uncomplicated UTI in the lower urinary tracts. Pyelonephritis can result in a rise in the number of white blood cells, especially if the infection is acute.

IMPORTANT FACTORS TO TAKE INTO CONSIDERATION WHEN TREATING A UTI.

The aim with treatment is to eliminate the bacterial presence in the urine and urinary tracts for a sufficient duration of time, so that the urinary tract mucosal lining and the local defence mechanisms are given an opportunity to recover. The majority of antimicrobial agents are excreted, to a large extent, via the kidneys and this means that the urine concentration of the substance can be up to a hundred times higher than the plasma concentration. Particular caution should be taken when treating a patient with reduced kidney function as the majority of antibiotics are excreted via the kidneys. In such cases, the antibiotic dose should either be reduced or the dose interval increased (8, 9).

UNCOMPLICATED UTI IN DOGS

ETIOLOGY

Uncomplicated UTI is the most common form and, in approximately 75% of cases in dogs, it is a question of a single episode without recurrence. In these cases, there is an absence of any underlying structural, neurological or functional factors responsible for the UTI, and the infection clears up quite quickly once treatment has been started. An uncomplicated infection can arise due to a temporary reduction in the local defence and can heal spontaneously. Note that previously treated animals (relapse patients) and animals that have been hospitalised are both examples of patients that do not represent cases of uncomplicated UTI.

DIAGNOSIS

Common clinical signs are haematuria, dysuria and foul-smelling urine. A urine sample reveals an active urinary sediment with the presence of white and red blood cells, epithelial cells and bacteria. The urine culture demonstrates **bacterial growth**. In the event of seemingly uncomplicated first-time problems in a young bitch, the urine culture can perhaps be omitted.

MANAGEMENT AND TREATMENT

The empirical treatment of a UTI usually consists of amoxicillin or ampicillin. These agents are excreted in their active form via the kidneys and, as a result, reach high concentrations in the urine; this means that they can even have good effect against infection with *E. coli*. Fluoroquinolones should not be used to treat an uncomplicated UTI unless the culture and determination of bacterial resistance have demonstrated that other antibiotics are unsuitable. The duration of treatment should be kept at a minimum and preferably not exceed seven days. Alternatively, treatment can be terminated two days after the dog's clinical signs have disappeared. Courses of treatment as short as three days have proven to be sufficient to treat an uncomplicated bacterial cystitis in humans (10, 11). It is very possible that the same is applicable for the treatment of uncomplicated canine bacterial cystitis.

COMPLICATED UTI IN DOGS

ETIOLOGY

A complicated UTI arises as a result of an underlying disorder (chronic renal failure, diabetes mellitus and hyperadrenocorticism are some typical examples) or a defect in the local defence mechanisms protecting the urinary tracts. Malformations, such as an ectopic ureter, urethral sphincter mechanism incompetence, diverticuli or fistulas as well as pathological disorders such as tumours or polypoid growths, all increase the risk of bacterial infection. Aside from any defects in the local defences, a complicated UTI can be the result of a deeply-rooted

infection in the kidneys or prostate. These infections usually require a considerably longer course of treatment (at least three weeks) than infections in the bladder and urethra.

DIAGNOSIS

It is important with a good diagnostic process in order to identify the underlying causes such as urinary stones, polyps, tumours, malformations, chronic prostatitis, pyelonephritis or systemic diseases. A urine culture and determination of bacterial resistance should always be performed before antibiotic treatment is started as well as one week after treatment has been terminated. A culture five to ten days into the course of treatment can even be indicated so as to confirm the actual treatment effect. Catheterisation of the urinary tracts should be avoided in infection-sensitive individuals. Urine samples should, whenever possible, be taken using cystocentesis. A cultivation of the ejaculate from male dogs with suspected prostatitis can also be performed.

It is important to differentiate between a relapse (where the infection was not completely treated) and reinfection (a new infection with another bacterial strain) as the underlying causes behind these two conditions differ somewhat. A "new infection" that arises more than two to three times per year is normally considered to be complicated. For more detailed information on the subject, see the list of references (2, 3).

MANAGEMENT AND TREATMENT

A complicated UTI, where a relapse has been established, can require a course of treatment lasting three weeks, sometimes longer, and the result is wholly dependent on whether the underlying cause can be eliminated. It is normally sufficient with a shorter course of treatment in cases of a new infection, and further treatment should be focused on the elimination of the underlying cause so that the animal does not suffer from recurring infections. In these cases, the choice of antibiotic should always be made in accordance with the results of the antimicrobial susceptibility tests. The product trimethoprim-sulfa can be prescribed to treat a male dog with suspected prostatitis. Here, fluoroquinolones are a possible alternative due to their ability to cross over the blood/prostate barrier. Doxycycline is also a fat-soluble substance and crosses over to the prostate. Doxycycline is mainly eliminated via the bile and this means that their effect is not as satisfactory when they are used to treat a UTI.

Lengthy or repetitive treatments with antibiotics are not risk-free for either the patient or for other individuals in its close vicinity. This must be taken into consideration if recurrent infections pose a large problem and the underlying cause can neither be determined nor sorted out,.

NEPHRITIS AND PYELONEPHRITIS

ETIOLOGY

The haematogenous transference of bacteria can result in both nephritis and pyelonephritis. An ascending infection with *E. coli*, *Proteus spp.*, staphylococci or *Klebsiella spp* that originates in the lower urinary tract is, however, far more common. The presence of urinary stones or cysts in the kidneys can be predisposing conditions for both infections and chronic renal failure.

DIAGNOSIS

In cases of nephritis, a destruction of the renal cells occurs as a result of the infection and ensuing inflammation. Clinical signs such as an impact on the general condition, fever,

abdominal pain, oliguria and dehydration can arise depending on the degree of infection and the extent of renal damage. Urine samples reveal a varying degree of pyuria, proteinuria, haematuria, cylinders and bacteriuria. Blood sample analysis may reveal neutrophilia and even azotemia, hyperkalemia and hyperphosphatemia if both kidneys are severely infected. Both the clinical findings upon examination and the changes in the laboratory parameters of the blood and urine samples are often less pronounced in cases of chronic pyelonephritis.

MANAGEMENT AND TREATMENT

Fluid replacement, rehydration and the rectification of any electrolyte disorders are of the utmost importance in cases of acute renal failure. In cases of pyelonephritis, antibiotic treatment should preferably be prescribed in accordance with the culture and antimicrobial susceptibility tests. The course of treatment is often at least three weeks and, in the cases of chronic pyelonephritis, sometimes up to six weeks (8). The choice and dose of antibiotic should be individualised bearing in mind any reduced renal function. When choosing an antibiotic in these cases, it must also be taken into account (as well as the individual antibiotic susceptibility of the cultivated bacteria) that the antibiotic primarily reaches the renal parenchyma by means of the blood. This differs from antibiotic treatment of a cystitis infection where the substance also comes into contact with the bladder wall via the urine. When treating cases of pyelonephritis one can therefore not utilise the advantage that high concentrations of certain antibiotics are attained in the urine itself (12).

FELINE IDIOPATHIC CYSTITIS (FIC)

Cats under ten years of age with clinical signs of cystitis are seldom suffering from a bacterial infection. Studies have shown that an increased urge to urinate in young cats is the result of a bacterial cystitis infection only in around 2-8% of cases (3, 4). The number of cats with a UTI increases somewhat with age, although then often secondary to primary conditions such as urinary stones and chronic renal failure, or in cats that have gone through an urethrostomy.

ETIOLOGY

Feline Idiopathic Cystitis is characterised by a combination of clinical signs such as haematuria and dysuria, yet without the existence of a bacterial infection. The problem is common and occurs in both male and female cats of all ages but is most frequent in younger to middle-aged cats (3). Clinical signs often develop very acutely yet, in the majority of cases, disappear without treatment within five to seven days (13, 14). The syndrome is, with all probability, not a primary bladder condition but is caused instead by a disorder that affects the bladder and many other parts of the body (3, 4).

DIAGNOSIS

Due to the lack of any specific test to diagnose Feline Idiopathic Cystitis, the disease remains a diagnosis of exclusion. A young cat with first-time lower urinary tract signs without any difficulty in emptying its bladder may empirically be assumed to be suffering from Feline Idiopathic Cystitis. It is important when managing these cases to give adequate information to the owner about the condition along with recommendations concerning the cat's household conditions. Pain-relief may be required. In the event of recurring problems, the patient should be examined with the help of diagnostic imaging and urine samples including urine culture. Haematuria and proteinuria in the absence of bacterial growth can be detected in a urine sample taken by means of cystocentesis. Cystoscopy can often illustrate an increased vascularisation and minor haemorrhages within the bladder wall. Biopsies taken from the

bladder wall display a varying degree of damage and haemorrhage within the submucosa as well as ulcerations, oedema and fibrosis (14). These changes do not necessarily disappear when the cat's clinical signs start to disappear.

MANAGEMENT AND TREATMENT

As the clinical signs usually spontaneously disappear most prescribed treatments appear to be effective as long as they do not, cause any injury to the animal. Many different forms of treatment have been tested over the years but few, or none, have so far been able to protect against relapse. An increased intake of water has, however, been shown to reduce the frequency of relapses (15). Research into this disorder indicates that its clinical signs arise as a consequence of both external and internal factors. An example of an external factor could be unsatisfactory conditions in the cat's home environment, and an increased catecholamine production is an example of an internal factor (16). Since we, at present, do not know how to manipulate the internal factors, it only remains for us to try and influence the cat's environment in a positive fashion, i.e. so-called multimodal environmental modification (MEMO; 3, 17). A compilation and evidence-based evaluation of a range of different drugs with the intention to relieve or cure the clinical signs of Feline Idiopathic Cystitis has been assimilated (18). Drugs such as antibiotics, the disposable infusion of subcutaneous fluid and prednisolone have all, in controlled trials, been found to be ineffective. The implementation of MEMO, including stress reduction in the cat's environment and an increased intake of water, are the recommendations for all these cats. As well as the aforementioned measures, pain-relief can also be necessary during the acute stage.

URETHRAL PLUGS IN CATS

ETIOLOGY

The aetiology behind the formation of urethral plugs is not known. The plugs usually consist mainly of matrix and to a lesser extent of minerals (principally magnesium ammonium phosphate, struvite). One hypothesis is that the increased presence of Tamm-Horsfall's mucoprotein in the urine forms a gel-like substance that entraps the crystals as well as red and white blood cells and epithelial cells. Feline Idiopathic Cystitis can be a predisposing condition behind the formation of plugs.

DIAGNOSIS

Common clinical signs are haematuria, dysuria or a total urinary blockage. The bladder is usually full, hard and tender which can be detected using abdominal palpation.

MANAGEMENT AND TREATMENT

The primary treatment in the case of a urethral blockage is to correct any disturbances of the fluid and electrolyte balance. The actual urethral blockage is treated thereafter and urine samples for culture are preferably taken at the same time. Antibiotics are **only** recommended in the unusual event of an actual infection. The prophylactic antibiotic treatment of cats that have been catheterised **is not indicated** as this can lead to the development of a resistant bacterial infection (19, 20). The above is also applicable even if the catheter will be in place for one or several days. Treatment with glucocorticoids is also not indicated in cats with a urinary catheter in place (20).

GENITAL ORGANS

Female dogs and cats have, under normal conditions, a bacterial flora in the vagina and vestibulum, and male dogs and cats have a normal preputial flora (1-5). The normal bacterial

flora consists, in both bitches and male dogs, of bacteria that are normally to be found in the posterior intestinal section as well as around the anus and vulva. It is, as a rule, a mixed flora of streptococci, *E. coli* and *Pasteurella spp.*, and yet even pure culture can occur in completely healthy animals (1-2). In female cats, the most commonly found bacteria within the vaginal flora are *E. coli*, streptococci and staphylococci but a pure culture of *E. coli* is also a common finding in clinically healthy female cats (3-4). In male cats, the most common aerobic bacteria are *E. coli* and *Pasteurella spp.* yet it is not unusual to find an anaerobic bacterial flora, most often *Bacteroides spp.* and *Fusobacterium spp.* (4). The vaginal flora in bitches and queens varies in its composition at each stage of the oestrous cycle, and the bacterial growth is usually far more extensive whilst the animal is in heat (1, 3-5). One can normally take for granted that the uterus is free from bacteria except during heat and parturition (5).

BEFORE MATING

Bacterial presence in the external genitalia of both cats and dogs is a normal finding. Normal flora is transferred between bitches and dogs during mating without there being any negative effect on the fertility (2). The vaginal flora in cats is not affected by whether they are mated or not (4). Studies have shown, however, that the normal flora of healthy bitches is affected by antibiotic treatment leading to a different composition of bacteria (6). Local treatment of the vagina of monkeys with amoxicillin has been shown to facilitate vaginal colonisation with uropathogenic *E.coli* (7).

Dogs and cats of both sexes should not be treated with antibiotics prior to mating. Bacterial presence in the genital organs is normal, and antibiotic treatment can create problems by disturbing this normal bacterial flora.

DURING PREGNANCY

The administration of medicines to pregnant bitches and female cats should be avoided as far as is possible. Information concerning the effects on the embryo and foetus is sparse and any knowledge derives mainly from studies carried out on laboratory animals (8).

In bitches, the critical period for embryo toxicity is between days 6-20 after the peak level of luteinising hormone has been reached (LH). During this period, any embryos have not yet implanted themselves but instead float freely inside the uterine milk; this milk has an equivalently high drug concentration as the extracellular fluid. In cats, implantation occurs on day 12-13 after ovulation, and the most critical period is between days 5-15 after mating (8). Consequently, the first two to three weeks after mating are the most critical in both dogs and cats.

Even if our knowledge concerning antibiotics is limited we know that their administration, wherever possible, should be avoided during pregnancy. Yet there are a number of antibiotics that probably are safe to use. Beta-lactam antibiotics such as ampicillin, amoxicillin and the cephalosporins are probably safe to use, as are macrolides and lincosamides (e.g. clindamycin). These antibiotics cross the placenta but have not been shown to be harmful for the foetus.

Other antibiotics that are probably safe if used with care, but where risks have been demonstrated using laboratory animals, are the sulphonamides and trimethoprim. Sulphonamides cross the placenta and lead to malformations in rats and mice but similar cases have not been reported in dogs. Neonatal jaundice has been reported in humans following

administration close to partus. Trimethoprim is teratogenic in rats, but this has yet to be reported in other species.

Aminoglycosides (these can be oto- and nephrotoxic), chloramphenicol (gives rise to reduced protein synthesis in the foetus) and metronidazole (teratogenic in laboratory animals, data is missing for dogs and cats) belong to the group of antibiotics that are potentially hazardous and should only be used as a last alternative, and then with the utmost of care.

Quinolones, tetracyclines and streptomycin are contraindicated during pregnancy. Quinolones give rise to articular cartilage defects; tetracyclines can lead to malformations of the bones and teeth and are hepatotoxic for the mother; streptomycin has a higher incidence of toxicity than the other aminoglycosides.

MALE DOGS AND MALE CATS USED FOR BREEDING

Several different antibiotics have been proven to have a negative effect on spermatogenesis. It has been demonstrated that trimethoprim-sulphametoxazole, doxycycline, nitrofurantoin and ofloxacin but not ciprofloxacin, norfloxacin or lomefloxacin have a negative effect on spermatogenesis in rats (9). Toxic levels (150 mg/kg) of enrofloxacin lead to disturbed spermatogenesis in mice (10). The clinical implications of treating male dogs and cats used for breeding are, to a large extent, unknown. Therapeutic doses of amoxicillin with clavulanic acid or griseofulvin have been reported not to affect the sperm quality in dogs (11, 12). Antibiotic treatment of healthy male dogs, due to its effect on the normal bacterial flora in the genital organs, is not recommended (see the section "Before Mating").

JUVENILE VAGINITIS

ETIOLOGY

In pubertal individuals, the vaginal epithelium is thin due to insufficient blood oestrogen levels and this, in certain cases, predisposes for so-called juvenile vaginitis. Normally, one of the bacteria from the vaginal normal flora is involved.

DIAGNOSIS

With the exception of a yellowish exudate around the vulva, the animal is usually without clinical signs.

MANAGEMENT AND TREATMENT

Vaginal infections usually resolve spontaneously in conjunction with the animal's first oestrous cycle. Local treatment with, for example, acidifying products for intravaginal application, vaginal gel or fermented milk products can relieve symptoms. An infection in the urinary tracts may follow, and need treatment.

VAGINITIS-VESTIBULITIS IN ADULT ANIMALS

ETIOLOGY

Vaginitis is often secondary to, for example, strictures, hermaphroditism, an inverted vulva or a foreign body (13, 14). Pure vestibulitis also occurs in dogs without any specific growth of bacteria (15). Infection with canine herpesvirus can give rise to vaginal vesicles in bitches.

DIAGNOSIS

Dogs and cats with vaginitis rarely have a poor general condition, but they usually have a yellow-green discharge and lick themselves a lot around the vulva. The mucosal lining can become oedematous and swollen. A vaginal examination including a vaginal cytological examination should be performed, possibly supplemented by bacterial sampling.

MANAGEMENT AND TREATMENT

Primary vaginitis is very unusual in cats. Measures should be taken against any predisposing factors in both dogs and cats if, that is, they have been identified (15). The use of conservative treatment is preferable when the symptoms are of a milder nature, as the majority of cases clear up spontaneously. Local treatment with, for example, vaginal acidifying pessaries, vaginal cream or fermented milk products can relieve symptoms in dogs. In the event of more severe symptoms, treatment is prescribed in accordance with the results of the culture and determination of the bacterial resistance (16, 17). Treatment with an oestrogenic preparation can be an alternative in spayed bitches.

ACUTE METRITIS

ETIOLOGY

Acute metritis is a bacterially induced uterine inflammation that normally occurs following a difficult birth or in conjunction with an abortion. Gram-negative bacteria such as *E. coli* and *Proteus spp.* are often the pathogens that reach the uterus but infection with staphylococci and streptococci can also occur.

DIAGNOSIS

The animal has a high temperature and a loss of appetite, and its general condition is most often poor. An abundant, malodorous, purulent discharge is usually seen emanating from the vulva. In order to be able to prescribe a targeted therapy, it is recommended that a bacterial sample be taken.

MANAGEMENT AND TREATMENT

Acute metritis can be life-endangering and treatment against septic shock can be required. It is important that, whilst waiting for the test results, antibiotic treatment is started quickly. Empirically, ampicillin/amoxicillin are reported to be effective and the advantage with using these substances is that the litter can remain with the mother. The animal's general condition must, however, be carefully monitored. In life-threatening situations, or alternatively if the animal's condition worsens or does not improve after about 24 hours of treatment with aminopenicillins, the recommended course of treatment is then to switch to trimethoprim-sulfa or a fluoroquinolone, yet in these cases, the puppies or kittens must be removed from the mother. Treatment should continue for approximately five to seven days or longer depending on the development of the disease. Combinations with uterine contractile agents can, in some cases, be indicated. In the case of metritis in a dog following an abortion, the risk that brucellosis is an underlying cause should be taken into consideration.

ENDOMETRITIS

ETIOLOGY

Endometrial infections arise because of interaction between the progesterone-affected endometrium and bacteria from the normal flora.

DIAGNOSIS

The diagnostics can be difficult. The clinical signs can vary and include a poor general condition, reduced fertility, infertility and a discharge. Examination of the vaginal cytological smears, vaginoscopy, ultrasound and the blood samples can serve as a guide when attempting to determine the possible extent of inflammation. Uterine biopsies can confirm the diagnosis. Bacterial samples are taken from the uterus or cranial vagina before antibiotic treatment.

MANAGEMENT AND TREATMENT

Prevention of the progesterone effect on the endometrium can in all probability improve results (for example, by treating the animal with aglepristone or a prostaglandin). Antibiotic treatment should be prescribed in accordance with the bacterial culture results as well as the determination of bacterial resistance. Chronic endometrial infections can be difficult to treat and often require a course of treatment of two weeks or more. Quinolones and trimethoprim-sulfa penetrate the genital tract effectively (18, 19). Follow-up consultations, to confirm that the animal's condition has not worsened and developed into a pyometra, are recommended. If the condition has not cleared up, an ovariohysterectomy is normally required.

PYOMETRA

ETIOLOGY

A pyometra arises due to an interaction between the progesterone-affected endometrium and bacteria from the normal flora. *E.coli* is the dominant agent in both dogs and cats.

DIAGNOSIS

Typical symptoms include a poor general condition, increased thirst and a discharge. The diagnosis is given when an enlarged, fluid-filled uterus is demonstrated after the animal has been in heat yet in the absence of pregnancy. The disease is more common in dogs than in cats and is often seen in older rather than younger animals.

MANAGEMENT AND TREATMENT

The treatment that gives the most reliable results is an ovariohysterectomy. . Treatment with antibiotics alongside uterine surgery is not recommended if the animal's general condition is not poor or only mildly to moderately affected. In the event of a severely affected general condition, antibiotic treatment is recommended postoperatively, primarily in order to protect against haematogenous dissemination. A suitable preparation that can prevent haematogenous dissemination is amoxicillin.

Medical treatment consists of preparations that counteract the effects of progesterone as its basis (for example, aglepristone, possibly combined with prostaglandins) and these are then used in combination with antibiotics. Medical treatment is an option in animals that are being used for breeding or in cases where an operation is preferably avoided. Preparations that are effective against Gram-negative bacteria are recommended whilst waiting for the results of the bacterial culture, the first-line treatment being fluoroquinolones and the second line treatment being trimethoprim-sulfa (20, 21). Follow-up appointments of once a week are recommended in order to make a decision about the length of treatment. In cats, antibiotic treatment with trimethoprim-sulfa over the course of a week and in combination with aglepristone on days 1, 2, 7 and possibly 14 achieved good results in nine out of ten cats with pyometra; this is with a follow-up period of two years (22).

MASTITIS

ETIOLOGY

Inflammation of the teat is a complication that normally arises during lactation, often after parturition, but also in rare cases during a false pregnancy (pseudocyesis) in dogs. The most common bacteria behind the infection are *E. coli* and staphylococci.

DIAGNOSIS

Mastitis can be an acute and life-threatening condition with systemic symptoms. In serious cases of acute mastitis, the affected teats are warm and tender and the bitch or cat has a poor general condition, fever, etc. The milk from an infected teat can be discoloured and sometimes blood-streaked. The milk's appearance can, if the animal is milked carefully, be judged from the drops that are pressed out. Abscesses can also occasionally form in the teat area. Bacteriological samples are taken from the infected milk. Bacteria can normally be found in the teat canal and upon the surrounding skin and any sampling must, therefore, be preceded by a thorough disinfection of the whole area; any bacteriological findings must be evaluated with caution.

The occurrence and clinical relevance of chronic mastitis in dogs and cats has been incompletely investigated.

MANAGEMENT AND TREATMENT

The treatment that is prescribed to treat mastitis depends on whether neonates will continue to nurse their mother. Abscesses should be opened and emptied. The infected teats should be massaged and emptied with the help of frequent manual milking. Even if the affected teats are taped over, in order to prevent the offspring from nursing, the pieces of tape can easily fall away. It is, therefore, only if the young animals have been weaned (and possibly hand-fed depending on their age) that one can totally discount an effect of the mother's treatment on them. In the majority of cases, septicaemia in puppies does not appear to be caused by the presence of bacteria in the mother's milk; there is, however, a risk (23).

Milk samples for bacteriological culture should always be taken and a course of antibiotic treatment lasting seven to ten days should be prescribed in accordance with the determination of bacterial resistance. The staining of milk smears in order to see whether cocci or rods are present can be a further guide, when choosing the antibiotic before the results of the bacterial culture are available.

Kittens and puppies are exposed to a number of different bacteria during the first months of their life and establishing their normal flora is an important process that will protect them from pathogenic micro-organisms. A nursing animal's intestinal flora is thought to be most affected by treatment with aminopenicillins, yet any considerable negative effect via the mother's milk has, however, not yet been described.

In the case of acute mastitis nursing neonates, amoxicillin is the agent most often used empirically pending the bacteriological diagnosis. If the bitch or cat is not suckling her young, quinolones are another option. The ultimate decision as to which antibiotic should be used must be guided by the determination of bacterial resistance.

CAESAREAN SECTIONS

Antibiotics in connection with caesarean sections are not indicated in uncomplicated cases. Perioperative antibiotic prophylaxis can be indicated in order to protect against haematogenous dissemination in cases where the uterus is injured or inflamed, where dead foetuses have begun to decompose, or where a very prolonged birth with a dilated cervix has resulted in a caesarean section. Suitable preparations are ampicillin or amoxicillin. Alternatively, the mother is spayed in conjunction with the caesarean section operation.

BALANOPOSTITIS / POSTITIS

ETIOLOGY

Balanoposthitis is normal in dogs but seen more rarely in cats. It is caused by the overgrowth of the normal bacterial flora; this may be secondary to the presence of a foreign body or a malformation. Inflammation caused by the canine herpesvirus does occur.

DIAGNOSIS

A discharge from the preputium and possibly a hyperaemic mucosa can be detected.

MANAGEMENT AND TREATMENT

Local treatment with, for example, chlorhexidine emulsion or another mild disinfectant. Alternatively, rinse with physiological NaCl solution (17). Measures such as the use of a collar can be taken in order to prevent the animal from licking itself.

ORCHITIS / EPIDIDYMITIS

ETIOLOGY

Causes can be testicular trauma such as puncture wounds or haematogenous dissemination. To be considered is the risk of brucellosis due to an increased trend to travel with dogs as well as a rise in international mating (24). Feline Infectious Peritonitis (FIP) can give rise to orchitis in cats (25-26).

DIAGNOSIS

The testicle and/or the epididymis become swollen and painful and the animal shows a reluctance to move. A bacterial culture is performed on the ejaculate or the urine. In the case of chronic orchitis-epididymitis, the affected testicle-epididymis is enlarged but not painful, and chronic inflammation can result in atrophy and fibrosis.

MANAGEMENT AND TREATMENT

If it is not important to preserve the dog's breeding value, it is recommended that the dog be castrated. If the dog's breeding value must be preserved and the orchitis/epididymitis is unilateral, the first choice of treatment is unilateral castration combined with antibiotic treatment; antibiotic treatment alone is seldom effective, and a testicle that has been inflamed often atrophies subsequently regardless (16). Using unilateral castration, the remaining testicle can be protected from any negative effects of the inflammation and temperature increase within the scrotum. Sterility is a common complication of acute orchitis. The first-line treatment for orchitis/epididymitis is fluoroquinolones (17) or in accordance with the bacterial susceptibility (16). The course of treatment should last for at least two weeks. Brucellosis as an underlying cause should be ruled out if the animal has been taken abroad.

An acute orchitis-epididymitis that fails to clear up becomes chronic and this is considerably harder to treat medically. Castration is recommended in cases of chronic orchitis.

PROSTATITIS

ETIOLOGY

Both acute and chronic infections are seen in the prostate. The infections are most frequently caused by *E. coli*, yet even *Staphylococcus aureus*, *Klebsiella spp.*, *Proteus mirabilis*, *Mycoplasma canis* and many other species can be responsible (16).

DIAGNOSIS

A dog with acute prostatitis displays symptoms such as a poor general condition, a pain response during rectal palpation of the prostate, fever, difficulties when urinating or defecating, a stiff gait, oedema of the scrotum, preputium or hind limbs and pollakiuria (16, 27). Dogs with a prostatic abscess, peritonitis or septicemia can exhibit symptoms of septic shock. Blood, bacteria and leukocytes can be detected in the urine, even if the sample is taken using cystocentesis. This is due to the normal flow of prostatic secretions through the prostatic urethra to the bladder in intact male dogs.

Chronic prostatitis can be difficult to diagnose. The most common symptoms are recurring urinary tract infections and a discharge from the urethra, yet sometimes there is a total absence of symptoms. In some patients, the sperm quality is worsened (both a worsened morphology and motility) and the animal's libido can be reduced due to painful prostatic contractions. The prostate is not always painful when palpated. As with acute prostatitis, blood, bacteria and leukocytes can be detected in the urine. Often, benign prostatic hyperplasia occurs simultaneously. Bacterial culture is performed using an ejaculate (the third fraction) or a urine sample. Samples taken following prostate massage can be recommended in cases when it is difficult to obtain an ejaculate. The fluid is analysed by means of cytologic evaluation and microbial culture. Ultrasound is also recommended for the diagnostics of prostatic disorders (28, 29). Prostatitis is unusual in cats but has been described (30).

MANAGEMENT AND TREATMENT

Treatment against prostatitis includes specific antibiotic treatment, based upon the bacterial culture and determination of bacterial resistance, possible castration or medical treatment in order to reduce the prostate size. Castration should not be performed before the dog has been treated with a course of antibiotics lasting five to seven days, so as to avoid the development of scirrhous spermatic cords (16, 29).

The antibiotics should be lipid soluble and not extensively protein-bound so that they can cross the prostate barrier. The pH in the prostatic fluid is <7.4 and this means that the alkaline antibiotics are able to accumulate in the prostatic fluid. To what extent the inflammatory process affects the blood-prostate barrier, so that even antibiotics that cannot normally cross can be used to treat a prostatitis, has not yet been fully examined. Fluoroquinolones penetrate the normal and chronically inflamed prostate equally well (31) and are the first-line treatment preference for a confirmed bacterial prostatitis. There are studies indicating that bacteria in the prostate survive in an environment protected by a biofilm, and both fluoroquinolones and macrolides are active in biofilms (32). Trimethoprim-sulfa and doxycycline are alternative preparations that can be used instead of quinolones. Macrolides and lincosamides also penetrate the prostate well and can be prescribed should they, in accordance with the culture results, be the most suitable choice. Abscesses require surgical treatment (drainage). The

duration of treatment is decided upon in accordance with the clinical development. Follow-up samples, taken towards the end of the course of treatment and one month after its conclusion, are recommended.

THE RESPIRATORY ORGANS

GENERAL INFORMATION ON THE RESPIRATORY ORGANS

Symptoms from the upper and lower airways can have various origins, for example, trauma, foreign body, dental problems, chemical irritation, allergy, virus, bacteria, fungal organisms, parasites, tumours. Bacterial airway infections are most often secondary to these predisposing conditions.

In the upper airways, nasal cavity and throat, there is a normal flora that is made up of numerous bacterial species (mixed flora). Bacteria can, under normal conditions, also be isolated from the lower respiratory tracts in both dogs and cats. Local defence mechanisms interact in order to eliminate these bacteria. The clinical relevance of finding bacteria in the respiratory tracts is consequently difficult to judge. Gram-negative bacteria such as *E. coli*, *Pasteurella spp.*, *Pseudomonas spp.*, *Proteus spp.*, *Klebsiella spp.* and *Bordetella bronchiseptica* are the dominating pathogens detected in infections of the lower respiratory tracts. Examples of Gram-positive bacteria are streptococci and staphylococci. *Pasteurella spp.* is most commonly detected in cats.

DIAGNOSTICS

- X-ray, magnetic resonance tomography (MRI), computed tomography (CT-scan), endoscopy, tracheal rinsing, bronchoalveolar lavage (BAL).
- Laboratory examinations: cytology and biopsy. Blood samples for haematology, PCR for viral diagnostics.
- Bacterial cultivation in the event of chronic or recurrent symptoms.

RHINITIS

ETIOLOGY

Primary rhinitis infections are unusual. Infectious agents responsible for rhinitis infections in cats feline upper respiratory infection can be, for example, the feline herpesvirus, calicivirus or *Chlamydophila felis*.

MANAGEMENT AND TREATMENT

Rhinitis infections are treated symptomatically with the focus aimed at the underlying cause. Antibiotics are not given in the first instance but can become necessary if signs of a secondary bacterial infection have been present for a while. Suitable antibiotic preparations are ampicillin, amoxicillin and fenoxymethylpenicillin. It is not unusual, despite antibiotic treatment, for there to be a recurrence of symptoms if the predisposing condition is not addressed.

Cats can become infected with *Chlamydophila felis* (previously known as chlamydia). Symptoms from the upper respiratory tracts often arise in combination with conjunctivitis. For treatment guidelines, see the section on eye diseases.

“Chronic snufflers” is the name given to cats that have been left with permanent damage of the nasal cavity due to viral rhinitis infections and are therefore predisposed to develop secondary bacterial infections. Antibiotic treatment is rarely indicated unless the animal’s general condition is poor. If antibiotic treatment is necessary, the preparation should be chosen in accordance with the culture result; where there is suspicion of osteomyelitis, the preparation should also be able to penetrate infection locations that are normally difficult to penetrate.

TONSILLITIS

ETIOLOGY

Tonsillitis is often seen as an acute inflammation of the tonsils in conjunction with pharyngitis. Primary bacterial tonsillitis infections in cats and dogs are unusual. Examples of conditions that can cause secondary tonsillitis are chronic vomiting and regurgitation, chronic gingivitis, tracheobronchitis and rhinitis. Lymphoma can also be responsible for enlarged tonsils in cats.

DIAGNOSIS

The investigation should be aimed at identifying the root cause. Swab samples from the tonsils for bacterial culture are of no diagnostic value. In the event of suspected chronic tonsillitis caused by bacterial infection, a bacterial cultivation from a tonsil biopsy is recommended but the cultivation result, as discussed in the text above, is difficult to interpret.

MANAGEMENT AND TREATMENT

Inflamed, swollen tonsils are not an indication for antibiotic treatment. Treatment of the predisposing condition often induces the tonsillitis infection to clear up. A tonsillectomy is an alternative in the event of chronic difficulties,.

TRACHEITIS/BRONCHITIS

ETIOLOGY

Tracheitis/Bronchitis are prevalent conditions in dogs and are more commonly known as “kennel cough”. Various different agents in conjunction with one another are responsible for the infection. Dominating pathogens are parainfluenza and *Bordetella bronchiseptica*. Other agents that can be detected are the canine herpesvirus, reovirus, the canine adenovirus type 2 and *Mycoplasma* spp.

MANAGEMENT AND TREATMENT

The infection is treated symptomatically. Antibiotics are not prescribed in uncomplicated cases. Antibiotic treatment is indicated if there are signs that the bacterial infection has reached the lower respiratory tracts. The infection’s combination of bacterial agents means that tetracyclines are a suitable choice of antibiotic. In the event of chronic difficulties alongside signs of bacterial infection, a bacterial culture should be performed and treatment prescribed in accordance with the bacterial findings and determination of bacterial resistance.

PNEUMONIA

ETIOLOGY

Bacterial pneumonia occurs in dogs but is unusual in cats. According to literature on the subject, the bacteria that are isolated in cases of pneumonia are opportunists such as *E. coli*,

Klebsiella spp., *Pasteurella* spp., *B. Bronchiseptica*, staphylococci, streptococci and mycoplasmas.

Damage caused by aspiration pneumonia is not always caused by the development of bacterial pneumonia. Acid from the stomach can give rise to chemical pneumonia, and inhaled feed can lead to inflammation and obstruction of the airways.

DIAGNOSIS

An examination of the animal should be performed in order to determine any possible predisposing condition responsible for the pneumonia, e.g. aspiration, a foreign body, a virus infection, mycosis, neoplasias, lung parasites, diseases of the bronchi and congenital defects. Diagnosis is obtained with the help of x-ray, blood samples (leukocytosis with a “left shift”), a tracheal rinsing test, BAL, an examination of the cytology and a bacterial culture including the determination of bacterial resistance.

MANAGEMENT AND TREATMENT

Antibiotics are always prescribed to treat bacterial pneumonia. The choice of antibiotic is made based upon empirical experience. Empirically, amoxicillin and the cephalosporins often have effect. In cases where oral treatment is the best option, doxycycline is an option. Where possible, the antibiotic should be chosen based on the results of the bacterial culture and the determination of bacterial resistance. Treatment should lead to an improvement within two to three days otherwise consider switching to another antibiotic. The course of treatment should still continue for about a week after the clinical symptoms have disappeared. The total course of treatment is often between two to six weeks.

Routine treatment of aspiration pneumonia is controversial as any injury can be purely chemical. Antibiotic treatment is prescribed when a secondary bacterial infection has been confirmed or in the event that another supportive treatment has not had effect.

MOUTH

ETIOLOGY AND GENERAL INFORMATION

The oral cavity is normally a very bacteria-rich environment and the majority of bacteria have not yet been identified. The environment in a healthy mouth has an oxygen tension of around 12-14% as opposed to air that normally consists of about 21% oxygen. The oxygen tension in the periodontal pockets is only about 1-2%. The various bacterial species that colonise the mouth are therefore, to a large extent, anaerobic or aerobic/facultative (1).

All interventions in the mouth raise bacteraemia that is normally taken care of by the immune system (2).

DIAGNOSES

Coating on the teeth cause a local inflammation in the gum, namely *gingivitis*, which is reversible only if the bacterial coating on the teeth is removed. It is common with gingivitis in conjunction with viruses. Other predisposing factors are illnesses or medication that suppress the immune system.

In cases where there is a loss of supporting tissue around the tooth, *paradontitis* is not reversible. Careful hygiene can suspend the process.

If the oral mucous membranes are involved, the infection is called a stomatitis. Stomatitis infections are extremely painful. Chronic stomatitis infections, which mostly affect cats, are often idiopathic and are sometimes accompanied by secondary bacterial infections.

Root abscesses and open fractures are conditions where the jawbone is also involved.

MANAGEMENT AND TREATMENT

The removal and cleaning-up of the infection, combined with surgical freeing so as to facilitate cleaning, is often sufficient for infections or inflammation in the oral cavity to be self-limiting.

Chlorhexidine is a well-tested antiseptic in the oral cavity and is used in conjunction with surgical procedures as well as for follow-up care.

PROPHYLACTIC TREATMENT

Reports based on research investigating the basis for and need of prophylactic treatment combined with dental treatments in humans have been published. The results are not conclusive but it has been assessed, based on clinical grounds, that a single prophylactic treatment given to risk patients is justifiable (3).

EXAMPLES OF CONDITIONS OR SITUATIONS WHERE PROPHYLACTIC ANTIBIOTIC TREATMENT CAN BE INDICATED

- Immunodeficiency disease or immunosuppressive therapy.
- Simultaneous aseptic operation (e.g. when the patient is elderly or has an existing condition that means that repetitive anaesthetic treatment is not recommended).
- Pulp amputation (when the objective is a decontamination of the operational area).
- Heart murmurs are NOT an indication for antibiotic treatment. Only cases of endocarditis, which is an extremely unusual diagnosis in dogs, can be justifiably treated with prophylaxis.

For information on choosing an antibiotic and principles for administration, see the chapter on “The Perioperative Use of Antibiotics”.

GASTROINTESTINAL TRACT

There are few indications for the antibiotic treatment of gastrointestinal diseases.

The animal’s age, vaccination status, type of feed, whether the symptoms are acute or recurring, the presence of blood in the stool or the vomit, fever, similar outbreaks in the patient’s surrounding environment, possible enteropathogens that have been isolated from persons or animals in the household, and any symptoms in the owner or others in the household is all important information. A standard clinical examination can be supplemented with, for example, an ultrasound, an x-ray and/or endoscopic examination for biopsy and histological examination.

ACUTE GASTROENTERITIS

The normal bacterial flora in the lower small intestine is a mixture of aerobes, anaerobes and facultative anaerobe bacteria. Commonly detected facultative anaerobic species are

staphylococci, streptococci, corynebacteria, lactobacilli, enterococci and *Enterobacteriaceae* such as *E. coli* and *Proteus* spp. Amongst the anaerobic species that can be found are, for example, Clostridia and *Bacteroides* spp.

The bacterial flora in colon in a dog consists of more than 90 % of anaerobic bacterial species (e.g. *Bacteroides* spp., and Clostridia). Examples of facultative anaerobic bacteria are different species from the *Enterobacteriaceae* as well as lactobacilli, streptococci and enterococci. One study shows that the bacterial flora in a cat is more evenly distributed between aerobic bacteria (mostly *E. coli* and lactobacilli) and anaerobic bacteria (mostly *Clostridium perfringens* and *Bacteroides* spp.).

ETIOLOGY

Causes of acute vomiting/diarrhoea in dogs and cats can be, for example, feed-related (intolerance, sudden change of feed, toxins); toxins (feed-related or otherwise); virus (parvovirus, coronavirus, rotavirus, astrovirus, picornavirus); parasites; acute pancreatitis; anatomical (for example, invagination).

Bacterial infections in the gastrointestinal tract can occur but are not common.

DIAGNOSTICS

LABORATORY EXAMINATIONS

- A blood count
- Faecal samples: The presence of mucous or blood. The presence of parasites. The presence of the parvovirus and possibly another virus. Bacteriological examination (culture or toxin determination) can be necessary if the animal develops a poor general condition and/or haemorrhagic gastroenteritis as well as chronic diarrhoea. The examination must always have a specific hypothesis. The results can be difficult to interpret if they determine the presence of bacteria that can also occur without necessarily giving symptoms.
- Cytology from the rectal mucosa.
- Histological examination of a biopsy.

MANAGEMENT AND TREATMENT

Bacterial infections in the gastrointestinal tract are not common. Antibiotic treatment is therefore not normally indicated.

Symptomatic treatment – fluid and electrolyte therapy parenterally/per os.

Antibiotic treatment is only indicated in the event of an extremely poor general condition, haemorrhagic enteritis combined with fever and in cases of a reduced immunological status. It is not unusual for the animal to have diarrhoea with a mild to moderately blood-streaked stool, yet this alone is not an indication for antibiotic treatment. The aim of antibiotic treatment is to counteract sepsis and not to treat the bowel disorder. The antibiotic should be effective against Gram-positive, Gram-negative and preferably also anaerobic bacteria; examples are amoxicillin or trimethoprim-sulfa. Fluoroquinolones should be reserved for treating life-threatening conditions.

GASTRITIS

The importance of *Helicobacter* spp. in connection with gastritis in dogs and cats is not yet clear. Neither has any association between *Helicobacter* spp. and gastric ulcers been made in animals. Different species have been determined in the stomach in clinically normal dogs and cats. *Helicobacter* spp are microaerophilic Gram-negative bacteria from the same group as *Campylobacter* spp. The detection of bacteria is made by means of a biopsy from the stomach followed by its histological examination.

SPECIFIC BACTERIAL ENTERITIDES

CAMPYLOBACTER

Campylobacter spp. do not usually give rise to symptoms. Illness with any clinical relevance is usually only seen in younger animals. The symptoms are then a watery and possibly bloody diarrhoea, possible vomiting, inappetence and mild fever. The diagnosis is confirmed using culture and special cultivation methods. Treatment is only necessary in the event of an extremely poor general condition and when there is a risk of sepsis; suitable preparations are macrolides such as erythromycin.

As the infection is a zoonosis, the animal's owner should be informed as to the risk of infection to persons in the animal's environment.

SALMONELLA

Different serovariants of *Salmonella* such as *S. Typhimurium* can be present in dogs and cats without giving any detectable symptoms. Clinical symptoms, when they occur, can consist of an acute mild to severe diarrhoea that may or may not be blood-streaked. Fever and sepsis can develop. The diagnosis is obtained by means of the bacteriological cultivation from a faeces sample. Methods of selective cultivation should be used. In the event of sepsis, the diagnosis can be obtained from a blood culture.

Salmonella infections in outdoor cats are often seen during late winter or early spring. Cats can become infected from small birds. The species is *Salmonella Typhimurium*. The cat's symptoms are often fever, loss of appetite, vomiting and diarrhoea that can be blood-streaked. Many cats only have mild symptoms and some cats never exhibit any symptoms at all. The infection is most often self-limiting. Some cats need supportive therapy. The diagnosis is obtained by means of faeces culture.

Antibiotics **should not be prescribed unless the symptoms are life threatening** i.e. such as diarrhoea that is heavily blood-streaked, shock and a risk of sepsis. Treatment with antibiotics *is thought to increase* the risk that the animal will become a carrier for a longer period.

When antibiotics are required in accordance with the above, the choice of antibiotic must be made empirically; it is very important, however, that the diagnosis and choice of antibiotic is followed up with a bacteriological examination. Salmonella that is isolated from Swedish animals is often susceptible to the majority of antibiotics, and ampicillin and amoxicillin are therefore suitable empirical choices. Multiple antibiotic-resistant bacteria are relatively common in other countries.

A new culture should be done a short time after the clinical symptoms have disappeared, in order to determine whether the infection is still actually present.

It is very important that the animal's owner is informed of how the risks of contagion between humans and animals can be reduced by implementing hygiene measures. In Sweden

salmonella is governed by the disease control law on zoonosis , and cases of salmonellosis must be reported to the Swedish Board of Agriculture and the County Administrative Board.

CLOSTRIDIA

Clostridium perfringens are Gram-positive anaerobic rods that constitute part of the normal flora in the bowel. Enterotoxin from clostridia can be one cause of acute haemorrhagic gastroenteritis. Toxin-producing *C. Difficile* has also been reported as giving rise to pseudomembranous colitis in dogs.

Acute clostridia infections are most often self-limiting and antibiotics are therefore very rarely necessary. An increased intake of dietary fibre can be favourable, since it leads to a lower pH in the colon and inhibits sporulation. If antibiotic treatment of *C. Perfringens* associated enteritis is nevertheless considered necessary, suitable substances are penicillin or ampicillin/amoxicillin.

E. COLI

The significance of enteropathogenic or enterotoxin-producing *E. coli* in connection with acute and chronic diarrhoea in dogs and cats is not yet clear.

SIBO, ARD AND IBD

“Small intestinal bacterial overgrowth” (SIBO) in dogs is defined as an abnormally high total amount of bacteria, aerobic and anaerobic, in the small intestine. “Antibiotic responsive diarrhoea” (ARD) is defined as a condition where the diarrhoea ceases with antibiotic treatment but recurs once the antibiotic treatment is terminated. “Inflammatory bowel disease” (IBD) is a chronic inflammation of the bowel.

Differential diagnostics can be difficult and a thorough investigation of the underlying cause is required. The course of treatment chosen should be guided by the results of the investigation.

COLITIS

The significance of bacteria as a cause of acute or chronic colitis has not yet been clearly defined.

Acute colitis in dogs is relatively common; it can arise as a separate condition, yet it is more commonly seen together with enteritis. The cause is often dietary. Treatment is symptomatic with fluid replacement and antibiotics, if deemed necessary. Acute colitis in cats is a much more unusual condition, probably due to the fact that cats have other eating habits.

What is responsible for chronic colitis in dogs and cats has not yet been firmly established. A contributing factor is thought to be an effect on the local immune defences. There are different classifications of colitis based on histological findings, e.g. lymphocytic-plasmacytic, eosinophilic, and histiocytic ulcerative colitis.

In cases of chronic colitis, immunosuppressive treatment with, for example, corticosteroids is often deemed necessary. Follow-up treatment with sulphasalazine and olsalazine may be necessary. Metronidazole often has an effect against chronic colitis. It is not clear as to how

the effect is mediated. Aside from the effect against anaerobic bacteria and protozoa such as *Giardia* sp., an immunosuppressive effect has also been demonstrated.

LIVER

Diseases of the liver are a complex group of diseases that are seen in both dogs and cats. There are, however, differences in the clinical symptoms as well as histopathological differences between the two species.

Liver diseases can be primary or secondary, acute or chronic. The classification of chronic liver diseases is still being discussed as to whether it should be made according to aetiology or morphology.

Primary infectious liver diseases (bacterial, viral or mycoses) are unusual in Sweden.

Antibiotic treatment is indicated in cases of acute suppurative cholangiohepatitis and if there is risk of hepatic encephalopathy. If antibiotic treatment is deemed necessary, non-hepatotoxic substances that have penetration into the liver and bile should be prescribed. Antibiotic alternatives to treat cholangiohepatitis are ampicillin, amoxicillin, cephalixin or fluoroquinolones. Metronidazole has been recommended to treat hepatic encephalopathy.

PANCREAS

Diseases of the exocrine pancreas can be divided up into acute or chronic pancreatitis and exocrine pancreatic insufficiency (EPI). Bacterial infections in the pancreas are unusual. Antibiotic treatment is only indicated if there is a risk of sepsis or disseminated intravascular coagulation (DIC).

EYES

CONJUNCTIVITIS IN DOGS

ETIOLOGY

Conjunctivitis of primarily bacterial origin is unusual in dogs.

Examine the dog for predisposing conditions such as a pathologically low tear production, trichiasis, distichiasis, cilia, a foreign body, an allergy, draught, dust, smoke, tear film deficiencies, anatomical eyelid defects, etc. Hypersensitive reactions as a response to treatment with topical agents, such as neomycin and benzalkon chloride, can arise and lead to a conjunctivitis that does not respond to treatment (1).

Conjunctival hyperaemia can also be a symptom of a condition in the adnexa or in the inner eye.

Follicular conjunctivitis is not a symptom of bacterial or viral infection (2, 3).

DIAGNOSTICS

Examine the animal to find the primary cause as stated in the above text.

Perform cytology and bacterial culture testing for the determination of bacterial susceptibility.

Symptomatic bacterial conjunctivitis infections are often associated with findings of *Staphylococcus sp.* and other Gram-positive organisms (4,5); the normal conjunctiva is, however, seldom sterile. A positive bacterial culture is obtained in between 46-90% of healthy dogs. The results mostly consist of Gram-positive aerobes such as coagulase-positive *Staphylococcus spp.* and other staphylococci as well as *Streptococcus spp.* (6-10). Gram-negative bacteria occur in about 7-8% of cases (8-10), anaerobes are unusual (6-10). There is also a large risk that samples from the conjunctiva can become contaminated with bacteria colonising the adjacent skin. It is, therefore, of the utmost importance that the relevance of different bacteriological findings is always judged in relation to the clinical signs. The extent of the growth and the possible existence of mixed flora should also be taken into consideration.

MANAGEMENT AND TREATMENT

In many cases, local cleansing of the eye in conjunction with treatment of the predisposing condition is sufficient.

Even in cases of follicular conjunctivitis, rinsing gives the best effect and can sometimes be combined with symptomatic topical corticosteroid/antiinflammatory treatment (1). Topical antibiotic treatment may be given on a temporary basis if there is a clear indication that a secondary infection exists.

In cases of neonatal conjunctivitis drainage, i.e. an opening of the closed eyelids, and rinsing is of the utmost importance. Local antibiotic treatment is prescribed thereafter together with artificial tears until the puppy's own tear production has become established.

When treatment of bacterial infections is needed, the first-line choice is fusidic acid, alternatives are, for example, chloramphenicol and tetracycline (4). Local treatment is always sufficient (4).

FELINE CONJUNCTIVITIS

ETIOLOGY

Primary bacterial conjunctivitis infections in cats are mainly caused by *Chlamydophila felis* and *Mycoplasma*. Herpesvirus can also cause conjunctivitis in cats.

The number of cats in the group also has considerable effect on the infectious pressure.

DIAGNOSTICS

Asymptomatic carriers of *Chlamydophila felis* do exist.

Bacterial cultures from the conjunctiva of healthy cats are negative in 65% of the cases (11), but if bacteria are demonstrated, *Staphylococcus aureus* and *Staphylococcus epidermidis* are most commonly detected.

A PCR test for many agents, such as, *Chlamydophila*, *Mycoplasma* and herpesvirus, can be performed. A negative test result does not exclude the possibility of infection. The highest

probability of attaining a positive test result is when the sample is taken during the acute stage of the condition.

Determination of the antibody titres, perhaps as paired samples, can be of some value.

Cytological examination can be of value for the diagnostics (12). *Chlamydomphila felis* is considered to be a zoonosis, yet transmission between cats and humans is probably rare.

MANAGEMENT AND TREATMENT

An infection with *Chlamydomphila felis* in cats is most effectively treated systemically with tetracycline. In order to eliminate the infection, a treatment lasting four weeks is recommended (13). If the infected cat is kept together with other cats, all of the cats should be treated simultaneously.

Since the treatment is long-lasting and includes several animals, the diagnosis should first be confirmed microbiologically.

Cats living in single-cat households can empirically be treated with locally administered tetracyclines or alternatively chloramphenicol. These should be administered topically four to five times a day, and for one to two weeks after the patient has become free of clinical signs. Topical treatment is not, however, sufficient to eliminate bacterial carriership (14) and if clinical signs reappear, standard antibiotic treatment is recommended.

Infection with *Mycoplasma felis* in cats can be treated with tetracyclines, yet few studies are available which look into different treatment regimes. In the event of recurrent problems and a confirmed diagnosis in a multi-cat household, treatment regimes recommended for the treatment of chlamydia infections can be an option.

The risk of enamel hypoplasia and tooth discolouration or skeletal effects in young animals is considered to be smaller when using doxycycline as compared to tetracycline (15, 16).

Vaccination can alleviate clinical signs but does not protect against infection. A vaccinated cat can carry the organism and be a potential source of infection.

BLEPHARITIS

ETIOLOGY

Blepharitis can be a solitary disease involving either part of or all of an eyelid, or it can be part of a more general skin disease. Staphylococci or streptococci are often responsible, frequently in combination with an immunological reaction.

Immune-mediated blepharitis occur and also blepharitis due to infections such as demodicosis, sarcoptic mange and leishmaniosis.

DIAGNOSTICS

The diagnosis is often made based upon the macroscopic clinical signs. Secretion from the inflamed Meibomian glands or pyogranuloma can be sampled for bacteriological culture and cytological examination.

MANAGEMENT AND TREATMENT

In the event of a bacterial infection, topical treatment with fusidic acid in conjunction with eyelid cleansing is the first-line treatment preference. Systemic antibiotic treatment according to dermatological principles, and local or oral corticosteroid/antiinflammatory therapy may be required in difficult cases.

KERATITIS

ETIOLOGY

Keratitis infections are very rarely caused by bacteria usually there is a mechanical or immunological explanation. Herpes-related keratitis occurs in cats.

DIAGNOSTICS

Clinical examination. Cytological and bacterial examination and possibly a biopsy.

MANAGEMENT AND TREATMENT

Eliminate any mechanical causes such as eyelid defects, a pathologically low tear production, etc. Anti-inflammatory treatment and a lubricating tear substitute, preferably with hyaluronic acid.

Keratitis and a low tear production can be treated using ciclosporin.

CORNEAL ULCERS

ETIOLOGY

Corneal ulcers are rarely of primarily bacterial origin. Trauma, cilia, eyelid defects, etc, are more frequently responsible for the condition in younger dogs and should always first be excluded.

Chronic ulcers, with a diminished ability to heal the corneal epithelium occur mostly in older dogs.

Pseudomonas and beta-haemolysing streptococci can cause so-called melting ulcers.

DIAGNOSTICS

Corneal ulcers can be classified according to how deeply they penetrate. This can be determined with the help of biomicroscopic examination (slit-lamp) and colouring with fluorescein

In the event of chronic ulcers that do not respond to treatment as expected, or in cases of progressive and deep or perforating ulcers, bacteriological and cytological examination should be performed.

In cases of so-called melting ulcers, where bacterial proteases and collagenases break down the stroma and give it a light blue colour, cytological samples are taken from the wound edge in order to give immediate guidance as to the choice of antibiotic. However, bacteriological culture and a determination of the bacterial susceptibility should also be done as confirmation.

TREATMENT

Mydriatica, for example atropine, should be administered if the patient has miosis, an abnormal pupil reflex, or deep ulcers where there is a risk of perforation.

For **primary non-bacterial superficial ulcers**, topical antibiotic treatment is prescribed as a means of protection throughout the period of healing. Fusidic acid or chloramphenicol are alternative preparations.

For **chronic or indolent ulcers** with epithelium defects, mechanical debridement of the ulcer edges is often required, often with repetitive treatments in order to promote healing. A lubricating tear substitute can suffice as the only medical treatment in such cases.

For **deep stromal ulcers** where there is risk of perforation, or where perforation has already occurred, a local antibiotic without an ointment base and with good penetration into the cornea, should be prescribed. Bacterial culture is recommended. First-line treatments are chloramphenicol or alternatively tetracycline. Systemic antibiotic treatment is indicated, in addition to the above, in the event of actual perforation; penicillin or amoxicillin are suitable options.

For **melting ulcers** an intensive local antibiotic treatment with, for example, fluoroquinolones (such as ciprofloxacin) should be administered and systemic antibiotic treatment together with antiprotease treatment should also be prescribed due to the risk of perforation. The choice of antibiotic should be guided by the cytological determination and culture results.

UVEITIS

ETIOLOGY

Uveitis can be triggered by a multitude of different factors; however, the reason is rarely bacterial as long as the cornea is not perforated.

Causes of uveitis can be, for example, toxinemia (such as in the case of a pyometra), a systemic disease or local infection, glaucoma, trauma, bleeding, neoplasia, lens protein-induced or a condition with an immunological background. Idiopathic uveitis also occurs.

Uveitis can also be part of or a general disease with agents such as *Borrelia*, *Anaplasma*, *Leptospira*, the herpesvirus, distemper virus, *Toxocara*, *Toxoplasma*, *Leishmania* and others, or septicemia (regardless of the origin).

Interacting systemic diseases such as FIP, FeLV and toxoplasmosis, etc, occur in 38-70% of cases in cats (17-19). Idiopathic lymphocytic-plasmocytic uveitis is the most common (20).

DIAGNOSTICS

Clinical signs include blepharospasm, miosis, the presence of cells in the anterior eye chamber, ciliar injection and conjunctival hyperemia, corneal oedema, hypopyon, hyphema, a swollen iris and cataracts.

Perform an ophthalmologic examination. Consider adding an examination using ultrasound if the posterior segment cannot be inspected.

Haematology, serology, urine tests, titre controls (with, for example, the aforementioned diseases in mind) and vaccination status. Local bacterial sampling by means of paracentesis is seldom necessary.

MANAGEMENT AND TREATMENT

Exclude or verify systemic disease and treat accordingly. Local and/or systemic anti-inflammatory treatment, depending on the clinical signs.

Systemic antibiotic treatment is used to treat uveitis if there is another disease which requires such treatment, or in cases where the cornea is perforated. The choice of antibiotic is made in accordance with the primary cause. Antibiotics are administered locally if a purulent discharge indicates the actual presence of infection or in the event of a corneal ulcer. Topical mydriatica treatment can be indicated.

RETROBULBAR ABSCESS

ETIOLOGY

For example, foreign body, trauma or encroachment from nearby infections in the nasal or oral cavities such as from a tooth root. Often Gram-positive bacteria.

Retrobulbar cellulitis is defined as a diffuse inflammation without the presence of pus in the orbital tissue that can precede the formation of an abscess (21).

DIAGNOSTICS

Clinical symptoms often include acute unilateral exophthalmus; third eyelid prolapse and conjunctival hyperemia; pain on opening the mouth. Punction (preferably from the oral cavity), ultrasound, MRI, cytology and bacterial culture including both aerobic and anaerobic culture.

MANAGEMENT AND TREATMENT

Drainage if possible. Anti-inflammatory treatment often combined with systemic antibiotic therapy with good penetration into abscesses, for example, clindamycin, preferably following the determination of bacterial resistance. A Gram-positive or mixed flora is often present (21).

DACRYOCYSTITIS

ETIOLOGY

For example, a foreign body, trauma or encroachment from other nearby infections (teeth). A culture often demonstrates the growth of opportunistic bacteria such as *Staphylococcus sp.*, *Streptococcus sp.*, *Proteus sp.* and *Escherichia sp.* (22).

DIAGNOSTICS

Clinical symptoms. Try to identify the underlying cause such as those listed above. Cytology, aerobic and anaerobic culture on the exudate (23). X-ray of the teeth.

MANAGEMENT AND TREATMENT

Rinse the tear canal repeatedly. Initially, apply topical antibiotic treatment in the form of eye drops (23): chloromycetin is the first-line treatment. Use systemic antibiotic treatment for difficult cases (23) with, for example, amoxicillin or clindamycin or preferably use a preparation that is chosen in accordance with the determination of bacterial susceptibility. Local and systemic anti-inflammatory treatment.

TICK-BORNE BACTERIAL INFECTIONS

CANINE GRANULOCYTTIC ANAPLASMOSIS

ETIOLOGY

Canine granulocytic anaplasmosis (or canine granulocytotropic anaplasmosis) is caused by the bacteria *Anaplasma phagocytophilum*, whose predominant vector in Sweden is the commonly found tick *Ixodes ricinus* (1). The infection was previously known as granulocytic ehrlichiosis, but this is a misnomer nowadays as the bacteria has since been classified as a member of the genus *Anaplasma* and not *Ehrlichia* (2).

Both dogs and humans, and even other animal species, can fall ill as a result of infection with *A. phagocytophilum*. There are isolated cases that have been reported in literature of clinical manifestations in cats with similar symptoms to those found in dogs (3, 4).

The canine pathogen *Ehrlichia canis* that is often mentioned in literature does not naturally exist in Sweden. *E. canis* can, on the other hand, be encountered in imported dogs or dogs that have returned from Southern Europe.

These treatment recommendations are only valid for canine granulocytic anaplasmosis.

DIAGNOSIS

Great precision is required in order to determine and diagnose canine granulocytic anaplasmosis. The diagnosis is based upon a medical history with potential tick exposure, clinical suspicion and specific laboratory examination.

The agent can be demonstrated in the blood during the acute stage of the disease by means of PCR examination. The method is very sensitive and specific and a positive result can be obtained in about a week before any determinable morulae appear in the blood (5).

By examining blood smears during the acute stage of the disease, morulae can be determined in neutrophils. The procedure is, however, less sensitive and less specific than PCR examination.

A serological examination with the aim to detect antibodies specific for *A. phagocytophilum* can be performed. A positive result means that the dog has been infected at some time during its life. The value of a positive result is limited, since many dogs never actually become ill as a result of infection and, furthermore, the seroprevalence in large areas of Sweden is high. The clinical assessment must always govern the interpretation of the laboratory results.

Antibody titres persist for many months and dogs can become reinfected. High titres can consequently be determined with repeated laboratory tests over a long period of time. Repeated sampling, if the first examination displays a high titre, is not necessary regardless of whether the dog is to be treated or not (as long as there is no suspicion of a false positive examination result). A serological examination performed in the absence of clinical symptoms is also not necessary.

Repeated sampling is indicated in cases where there is a clinical suspicion of granulocytic anaplasmosis and where there was an absence of or alternatively a low titre determined during the first sample examination. In such cases, paired samples are taken (i.e. the first sample is analysed once again alongside the second sample taken two weeks later) in order to determine if there is an increase in titre that in itself signifies acute infection. If at all possible, (i.e. if whole blood and not just serum has been stored) a PCR examination can also be performed on the first blood sample.

MANAGEMENT AND TREATMENT

In cases where the clinical signs and specific laboratory analyses indicate actual disease, doxycycline is considered to be the first-line treatment when treating canine granulocytic anaplasmosis.

Antimicrobial susceptibility testing of *A. phagocytophilum* has shown that it is sensitive for doxycycline, rifampicin and fluoroquinolones (6,7).

There is a lack of research focusing on the optimal duration of treatment for dogs and cats. The majority of dogs with acute granulocytic anaplasmosis respond quickly to treatment and are often symptom-free within 24-48 hours. A course of treatment lasting 10 days is sufficient to eliminate clinical manifestations. Any recurrence of clinical signs has not been documented in dogs with a course of treatment of this length (4, 8-10). Persisting clinical signs or relapses have also not been reported in humans with symptomatic *A. phagocytophilum* infection following seven to ten days of treatment with doxycycline (11-13). A course of treatment for dogs shorter than 10 days has not, however, been tried out according to published studies on the subject.

There is no evidence to support the need for long-term treatment, as there is no evidence to suggest that a chronic condition can develop (4,8,14). Asymptomatic persistent infection has, however, been reported in dogs that are receiving cortisone therapy (10,15).

Careful follow-up of treatment is recommended. If the patient does not respond to treatment with doxycycline, there is a high probability that the animal is suffering from another illness simultaneously.

Doxycycline is the first-line treatment to treat canine granulocytic anaplasmosis in puppies. The risk of enamel hypoplasia and tooth discolouration is thought to be less when using doxycycline than when using tetracycline. These risks should be weighed up against the risks of a serious infection (16,17).

PROPHYLAXIS

Prophylaxis consists of the prevention of tick infestation with the help of veterinary drugs where required, combined with a regular daily examination of the animal's coat so as to remove any ticks before they are able to transfer infection to the pet.

LYME BORRELIOSIS

ETIOLOGY

Lyme borreliosis is caused by spirochetes that belong to the group *Borrelia burgdorferi*. Both humans and animals are infected mainly by the bite of an infected tick (*Ixodes spp.*). The tick *Ixodes ricinus* is very common in large areas of Sweden (1). In a Swedish study carried out between 1991-1994, 6% of the dogs that were examined in the province of Götaland were seropositive for *B. burgdorferi* and the corresponding number in the province of Svealand was 4% (18). In the dogs that were examined, there was no clinical suspicion of Lyme borreliosis.

At least six different *Borrelia* species have been demonstrated in dogs; the species *B. afzelii* and *B. garinii* and to a lesser extent *B. burgdorferi* sensu stricto have been detected in Sweden. Cats can become seropositive and have been infected experimentally but naturally occurring disease has not been reported (4,19).

DIAGNOSIS

It is often difficult to confirm the diagnosis clinical Lyme borreliosis in dogs and great precision is therefore required.

The majority of infected dogs (up to 95%) never develop clinical symptoms (20). In a minority of animals, the bacteria migrate from the skin to the connective tissue (including joints) that is situated in close proximity to the tick bite. Clinical disease develops in these animals, presumably as a consequence of the body's inflammatory response. The pathogenesis is, however, unclear.

The description of clinical signs that exists in literature discusses, to a large extent, infections with *Borrelia* spp. that dominate in North America (principally *B. burgdorferi*). Typical clinical signs that are described are fever, inappetence, lethargy, lymphadenopathy and wandering lameness related to polyarthritis. Fever and polyarthritis have been documented in experimental infection (4,21). A variety of other syndromes have, according to literature on the subject, been associated with the presence of antibodies against borrelia, i.e. without a secure diagnosis .

With the help of PCR examination, one can attempt to detect the agent within the synovia from the affected joint and from skin adjacent to the affected joint. Despite the method's high sensitivity, a negative test result does not exclude the possibility of Lyme borreliosis should the presence of clinical signs in themselves give rise to clinical suspicion. A skin biopsy taken from the location where the infected tick punctured the skin constitutes good test material, yet in practice it is often impossible after the event to know where on the dog this occurred. Samples can also be taken from the skin areas where the dog most often becomes bitten by ticks. *Borrelia* organisms can remain in the tissue, however, for long periods without actually causing disease and a positive test result should, in such cases, be interpreted with care (21). PCR does not differentiate between living and killed organisms either. Blood is not recommended as examination material, as the bacteria mostly migrate to the tissues and the chances of actually demonstrating the agent in the blood are therefore low (21).

Serological examination for antibodies specific for *B. burgdorferi* can be performed. A negative test result means, in the vast majority of cases, that the dog is not infected with borrelia. A positive result means that the dog has, at some point, been infected. Up to 95% of

dogs that have been infected never actually develop clinical signs as a result of their infection, and the clinical relevance of a positive test result can be difficult to interpret. Antibody titres can remain for years and the dog can be reinfected. High titres can therefore be determined by means of repeated testing over a long period of time. A detectable rise in titre has normally occurred by the time the clinical symptoms have actually started to manifest themselves.

The plausibility of the diagnosis is based upon the likelihood of tick exposure, the presence of clinical signs typical for Lyme borreliosis in dogs, the elimination of other differential diagnoses, combined with the detection of antigen or antibodies (4, 22, 23). The clinical assessment must always guide the interpretation of the test results.

TREATMENT

Approximately 95% of the dogs that are seropositive for borrelia never actually develop clinical signs and it is of the utmost importance to be confident that the diagnosis is correct before starting treatment.

Since it is very difficult to make a confident diagnosis, antibiotics have often been used as a diagnostic tool. In the case of Lyme borreliosis in dogs, there is often an improvement of the clinical signs within 24-48 hours following the first administration of antibiotics. Such a clinical improvement must, however, be interpreted with great care, as lameness due to borreliosis can be intermittent and often disappears within days or weeks, regardless of any antibiotic treatment. Doxycycline has also been shown to have anti-inflammatory and chondroprotective qualities in damaged joints in cases of non-infectious arthritis (4,24).

Currently there is insufficient available research on which to define the optimal treatment of dogs with symptomatic borreliosis. This is due to the existence of different strains of borrelia, diagnostic difficulties and difficulties with inducing the disease in experimentally infected dogs (23). The present treatment recommendations for dogs are often based upon the extrapolation of human medical results, and the treatment studies that have been done on dogs display varying results.

In the case of humans, the Medical Products Agency in Sweden recommends a course of treatment lasting 10-21 days, depending on the particular manifestations of the Lyme disease. Longer treatments have not been reported to have a better effect. Humans often suffer from persistent symptoms for more than three months after the infection has been treated. Why there should be a continuation of symptoms is not yet clear but it is known that repetitive treatment with antibiotics in arthritic conditions is fruitless. It is thought that infection in humans does not often manifest itself through clinical symptoms and is, to a large extent, self-limiting (25)

Reports in literature concerning the treatment of dogs with Lyme borreliosis mostly recommend a treatment with doxycycline or amoxicillin for a duration of three to four weeks (4, 17, 19, 23). Doxycycline is often named as the first-line treatment preference since the substance, with its high lipid solubility, has a good distribution within the different tissues (26). An additional reason as to why American authors advocate doxycycline as the first-line treatment option is because the substance is also active against a number of other North American tick-borne infectious agents, and co-infections do occur (23).

Amoxicillin is recommended to puppies if there is concern for enamel hypoplasia and tooth discolouration. The risk is, however, considered to be lower when using doxycycline compared with tetracycline (16, 17).

PROPHYLAXIS

As things stand today, there is no animal vaccine available against the borrelia species present in Sweden. Prophylaxis consists of the prevention of tick bites with the help of veterinary drugs where required, in conjunction with regular inspection of the animal's coat in order to remove any ticks before they have managed to transmit infection.

4) GENERAL CONSIDERATIONS REGARDING THE CHOICE OF ANTIBIOTICS

CHOICE OF ANTIBIOTIC

In order to make the best choice of antibiotic in a clinical situation where antibiotic treatment is required, a good knowledge of the relevant alternative substances is necessary. The choice is made based on, for example, the substance's pharmacokinetics, the risk of side effects, interaction, its activity against different types of micro-organisms, the occurrence of bacterial resistance with its various mechanisms and whether the antibacterial effect is bactericidal or bacteriostatic. Individuals with a depressed immune system should, whenever possible, be treated using bactericidal substances. Sometimes a substance's formulation can be the deciding factor as to which substance is actually prescribed.

Concerning the prescription of products to treat conditions for which they are not authorised, or where the product is not authorised for the animal species in question, such situations put high demands on the prescribing veterinarian and it is important that he/she has a good knowledge of the characteristics listed above.

The bacterial susceptibility. The bacterial susceptibility for different substances is measured in terms of the minimum inhibitory concentration (MIC) and is expressed in $\mu\text{g/mL}$ or mg/L . Higher concentrations than MIC are often required to have an effect *in vivo*, as the antimicrobial substances are bound in varying degrees to different tissue components, e.g. plasma proteins.

Antibiotic susceptibility testing. When choosing an antibiotic, the determination of the bacterial susceptibility is increasingly important to support the decision. Methods must be standardised and quality controls rigorous. An erroneous antimicrobial susceptibility test can give misleading results. As a rule, the susceptibility testing in routine diagnostics is carried out using dilution or diffusion methods. Regardless of the method employed, a selected substance is often used to represent a whole class of substances.

In order to facilitate interpretation, a system is utilised where the results are classed as susceptible (S) where MIC is less than a given value, or resistant (R) if the value is higher than a given limit value. An intermediary category (I) is also used for certain antibiotics. The criteria for interpretation have been formulated for standard antibiotic treatment, where the actual MIC value is related to the plasma concentration of the antimicrobial substance using a normal dose. If a bacterium is classified as resistant (i.e. belongs to the resistant category), it

generally means that treatment with any antibiotic out of the same class of antibiotics will not be successful. Very high concentrations at the site of infection can be achieved using local treatment; sometimes even bacteria that have been categorised as resistant can actually be sufficiently inhibited and a satisfactory therapeutic effect can be achieved. Sensitive bacteria should, in principle, be inhibited by treatment. The investigations are, of course, carried out in the laboratory using standardised conditions whereas the actual clinical outcome of a treatment can be affected by many other factors, e.g. at what point during the course of infection the treatment is started, the site of infection, the animal's own defences and so on. Bacteria that are classed as intermediary can be treatable if the infection is localised in an organ system where very high antibiotic concentrations can be achieved. Such is the case, for example, with ampicillin and the urinary tract.

Pharmacokinetics and dynamics. The pharmacokinetics describe the absorption, distribution, metabolism and excretion of the antibiotics within the body: this can vary between different species as well as on an individual level. In order to quantify the distribution of a substance in the body, the term volume of distribution is used and expressed in L/kg. If the volume of distribution is <0.5 L/kg it means that the substance probably is distributed within the extracellular space (where the majority of the pathogens actually reside). A large volume of distribution (>1 L/kg) means that the antimicrobial substance probably passes biological membranes and is well-distributed in the tissues. This often results in high intracellular concentrations. A large volume of distribution means that the total tissue concentrations are high, however, only the non-tissue bound concentration of the antibiotic is active on the micro-organisms. The free concentration in plasma is therefore the best marker of a substance's effect.

In the case of certain antibiotics, e.g. beta-lactams and macrolides, the time that the antibiotic concentration at the site of infection is greater than MIC is the factor determining the treatment's effect (*time-dependent antibiotics*). How high the concentration is in relation to MIC is of less importance; it matters only that it is higher. For other types of antibiotics such as fluoroquinolones and aminoglycosides, the cidal effect is dependent on the concentration of the antimicrobial substance: the higher the concentration the better the effect. These antibiotics are called *concentration-dependent antibiotics*.

By combining the substances' pharmacokinetics and pharmacodynamics the so-called PK/PD indices can be obtained. These indices describe the relation between the pharmacokinetics and dynamics that is of the most significance for the substance's effect. They are used when, for example, the dosage and dosing interval for a drug are being tried out. The PK/PD-indices are: $T > MIC$ (the duration that the antibiotic concentration is above the value of the MIC, time-dependent); C_{max}/MIC (the highest concentration (C_{max}) that is reached in relation to the MIC, concentration-dependent) and AUC/MIC (the area under the concentration-time curve/MIC ratio; concentration-dependent but also, to a certain extent, time-dependent).

Combination therapy. Antibiotics whose antimicrobial mechanisms work in different ways can, when administered simultaneously, have an increased effect, i.e. so-called synergism. Other combinations can have the opposite effect so that substances actually inhibit one another, in this case so-called antagonism. The interaction between different antibiotics can be very complex and consequently only well-tested combinations should be used.

Duration of treatment. The variables that determine the duration of treatment have not been defined. Clinical experience of how different types of infections respond to treatment is

important in order to ascertain the length of treatment that is required. Chronic infections, and especially intracellular infections, usually require a considerably longer course of treatment than acute infections. An old rule of thumb is that the treatment of acute uncomplicated infections should continue for an extra two days from the point in time when the patient is symptom-free.

INFORMATION TO ANIMAL OWNERS

Antibacterial drugs have a central position in patient care, regardless of whether the treatment is aimed at animals or humans. Antibacterial agents both relieve and cure but can also give rise to problems. The prescriber/veterinarian must take a number of factors into account when choosing the form of treatment. These factors even include as to whether the illness in question actually requires that an antibacterial agent be prescribed. For a number of conditions, it is preferable to choose a completely different course of treatment so that the patient can avoid treatment with an antibacterial substance. There is much to achieve by avoiding the use of an antibacterial substance: on the one hand, the risk of bacterial resistance against the antibiotic is kept to a minimum and, on the other hand, the patient avoids the possible side effects that a course of antibiotics can induce in the form of gastrointestinal disturbances.

Is it absolutely necessary to prescribe an antibacterial agent in order to treat this patient? The question must always be asked. On numerous occasions the answer can be “let’s wait” and the animal’s owner can, for example, be advised to measure the body temperature daily, in order to ascertain whether the infection has actually taken hold. In other cases, treatment with an antibacterial substance is indicated but the period of treatment can be made shorter.

When a condition requires treatment with an antibacterial agent the result can, despite everything, be unsatisfactory or even negligible if the animal’s owner has not understood why the treatment has been prescribed and/or how the drug in question should be administered. In some cases, antibacterial drugs give a fast relief of clinical signs whereby the animal’s owner can be tempted to discontinue the treatment. This is not advantageous since a course of treatment that is terminated too early can result in relapse.

For a course of treatment to be successful, it is important that the animal’s owner can actually manage (for practical reasons) to administer the drug to the animal. Even if oral drugs are the most suitable form of administration, the owner can experience difficulties with this method, especially when administering an oral formulation to a cat. If the owner does not have previous experience of administering medicine to its animal, it is advisable to demonstrate the procedure. In cases where the owner has, on a previous occasion, had difficulties to administer medication to the animal, it is even more important that practical advice is given together with the prescription. It is also advisable to make an attempt to try and solve the owner’s specific problems concerning the administration of the medication.

When the animal’s owner can not give the medication directly in the form of tablets, capsules or liquid orally, an attempt can be made to mix it into some of the animal’s feed and/or a small morsel of food. Paste formulation can, in the right context, constitute an advantage. To avoid that the animal does not selectively omit eating the medication, the tablet can sometimes be crushed. Not all tablets lend themselves to being crushed, e.g. depot tablets, and this is important information to be aware of in conjunction with the prescription. Information concerning the above can be found in FASS and FASS VET. Alternatively, advice can be

sought from a pharmacy or the drug manufacturer. One should also be aware of whether the formulation should be taken together with food or not.

To wash one's hands after administering the medication should be self-explanatory.

Information concerning the possibility of side effects should be taken up in connection with the prescription of all antibacterial agents.

THE HANDLING OF MEDICINES

STORAGE RECOMMENDATIONS AND EXPIRY DATE

All drugs should be stored in such a manner that unauthorised individuals, including children and animals, can not come into contact with the product.

Medications should also be suitably stored so that the product's quality is not compromised in any way. A number of factors can negatively affect the quality if storage occurs under unsuitable conditions. Examples of factors that can affect the quality are heat and sunlight. So as not to compromise the medicine's quality, the manufacturers storage recommendations should always be followed. Medicines, whose date of expiry has expired, should naturally not be used.

The practical handling of medicines should be carried out in such a way that confusion cannot occur. Furthermore, medications should be stored in their original packaging, i.e. the medication should not be transferred or poured over into other packaging. The practical handling of medication also includes the hygienic aspect. By this we mean, for example, that the membrane on the injection bottles are wiped with alcohol preceding needle penetration; and even that personal hand hygiene is good with reference to all handling of medication regardless of the dosage form.

PHARMACEUTICAL WASTE

Pharmacies in Sweden collect pharmaceutical waste from the general public as a social service. The animal owner can, therefore, leave any pharmaceutical waste at the pharmacy. The pharmacy is, on the other hand, not required to collect pharmaceutical waste from traders of any form, a category of customers that includes also practising veterinarians. In this context, the veterinarian is considered a tradesman and, alongside animal owners with extensive operations, they are responsible for the disposal of their pharmaceutical waste. Pharmacies sell a special disposable waste box suitable for the medicines used by traders. Also cannulae and scalpels used in veterinary practice can be put into puncture proof containers which are then placed into the disposable waste box. This waste box can then be deposited at any pharmacy. The price of the disposable waste box includes handling, transport and combustion.

What role the pharmacy will continue to play with regards to pharmaceutical waste disposal following the planned re-regulation of the pharmacy market in 2009 is, at the time of writing unclear.

The municipality's environmental and health-protection administration can give advice as to local regulations governing pharmaceutical waste from traders. The environmental and health-protection administration can also give out information concerning the suitable transport of pharmaceutical waste.

5) AVAILABLE ANTIBIOTICS

BETA-LACTAM ANTIBIOTICS

Beta-lactam antibiotics is a large and important class of antibiotics with a bactericidal effect. A common denominator for the group is that the structure contains a so-called beta-lactam ring that is important for both the antimicrobial activity and for triggering potential allergic reactions. The beta-lactam class contains the penicillins, the cephalosporins and the cefamycins.

BETA-LACTAM ANTIBIOTICS – PENICILLINS

The penicillins are derived from 6-aminopenicillenic acid and differ from one another with respect to their side chain. The type of side chain is crucial for the molecule's antibacterial activity and spectrum as well as for how sensitive the substance is for bacterial beta-lactamases (enzymes which break down the beta-lactam ring).

Mechanism of action. Beta-lactam antibiotics act by binding to special proteins in the bacterial cell wall and, by doing this, they inhibit cell wall synthesis. The bactericidal effect is due to the inhibition of bacterial autolysis.

Mechanisms of resistance. Production of *beta-lactamases* is the most common mechanism of resistance against beta-lactam antibiotics both in both Gram-positive and in Gram-negative bacteria. The resistance property is usually transferable. The most common type of beta-lactamase, penicillinase, is commonly detected in *Staphylococcus pseudintermedius* in Sweden as well as in other countries. Isoxazolyl penicillins can withstand the effect of penicillinases. Beta-lactamase inhibitors such as clavulanic acid (see below) effectively inhibit many beta-lactamases from both Gram-positive and Gram-negative bacteria.

Meticillin resistance in staphylococci arises when the protein that the beta-lactams bind to is modified. This mechanism gives rise to cross-resistance against all the beta-lactam antibiotics (also cephalosporins and cefamycins). In Sweden, the prevalence of meticillin resistant *S. pseudintermedius* (MRSP) in dogs is increasing. Meticillin resistant *S. aureus* (MRSA) has also been recorded from dogs and cats. Infection with meticillin resistant coagulase-positive staphylococci in animals is notifiable in Sweden.

Resistance against penicillins in beta-haemolytic streptococci has yet never been reported.

Pharmacokinetics and dynamics. The volume of distribution is small, most often less than 0.3 L/kg. Passage over biological membranes is limited due to the high-degree of ionisation at physiological pH, so the substances mostly distribute themselves within the extracellular space. The half-life is often short and the majority of beta-lactams are excreted into the urine in their active form (with the exception of nafcillin).

The antibacterial effect is, above all, correlated to how long the concentration is greater than MIC (time-dependent).

AMPICILLIN/AMOXICILLIN (AMINOPENICILLINS)

Ampicillin (QJ01C A01) and amoxicillin (QJ01C A04) are semi-synthetic penicillins with an expanded antibacterial spectrum. Amoxicillin and ampicillin have the same antibacterial spectrum and activity against susceptible bacteria (for more information see the section “Beta-lactam antibiotics combined with beta-lactam inhibitors”).

ACTIVITY AND RESISTANCE

- **Good activity** (MIC \leq 1 $\mu\text{g/mL}$) against many Gram-positive and the majority of anaerobic bacteria as well as Gram-negative rods such as *Pasteurella* spp., *Moraxella* sp. and *Bordetella* sp.
- **Moderate activity** (MIC 2-8 $\mu\text{g/mL}$) against *E.coli* and *Proteus mirabilis*.
- **Unsatisfactory activity** (MIC $>$ 8 $\mu\text{g/mL}$) against *Klebsiella* sp., other *Proteus* spp. but not including *P.mirabilis* and *Pseudomonas* spp.

Acquired resistance in by production of beta-lactamases is very commonly detected in staphylococci found in dogs from Sweden, is common: in, for example, *E. coli* and probably also occurs in *Bordetella* sp. Meticillin resistant *S. pseudintermedius* (MRSP) are increasingly occurring.

Widespread resistance against ampicillin in bacteria such as *E.coli*, *Bordetella* sp. and Gram-negative anaerobic bacteria isolated from dogs has been reported in many countries. Resistance against *Pasteurella* sp. has also been reported.

PHARMACOKINETICS AND DYNAMICS

The half-life is short in dogs and cats. Half-lives between 45-80 minutes are reported in literature on the subject. A maximum serum concentration (6-8 $\mu\text{g/ml}$) for amoxicillin is arrived at after approximately two hours with an oral dose of 10 mg/kg.

The volume of distribution is small (0.2-0.3 L/kg). The substance spreads out into the extracellular space but passage over biological membranes is limited due to a high degree of ionisation at physiological pH.

The bioavailability after oral administration is better for amoxicillin (60-90%) than for ampicillin (20-40%). This means that the plasma concentrations (after oral administration) for amoxicillin are two to three times higher than for the corresponding dose of ampicillin. The amount of amoxicillin that is absorbed is not affected by the intake of food.

The substances are principally eliminated in their active form via the kidneys by means of filtration and tubular secretion. This means that, in relation to the plasma concentrations, very high urine concentrations are reached.

The plasma protein binding is low. For amoxicillin, it is 13-20% in dogs.

The effect of ampicillin is bactericidal and correlates to the duration of time that the concentration is greater than MIC (time-dependent).

COMMENT

Local reactions can arise following the subcutaneous administration of amoxicillin. A number of reports concerning these side effects (swelling and even necrosis) have been made to the Medical Products Agency

BENSYPENICILLIN

Bensylpenicillin (QJ01C E01) is a derivative of 6-amino penicillanic acid and is intended for parenteral use. Only bensylpenicillin procaine (QJ01C E09) is authorised for use in dogs and cats.

ACTIVITY AND RESISTANCE

- **Good activity** ($MIC \leq 0.25 \mu\text{g/mL}$) against Gram-positive cocci (streptococci), rods and anaerobic bacteria.
- **Less, yet still good activity** against small Gram-negative rods such as *Pasteurella* sp and *Moraxella* sp. ($MIC \leq 1 \mu\text{g/mL}$).
- **Unsatisfactory activity** ($MIC > 8\mu\text{g/mL}$) against, for example, *Enterobacteriaceae* and *Bordetella* sp.

Acquired resistance in the form of beta-lactamase production is common in *S. pseudintermedius* in dogs in Sweden.

Meticillin resistant *S. pseudintermedius* (MRSP) are increasingly occurring.

Resistance in Gram-negative anaerobic bacteria and *Pasteurella* sp. has been reported in other countries.

PHARMACOKINETICS AND DYNAMICS

Bensylpenicillin is available in injectable formulations either as readily-soluble bensylpenicillin sodium with a short half-life (approximately 40 mins) or as bensylpenicillin procaine. Bensylpenicillin and procaine together form a sparingly soluble salt. Following an intramuscular injection with bensylpenicillin procaine, the bensylpenicillin is released slowly from the procaine and is absorbed thereafter into the blood. This means that the half-life and consequently the duration are extended considerably compared with an injection with readily-soluble bensylpenicillin sodium.

The volume of distribution is small (0.2-0.3 L/kg). The substance is distributed into the extracellular space and passage over biological membranes is limited due to a high degree of ionisation at physiological pH.

Bensylpenicillin is principally eliminated in its active form via the kidneys by means of filtration and tubular secretion. This means that very high urine concentrations, in relation to the plasma concentration, are reached.

The plasma protein binding is about 45%.

The effect of bensylpenicillin is bactericidal and correlates to the duration in which the concentration exceeds that of MIC (time-dependent).

COMMENT

Penicillin procaine should not be administered at the same time as sulphonamides. Procaine can impede the effect of sulphonamides due to fact that procaine is converted into PABA (a sulfa antagonist).

FENOXYMETHYLPENICILLIN

Fenoxymethylpenicillin (J01C E02) is an acid-stable derivative of 6-amino penicillanic acid intended for oral use. The substance is, for the present (October 09), not authorised in Sweden for use in dogs and cats.

ACTIVITY AND RESISTANCE

See the section concerning bensylpenicillin

PHARMACOKINETICS AND DYNAMICS

The half-life in plasma is about 40 minutes. With a dose of 66 mg/kg given orally to a dog, the maximum plasma concentration (approximately 18 µg/mL) is reached after about one hour.

Distribution and excretion – see the section on bensylpenicillin.

The bioavailability and rate of absorption is reduced when food is ingested simultaneously. The bioavailability in humans is between 60-70%.

The plasma protein binding is approximately 60%.

The effect of fenoxymethylpenicillin is bactericidal and correlates to the duration of time that the concentration exceeds that of MIC (time-dependent).

ISOXAZOLYL PENICILLINS

Isoxazolyl penicillins, or penicillinase-stable penicillins, are semi-synthetic derivatives of penicillin where the side chains protect the beta-lactam ring from degradation by penicillinase.

At the time of writing, there are no substances of this class authorised for use in dogs and cats. In human medicine, cloxacillin (J01C F02), dicloxacillin (J01C F01) and flucloxacillin (J01CF05) are used..

ACTIVITY AND RESISTANCE

- **Good activity** ($MIC \leq 1\mu\text{g/mL}$) against streptococci and staphylococci, even if they are penicillinase-producing.
- **Unsatisfactory activity** ($MIC > 2\mu\text{g/mL}$) against Gram-negative rods (including *Pasteurella* spp.) and anaerobic bacteria.

Meticillin resistant *S. pseudintermedius* (MRSP) are increasingly occurring.

PHARMACOKINETICS AND DYNAMICS

The half-life for dicloxacillin in dogs is about 30 minutes. The distribution is similar to the other penicillins (see above). The bioavailability is low (about 20%) and is reduced by the simultaneous intake of food.

The degree of plasma protein binding is high.

The substance is excreted in its active form via the urine.

The effect of isoxazolyl penicillins is bactericidal and correlates to the duration of time that the concentration exceeds that of MIC (time-dependent).

COMMENT

Isoxazolyl penicillins have a narrower spectrum than penicillin, and the only indication is an infection that is caused by penicillinase-resistant staphylococci. The risk of an effect on the remaining normal bacterial flora is therefore minimal. The conditions that are discussed in literature are staphylococcal infections in the skin, joints and skeleton.

BETA-LACTAM ANTIBIOTICS COMBINED WITH BETA-LACTAM INHIBITORS

AMOXICILLIN/CLAVULANIC ACID

Amoxicillin has been described earlier (see the section on “Beta-Lactam Antibiotics – Penicillins”). Clavulanic acid has a very low antibacterial activity but contains a beta-lactam ring that inhibits the bacterial beta-lactamase enzyme by binding to it. The binding is either irreversible or the complex dissociates slowly. As the beta-lactamases are inhibited by clavulanic acid, the amoxicillin remains active.

Amoxicillin in combination with clavulanic acid (QJ01C R02) are available for both oral and parenteral use.

ACTIVITY AND RESISTANCE

For non-beta-lactamase producing bacteria, the spectrum is identical to that of amoxicillin.

- **Good activity** (MIC ≤ 1 $\mu\text{g/mL}$, for amoxicillin) against Gram-negative rods (such as *Pasteurella* sp., *Moraxella* sp. and *Bordetella* spp.), many Gram-positive bacteria, beta-lactamase producing staphylococci and the majority of anaerobic bacteria.
- **Moderate activity** (2-8 $\mu\text{g/mL}$) against *E. coli* *Klebsiella pneumoniae* and *Proteus mirabilis*.
- **Unsatisfactory activity** (MIC > 8 $\mu\text{g/mL}$, for amoxicillin): Beta-lactamases from other *Proteus* spp. and *Enterobacter* sp. and *Pseudomonas* sp. are insensitive to clavulanic acid and the resulting activity is therefore inadequate.

Meticillin resistant *S. pseudintermedius* (MRSP) are increasingly occurring.

Resistance in Gram-negative bacteria can occur as a result of a greatly increased production of beta-lactamase. The formation of beta-lactamases to which clavulanic acid cannot bind also occurs.

PHARMACOKINETICS AND DYNAMICS

The pharmacokinetics for amoxicillin are described in the section “ampicillin / amoxicillin”.

Clavulanic acid is relatively stable in an acidic pH and is absorbed quickly following oral administration. In dogs, the maximum serum concentration (1.5 $\mu\text{g/mL}$) is reached within one hour and in cats (3 $\mu\text{g/mL}$) within half an hour, with a dose of 2.5 mg/kg.

After subcutaneous injection, the maximum serum concentration (2.4 µg/mL) in dogs is reached within one hour, with a dose of 1.75 mg/kg.

The volume of distribution in dogs is 0.3 L/kg, and clavulanic acid displays similar distribution patterns to amoxicillin.

Clavulanic acid is metabolised in dogs; it is thought, however, that the concentration of the active substance is high in the urine, but considerably lower than its partner, amoxicillin.

The plasma protein binding in dogs is 13-19%.

The effect of amoxicillin correlates to the duration of time that its concentration is greater than MIC (time-dependent).

COMMENT

In order to minimise the risk of resistance development, any use of the combination with clavulanic acid should be limited to situations where an infection with beta-lactamase bacteria has been confirmed, e.g. urinary tract infections caused by beta-lactamase-producing staphylococci. The combination probably favours the occurrence of meticillin resistant staphylococci.

BETA-LACTAM ANTIBIOTICS – CEPHALOSPORINS AND CEFAMYCINS

Mechanism of action. Beta-lactam antibiotics act by binding to a special protein in the bacterial cell wall and consequently inhibit cell wall synthesis. The beta-lactam ring in the different cephalosporins (products from *Cephalosporium acremonium*) and cefamycins (products from the *Streptomyces* spp.) is, by its chemical configuration, protective against certain beta-lactamases, for example, penicillinase.

Classification. The different cephalosporins differ considerably from one another with regards to their spectrum of activity. Cephalosporins are often divided up into groups, so-called generations, that essentially reflect the differences in their spectrums of activity.

- *First* generation cephalosporins (cephalexin, cephadroxil, cephalotin) have the narrowest spectrum of activity. Their activity is good against Gram-positive cocci, including penicillinase-producing staphylococci but their activity against Gram-negative bacteria is more limited.
- *Second* generation cephalosporins (cefachlor, cefoxitin³ and cefuroxime usually have a better activity against Gram-negative bacteria than first generation substances. They are resistant against the effect of some beta-lactamases that are formed by Gram-negative bacteria.
- *Third* generation cephalosporins (ceftiofur, cefovecin, cefotaxime, ceftazidim and latamoxef⁴) have good activity against many Gram-negative bacteria since they are resistant against the effect of the beta-lactamases that inactivate the first and second generation cephalosporins.

³ Correctly speaking, this substance is a cefamycin.

⁴ Correctly speaking, this substance is a cefamycin.

- *Fourth* generation cephalosporins (cefepim, cefpirom and cefquinome) are resistant against the effect of several of the beta-lactamases that can break down the third generation cephalosporins.

Mechanisms of resistance.

Meticillin resistant *S. pseudintermedius* (MRSP) are increasingly occurring. Resistance against cephalosporins in Gram-negative bacteria occurs when there is beta-lactamase production with an affinity for the different cephalosporins (cephalosporinases). There are several hundred different beta-lactamases with effect against cephalosporins and this antibiotic group is usually divided up into different generations according to how “broad a spectrum” they have: i.e. whether they are only active against first and second generation cephalosporins or whether they also break down the preparations that constitute the later generations of cephalosporins. Some of these beta-lactamase enzymes are inhibited by clavulanic acid whereas others are not.

Resistance in *E. coli* and other *Enterobacteriaceae* against the third generation cephalosporins by means of enzyme production e.g. “extended spectrum beta-lactamase” (ESBL) or AmpC, conveys cross-resistance against, for example, cefotaxime, ceftazidim and other closely related cephalosporins. These cephalosporins are used in Sweden to treat humans in critical medical situations. Findings of ESBL producing bacteria in humans is notifiable in accordance with the Disease Control Act.

Pharmacokinetics and dynamics. The volume of distribution is small, often less than 0.3 L/kg. Passage over biological membranes is limited due to a high degree of ionisation at physiological pH and the substances then distribute themselves within the extracellular space. The half-life is often short and the majority of cephalosporins are excreted into the urine in their active form (with the exception of some substances, that have a high molecular weight and high degree of protein binding, that are excreted via the bile). A few cephalosporins intended for oral administration are prodrugs, which means that it is in fact the metabolites that are the active substance.

The antibacterial effect correlates principally with the duration of time that the concentration exceeds that of MIC (time-dependent).

CEPHALEXIN

Cephalexin (QJ01D A01) is an antibiotic from the cephalosporin family intended for oral use (first generation).

ACTIVITY AND RESISTANCE

- **Good activity** (MIC \leq 2 $\mu\text{g/mL}$) against Gram-positive bacteria such as streptococci and staphylococci (even beta-lactamase producing) as well as the majority of anaerobic bacteria.
- **Moderate activity** (MIC 4-16 $\mu\text{g/mL}$) against Gram-negative rods such as *E. coli*, *Klebsiella* sp., *Proteus mirabilis* and *Pasteurella* sp.
- **Unsatisfactory activity** (MIC $>$ 16 $\mu\text{g/mL}$) against, amongst others, enterococci, *Pseudomonas* sp., *Enterobacter* sp. and indole-positive strains of *Proteus* sp.

With regards to resistance, see the introductory section found under “Cephalosporins and Cefamycines”.

PHARMACOKINETICS AND DYNAMICS

The half-life for cephalexin is two to four hours in dogs and one to two hours in cats. The maximum concentration in serum (26-34 µg/mL) after an oral dose of 25 mg/kg body weight is reached within one to two hours in dogs.

The substance is distributed into the extracellular space and passage over biological membranes is limited due to a high degree of ionisation at physiological pH.

Cephalexin is stable under acidic conditions. The bioavailability is about 75% in both dogs and cats.

Excretion occurs principally via the kidneys in the non-metabolised form.

The degree of plasma protein binding is low.

The effect of cephalosporins correlates to the duration of time that the concentration exceeds that of MIC (time-dependent).

CEPHADROXIL

Cephadroxil (J01D A09) is an antibiotic from the cephalosporin family intended for oral administration (first generation). Cephadroxil is, at the time of writing (January 2009) not available for veterinary use in Sweden.

ACTIVITY AND RESISTANCE

See the section discussing “Cephalexin” for information on the activity and the introductory section under “Cephalosporins and Cefamycins” for information on the resistance.

PHARMACOKINETICS AND DYNAMICS

The half-life for cephadroxil in serum is approximately two hours in dogs and about three hours in cats. The maximum concentration in serum (about 28 µg/mL after a single dose of 40 mg/kg body weight per os) in dogs and cats is reached one to two hours after intake.

Cephadroxil is stable under acidic conditions. Its distribution is similar to that found with other beta-lactam antibiotics. The substance is distributed into the extracellular space in the majority of tissues but any transport over biological membranes is limited.

More than 50% of the orally-administered dose is excreted in its unchanged form via the urine by means of glomerular filtration and tubular secretion within 24 hours.

The degree of plasma binding is 20% in dogs.

The effect of the cephalosporins correlates to the duration of time that the concentration exceeds that of MIC (time-dependent).

CEPHALOTIN

Cephalotin (J01D A03) is an antibiotic from the cephalosporin family intended for parenteral use (first generation). Cephalotin is, at the time of writing, not authorised for human medical or veterinary medical use in Sweden. It is, however, the substance that is used as the group representative for cephalosporins when it comes to bacterial resistance determination.

ACTIVITY AND RESISTANCE

See the section on “Cephalexin” for information on the activity and the introductory section under “Cephalosporins and Cefamycins” for information on resistance.

PHARMACOKINETICS AND DYNAMICS

The pharmacokinetics are similar to the pharmacokinetics in other beta-lactam antibiotics. The substance is distributed into the extracellular space in the majority of tissues but any transport over biological membranes is limited. There is a lack of specific information concerning the pharmacokinetics and dynamics in dogs and cats.

The effect of cephalosporins correlates to the duration of time that its concentration exceeds that of MIC (time-dependent).

COMMENT

Cephalotin is a substance that has been recommended for preoperative prophylactic treatment.

CEFOVECIN

Cefovecin (QJ01D A90) is an antibiotic from the cephalosporin family and is intended for parenteral use (third generation).

ACTIVITY AND RESISTANCE

- **Good activity** ($\leq 1 \mu\text{g/mL}$) against *Enterobacteriaceae* e.g. *E. coli* and *Proteus* spp. as well as *Pasteurella* sp., streptococci and anaerobic bacteria. The activity against staphylococci (even beta-lactamase producing) is somewhat lower.
- **Unsatisfactory activity** ($\text{MIC} \geq 8 \mu\text{g/mL}$) against *Pseudomonas* sp. and enterococci.

For information on resistance, see the introductory section under “Cephalosporins and Cefamycins”.

PHARMACOKINETICS AND DYNAMICS

Cefovecin differs from the other cephalosporins by its higher degree of plasma protein binding and long duration of effect. Cefovecin has an extremely long elimination half-life (about 5.5 days in dogs and about 6.9 days in cats). The substance is not absorbed after oral administration so it must be administered parenterally. The volume of distribution is low (0.1 L/kg) and the substance is eliminated in its unchanged form primarily via the kidneys.

The degree of plasma protein binding is high (96-98.7% in dogs and 99% in cats).

The effect of the cephalosporins is bactericidal and correlates to the duration of time that their concentration is greater than MIC (time-dependent).

COMMENT

Third generation cephalosporins should only be used to treat infections where there are no other suitable options, e.g. due to bacterial resistance against other antibiotics. Cefovecin's

very long half-life means that treatment cannot be terminated should side effects arise or if new information, e.g. the result of the culture and the determination of bacterial resistance, becomes available. Cefovecin should therefore be reserved for cases where treatment is of the utmost importance for animal welfare, and where the conditions for administration of medications in the animal's home are very unsatisfactory.

CEFTIOFUR

Ceftiofur (QJ01D A90) is an antibiotic from the cephalosporin family intended for parenteral use (third generation). Ceftiofur is not authorised in Sweden for use in dogs or cats.

ACTIVITY AND RESISTANCE

See the section on "Cefovecin" for information on activity and the introductory section under "Cephalosporins and Cefamycins" for information on resistance.

PHARMACOKINETICS AND DYNAMICS

Ceftiofur is not absorbed following oral administration but must be administered parenterally. Its distribution does not differ from the other beta-lactam antibiotics. The substance is distributed into the extracellular space in the majority of tissues but transport over the biological membranes is deficient. Ceftiofur is metabolised by plasma esterases into its active metabolite. Both the parent compound and the metabolite have a high degree of plasma protein binding. There is a lack of specific information concerning the pharmacokinetics and dynamics in dogs and cats.

The effect of the cephalosporins correlates with the duration of time that their concentration is greater than the value of MIC (time-dependent).

COMMENT

As is mentioned in the above text, ceftiofur is not authorised for use in dogs and cats. The substance is, however, the only short-acting cephalosporin from the third generation that is authorised for use in other animals in Sweden. The third generation cephalosporins should only be used to treat infections where other antibiotics cannot be used, e.g. because of bacterial resistance against other substances or in some cases where there is a life-threatening condition. In the latter case, the choice of antibiotic should be re-evaluated as soon as more information becomes available, e.g. if there is a clear improvement of the clinical condition, a more certain diagnosis or the result of the determination of bacterial susceptibility is available.

AMINOGLYCOSIDES

Mechanism of action. Aminoglycosides bind to the 30S subunit of the bacterial ribosome and thereby inhibit protein synthesis.

Activity. Many aerobic Gram-negative and some Gram-positive bacteria are, under normal conditions, susceptible to aminoglycosides. Anaerobic bacteria are insensitive to aminoglycosides, as oxygen is needed in order to transport the aminoglycoside into the bacterial cell. The activity against other bacteria is also reduced under anaerobic conditions. They are also highly affected by the pH and have highest activity in a slightly alkaline environment. The combination of aminoglycosides and beta-lactam antibiotics is synergistic.

Mechanisms of resistance. Acquired resistance is most often due to the production of plasmid-mediated enzymes that inactivate the aminoglycosides. A large number of such

enzymes have been described and their sites of activity vary. Some of these enzymes can only work with a specific aminoglycoside acting as the substrate and, in these cases, cross-resistance against other aminoglycosides does not occur. Other enzymes are less specific whereupon different patterns of cross-resistance can be encountered.

Pharmacokinetics and dynamics. For systemic use, there are only parenteral formulations as aminoglycosides are not normally absorbed from the gastrointestinal tract. The bioavailability following intramuscular or subcutaneous administration is more than 90%. Aminoglycosides distribute themselves within the extracellular space but accumulate in the renal tissue and in the inner ear where they can exert toxic effects. The volume of distribution for dogs and cats is 0.15-0.3 L/kg. The degree of plasma protein binding is low at less than 20%.

The antimicrobial effect is bactericidal and correlates best with the relationship between the maximum plasma concentration and the MIC-value (concentration-dependent).

Side effects. The toxic effects of aminoglycosides on the kidneys and inner ear means that their systemic use should be limited to the treatment of serious infections with Gram-negative bacteria, e.g. if other less toxic antibiotics are no longer effective and where the clinical situation requires immediate treatment. By only administering aminoglycosides once a day, the risks of renal injury are reduced yet the antimicrobial effect is maintained.

GENTAMICIN

Gentamicin (QJ01G B03, QD06A X07, QSC2C A90) is an aminoglycoside that is available for parenteral and local administration (ears).

ACTIVITY AND RESISTANCE

- **Good activity** ($MIC \leq 4 \mu\text{g/mL}$) against aerobic Gram-negative rods and staphylococci. Also activity against *Pseudomonas* sp. The activity is, however, severely reduced under anaerobic conditions.
- **Unsatisfactory activity** ($MIC > 4 \mu\text{g/mL}$) against streptococci and numerous other Gram-positive bacteria as well as anaerobic bacteria.

Resistance against gentamicin in Gram-negative bacteria, with the exception of *Pseudomonas* spp. from dogs and cats, is most probably still unusual in Sweden. Reports from other countries indicate that gentamicin resistance can be a problem within animal hospital settings.

PHARMACOKINETICS AND DYNAMICS

See above.

In the event of normal renal function, gentamicin has a half-life in serum of about two to three hours. The half-life is increased in the case of reduced renal function.

Gentamicin is not metabolised. Excretion is via the kidneys by means of glomerular filtration and very high concentrations (over 100 $\mu\text{g/mL}$) of active gentamicin is reached in the urine. Any excretion via the bile is insignificant.

The degree of plasma protein binding is low.

The antimicrobial effect correlates best with the relationship between the maximum plasma concentration and the MIC-value (concentration-dependent).

COMMENT

See above. Renal injuries as well as damage to the hearing and balance. By only administering aminoglycosides once day, the risk of renal injury is reduced yet the antimicrobial effect is maintained.

Chloramphenicol blocks the mechanism responsible for the transport of gentamicin into the bacterial cell and therefore acts antagonistically.

DIHYDROSTREPTOMYCIN

Dihydrostreptomycin (DHS) is an aminoglycoside intended for oral administration (QA07A A90) and for the local treatment of gastrointestinal conditions. In combination with different penicillins (QJ01R A01, QJ51R C24, QJ51R C23) it can be prescribed for both parenteral and local use.

ACTIVITY AND RESISTANCE

- **Good activity** ($MIC \leq 8 \mu\text{g/mL}$) against aerobic Gram-negative rods and staphylococci. The activity is, however, much less under anaerobic conditions.
- **Unsatisfactory activity** ($MIC > 8 \mu\text{g/mL}$) against *Pseudomonas* sp. and streptococci as well as many other Gram-positive bacteria. Anaerobic bacteria are insensitive.

Resistance against dihydrostreptomycin is widespread in Gram-negative bacteria (for example, *E. coli*) from dogs and cats in Sweden. Resistance is also fairly common in *S. pseudintermedius*.

PHARMACOKINETICS AND DYNAMICS

Dihydrostreptomycin cannot cross biological membranes and is not normally absorbed from the gastrointestinal tract, intact skin or mucosal linings.

There is a lack of specific information concerning the pharmacokinetics and dynamics in dogs and cats.

The antimicrobial effect is bactericidal and best correlates to the relationship between the maximum plasma concentration and the MIC value (concentration-dependent).

COMMENT

In the event of parenteral administration, the risks of injury to the hearing and balance must be taken into consideration (see above).

Oral administration of dihydrostreptomycin has been used to treat diarrhoea conditions in cats and dogs. Modern standard textbooks on the subject do not discuss this particular type of treatment as an option (for more information see the section on the “Gastrointestinal Tract”).

The combination of dihydrostreptomycin and penicillin has been reported to have a synergistic effect against bacteria that are susceptible or moderately susceptible to the two substances. It is doubtful as to whether this is the case in *in vivo* situations.

NEOMYCIN (FRAMYCETIN)

Neomycin (QD07C C01, QS01A A20, QS02C A01) is an aminoglycoside intended for local use (it is used in combination preparations). The name framycetin is synonymous with neomycin B.

ACTIVITY AND RESISTANCE

- **Good activity** ($MIC \leq 8 \mu\text{g/mL}$) against aerobic Gram-negative rods and staphylococci. Moderate activity against *Pseudomonas* sp. The activity is greatly reduced under anaerobic conditions.
- **Unsatisfactory activity** ($MIC \geq 8 \mu\text{g/mL}$) against streptococci and many other Gram-positive bacteria. Anaerobic bacteria are insensitive.

Resistance is uncommon in *E. coli* from dogs and cats in Sweden.

PHARMACOKINETICS AND DYNAMICS

See the above information on dihydrostreptoycin.

COMMENT

The preparation should not be used in the ears if the eardrum is perforated, as the effect is ototoxic.

MACROLIDES AND LINCOSAMIDES

Mechanism of action. Macrolides and lincosamides are structurally unrelated classes of antibiotics yet they have many characteristics in common. These antibiotics exert their effect by inhibiting bacterial protein synthesis by binding to the ribosomes (the 50S subunit).

Activity. The activity is generally good against many aerobic Gram-positive and anaerobic bacteria and also against chlamydiae and mycoplasma. The activity is insufficient against the majority of Gram-negative bacteria.

Mechanisms of resistance. Resistance depends often upon an alteration of the target structure and can either be caused by chromosomal mutations or by the transferable antibiotic resistance genes. Transferable antibiotic resistance is the most common mechanism, generally as so-called macrolide-lincosamide-streptogramin resistance (MLS_B -type) where cross-resistance occurs between the three classes. In in vitro antimicrobial susceptibility tests, bacteria carrying such resistance genes may be resistant against the majority of macrolides and lincosamides or only resistant against erythromycin. In the latter case, high-level resistance against all the macrolides and lincosamides can develop by means of one or two mutations.

Tylosin/spiramycin and lincosamides should consequently be avoided for the treatment of infections that are caused by bacteria classified as erythromycin-resistant.

The occurrence of resistance in against erythromycin in staphylococci isolated from dogs in Sweden increased greatly during the 1990s and such resistance is today common. Resistance against both macrolides and lincosamides has also increased and is today relatively common (>15%).

Pharmacokinetics and dynamics. Macrolides and lincosamides can easily cross biological membranes as they are lipophilic substances, weak bases and consequently to a large extent

un-ionised at physiological pH. The volume of distribution is therefore relatively large. This often leads to high intracellular concentrations. Any passage to the CNS is, however, insignificant in the event of intact meninges.

The effect is bacteriostatic in therapeutic concentrations but is thought to be bactericidal at high concentrations; this correlates directly with the duration of time that the concentration exceeds that of MIC (time-dependent).

ERYTHROMYCIN

Erythromycin (J01F A01) is a macrolide antibiotic that, at the time of writing, is not authorised for use on animals in Sweden.

ACTIVITY AND RESISTANCE

The spectrum of activity is similar that of tylosin (see the description below). The activity against normal bacteria such as staphylococci and streptococci is however higher (MIC < 0,5 µg/mL) than for tylosin. Resistance is commonly found in Gram-positive cocci from dogs, for more information, refer to the information above.

PHARMACOKINETICS AND DYNAMICS

The half-life is 60-90 minutes in dogs and cats. The volume of distribution is approximately 2 L/kg in dogs. The substance passes easily over biological membranes but transport to the central nervous system is only thought to be slight. Absorption following oral administration varies, partly dependent on the dosage form and partly dependent on the pH, the presence of food in the stomach and the stomach-emptying rate.

Erythromycin is excreted in its active form via the bile but is also metabolised in the liver. The excretion of active erythromycin into the urine is only 2-5% of the administered dose.

The degree of plasma protein binding is about 70-80%.

The effect is bacteriostatic in therapeutic concentrations but is thought to be bactericidal at high concentrations and correlates with the duration of time that its concentration exceeds that of MIC (time-dependent).

COMMENT

Following oral administration, abdominal pains, vomiting and diarrhoea are common side effects.

Erythromycin has been used in Sweden to treat pyoderma (*S. pseudintermedius*) in dogs.

TYLOSIN

Tylosin (QJ01F A90) is a macrolide that has been authorised for parenteral use.

ACTIVITY AND RESISTANCE

- **Good activity** (MIC ≤ 2 µg/mL) against Gram-positive bacteria including staphylococci and streptococci, Gram-positive anaerobes, chlamydia and mycoplasma.
- **Unsatisfactory activity** (MIC > 16 µg/mL) against *Pasteurella* sp. and Gram-negative bacteria such as *Enterobacteriaceae*.

Resistance is a common occurrence in Gram-positive cocci from dogs; see the above section on resistance.

PHARMACOKINETICS AND DYNAMICS

See the section above.

The half-life for tylosin in serum is about two hours.

The volume of distribution is 1.7 L/kg in dogs and cats. The substance passes easily over biological membranes but transport to the central nervous system is only thought to be slight.

Tylosin is excreted mainly via the liver in the bile and then to the faeces; less than 15% is excreted into the urine via the kidneys. Tylosin is also excreted into the milk of nursing animals.

Only about 40% of the administered dose of tylosin binds to serum proteins.

The effect is bacteriostatic in therapeutic concentrations but is thought to be bactericidal at high concentrations and correlates to the duration of time that its concentration exceeds that of MIC (time-dependent).

COMMENT

The most common side effects are gastrointestinal disturbances and pain during intramuscular injection.

CLINDAMYCIN

Clindamycin (QJ01F F01) is a lincosamide intended for oral use.

ACTIVITY AND RESISTANCE

- **Good activity** ($MIC \leq 1 \mu\text{g/mL}$) against Gram-positive bacteria such as staphylococci and streptococci as well as the majority of anaerobic bacteria.
- **Unsatisfactory activity** ($MIC > 4 \mu\text{g/mL}$) against aerobic Gram-negative rods (including *Pasteurella* sp.) and enterococci.

Resistance against lincosamides usually also includes resistance against macrolides (cross-resistance). Resistance in staphylococci against lincosamides is relatively common, for more information see introduction above.

PHARMACOKINETICS AND DYNAMICS

The plasma half-life is three to five hours. The volume of distribution in dogs is 1.5 L/kg. The substance passes easily over biological membranes and clindamycin reaches high intracellular concentrations. The tissue distribution is good which can explain the good effect when using it to treat infections that are difficult to access.

Clindamycin is absorbed quickly and almost completely following oral administration.

Clindamycin is excreted, mainly in its active form, in both the faeces (ca 70%) and the urine. A metabolite (N-desmethyl clindamycin) is around four times more active than the parent compound.

The protein binding in serum is high (93% in humans).

The effect is bacteriostatic in therapeutic concentrations but is thought to be bactericidal at high concentrations and correlates to the duration of time that its concentration exceeds that of MIC (time-dependent).

COMMENT

Clindamycin has a neuromuscular blocking effect that can potentiate the effect of other neuromuscular blocking agents.

FLUOROQUINOLONES

Mechanism of action. These substances act by inhibiting the bacterial DNA gyrase and this means that the bacterial DNA can not be duplicated. The effect is bactericidal.

Activity. Fluoroquinolones are very active against aerobic Gram-negative bacteria. certain mycoplasmata and rickettsiae are also susceptible. Regarding the fluoroquinolones that are presently available for use on animals in Sweden, the activity against Gram-positive bacteria is generally speaking lower but is normally sufficient for effective treatment. Anaerobic bacteria are relatively insensitive.

Mechanisms of resistance. Resistance is normally caused by means of stepwise mutations which results in a gradual increase in the MIC value. Mutational resistance always results in full cross-resistance within the class of antibiotic. This type of resistance is, today, the most common and is clinically the most important. Resistant strains can be selected during treatment, especially in the case of staphylococci and *Pseudomonas* sp. In recent years, several transferable (plasmid-mediated) mechanisms that reduce the susceptibility have been described. It is considered that these mechanisms may interact with the mutations.

Resistance against fluoroquinolones is as yet not a common occurrence in, for example, *E. coli* found in animals from Sweden but reduced susceptibility in staphylococci is somewhat more common.

Pharmacokinetics and dynamics. Fluoroquinolones cross easily over biological membranes because the substances are lipophilic and to a large extent un-ionised at physiological pH. The volume of distribution is consequently relatively large. This often results in high intracellular concentrations. The passage to the central nervous system varies between each fluoroquinolone but is thought to be sufficient from the therapeutic perspective.

The antibacterial effect correlates best with the relationship between the maximum plasma concentration or the area under the concentration-time curve/MIC ratio for the infecting bacteria (concentration-dependent).

Side effects. Articular cartilage damage has been reported in dogs that are not yet fully grown. Care should also be taken when treating seizure-prone animals as fluoroquinolones can act antagonistically against the neurotransmitter GABA. Retinotoxic effects have been reported in cats and high doses of fluoroquinolones should be avoided.

DIFLOXACIN

Difloxacin (QJ01M A94) is a fluoroquinolone that is authorised for oral use in dogs.

ACTIVITY AND RESISTANCE

- **Very good activity** (MIC \leq 0.25 $\mu\text{g/mL}$) against Gram-negative bacteria such as *Enterobacteriaceae* and *Pasteurella* sp.
- **Good - moderate activity** (MIC \leq 1 $\mu\text{g/mL}$) against Gram-positive cocci such as staphylococci and streptococci.
- **Moderate activity** (MIC $<$ 4 $\mu\text{g/mL}$) against *Pseudomonas* spp.
- **Unsatisfactory activity** against the majority of bacteria

See the introductory section for information on bacterial resistance.

PHARMACOKINETICS AND DYNAMICS

The bioavailability following oral administration is high at about 95%. With a dose of 5 mg/kg, the maximum plasma concentration (around 1.8 $\mu\text{g/mL}$) is reached after approximately three hours. The half-life is about nine hours. The volume of distribution is large at 4.7 L/kg and the substance distributes itself amongst the majority of tissues. The substance crosses biological membranes and high intracellular concentrations are reached.

80% of difloxacin is excreted in the faeces and the rest via the kidneys.

The antibacterial effect correlates best with the relationship between the maximum plasma concentration or the area under the concentration-time curve/MIC ratio for the infecting bacteria (concentration-dependent).

COMMENT

Articular cartilage damage has been reported in dogs that are not yet fully grown. Care should also be taken when treating seizure-prone animals as fluoroquinolones can act antagonistically against the neurotransmitter GABA. Retinotoxic effects have been reported in cats and high doses of fluoroquinolones should be avoided.

ENROFLOXACIN

Enrofloxacin (QJ01M A90) is a fluorofluoroquinone intended for oral and parenteral use.

ACTIVITY AND RESISTANCE

See the section on difloxacin for information on the activity and the introductory section for information on resistance.

PHARMACOKINETICS AND DYNAMICS

Enrofloxacin is absorbed quickly following oral administration and the bioavailability is high (84% in dogs). The maximum serum concentration (1.5 $\mu\text{g/mL}$) is, as a rule, achieved within two hours after an oral dose (5 mg/kg).

The volume of distribution is large (2.4 L/kg in cats and 3.7 L/kg in dogs) and the substance can easily cross biological membranes. Enrofloxacin crosses the blood-brain barrier and into the central nervous system but reaches lower concentrations than in plasma.

The biological half-life in serum is between three to seven hours in cats and three to five hours in dogs.

Excretion is via the urine (25%) and via the faeces (about 75%). Approximately 60% is excreted in its unchanged form and the remainder as other metabolites, e.g. ciprofloxacin to name but one.

The degree of protein binding in serum is low in dogs (14%) and cats (8%).

The antibacterial effect is bactericidal and correlates best with the relationship between the maximum plasma concentration or the area under the concentration-time curve/MIC ratio for the infecting bacteria (concentration-dependent).

COMMENT

High serum concentrations of enrofloxacin can lead to lesions of the articular cartilage and enrofloxacin should therefore not be prescribed to animals that are not yet full grown. Reports have also been made drawing a connection between enrofloxacin and seizure conditions; it is therefore wise to avoid using this preparation to treat animals that have a previous history of seizures, e.g. patients that suffer from epilepsy. Blindness due to retinotoxic effects has been reported in cats so the recommended dose should not be exceeded.

IBAFLOXACIN

Ibafloxacin (QJ01M A96) is a fluoroquinolone intended for oral use.

ACTIVITY AND RESISTANCE

See difloxacin for information on the activity and the introductory section for information on the resistance.

PHARMACOKINETICS AND DYNAMICS

The half-life in dogs and cats is around three to five hours. The maximum plasma concentration is 6-7 µg/mL following an oral dose of 15 mg/kg.

The bioavailability after oral administration is high and the degree of plasma protein binding is low.

The antibacterial effect correlates best with the relationship between the maximum plasma concentration or the area under the concentration-time curve/MIC ratio for the infecting bacteria (concentration-dependent).

COMMENT

Articular cartilage lesions have been reported in dogs that are not fully grown. Care should be taken when treating seizure-prone animals as fluoroquinolones act antagonistically against the neurotransmitter GABA. Retinotoxic injuries have been reported in cats and high doses of fluoroquinolones should be avoided.

MARBOFLOXACIN

Marbofloxacin (QJ01M A93) is a fluoroquinolone intended for oral use.

ACTIVITY AND RESISTANCE

See difloxacin for information on the activity and the introductory section for information on the resistance.

PHARMACOKINETICS AND RESISTANCE

The maximum plasma concentration of 1.4 µg/mL is achieved within two and a half hours following the administration of 2 mg/kg to dogs. The half-life in plasma is long, about 9-14 hours in dogs and 8-10 hours in cats.

Following oral administration, the bioavailability in dogs is high.

In dogs, two thirds of the given dose is excreted in its unmetabolised form via the urine.

The degree of protein binding is low.

The antibacterial effect correlates best with the relationship between the maximum plasma concentration or the area under the concentration-time curve/MIC ratio for the infecting bacteria (concentration-dependent).

COMMENT

Articular cartilage lesions have been reported in dogs that are not fully grown. Care should be taken when treating seizure-prone animals as fluoroquinolones act antagonistically against the neurotransmitter GABA. Retinotoxic injuries have been reported in cats and high doses of fluoroquinolones should be avoided.

ORBIFLOXACIN

Orbifloxacin (QJ01M A95) is a fluoroquinolone intended for oral use.

ACTIVITY AND RESISTANCE

See difloxacin for information on the activity and the introductory section for information on the resistance.

PHARMACOKINETICS AND DYNAMICS

The maximum plasma concentration of 2.3 µg/mL is reached within one hour following the administration of 2.5 mg/kg to dogs. The half-life in plasma is about six hours.

The bioavailability in dogs after oral administration is 100%.

In dogs, about 50% of the given dose is excreted in its unmetabolised form via the urine. The concentration of orbifloxacin in the urine following a normal dose (2.5 mg/kg body weight) is ca 100 µg/mL and lasts for around 12 hours from the time of administration. 24 hours after administration, the concentration in urine is around 40 µg/mL.

The antibacterial effect correlates best with the relationship between the maximum plasma concentration or the area under the concentration-time curve / MIC ratio for the infecting bacteria (concentration-dependent).

COMMENT

Articular cartilage lesions have been reported in dogs that are not fully grown. Care should be taken when treating seizure prone animals as fluoroquinolones act antagonistically against the neurotransmitter GABA. Retinotoxic injuries have been reported in cats and high doses of fluoroquinolones should be avoided.

TETRACYCLINES

Mechanism of action. Tetracyclines (oxitetracyclin and doxycycline) exert their effect by inhibiting the binding of tRNA to the bacterial ribosomes (30S subunit) and this in turn leads to the inhibition of protein synthesis. The effect is bacteriostatic.

Activity. Tetracyclines have a broad spectrum and good or moderate activity against Gram-negative and Gram-positive aerobic and anaerobic bacteria. Also chlamydiae, rickettsiae and the majority of mycoplasmata are susceptible. *Pseudomonas* spp. is resistant.

Mechanisms of resistance. Resistance is usually acquired through the uptake of transferable genes. Resistance is generally caused either by means of an active so-called efflux mechanism or by protection of the target structure on the ribosome. Resistance always implies cross-resistance against all of the tetracyclines.

Acquired resistance in bacterial species such as *E. coli* and *S. pseudintermedius* is widespread but is still unusual in, for example, *Pasteurella* sp. Concerning *Bordetella bronchiseptica*, there is no information available on the situation in Sweden.

Pharmacokinetics and dynamics. Tetracyclines are absorbed well when taken on an empty stomach but their uptake is substantially reduced when taken together with food (doxycycline is an exception) as they form complexes with divalent and trivalent ions (e.g. Ca^{2+} , Mg^{2+} , Al^{3+} and $\text{Fe}^{2+,3+}$). The tetracyclines are well-distributed within the majority of the body's tissues with the exception of the central nervous system, the prostate and the eyes. Doxycycline, which is more fat-soluble, can also cross over into the aforementioned tissues. Many believe, however, that the concentrations in the central nervous system are insufficient to fight the majority of bacterial infections but positive treatment results have been documented for fighting borrelia infection within the human central nervous system. Transport into the bacterial cell is active whereupon the tetracyclines' degree of protein binding is of limited importance.

The effect of tetracycline is bacteriostatic and is thought to depend on both the duration of time that the concentration is greater than MIC.

DOXYCYCLINE

Doxycycline (QJ01A A02) is a tetracycline derivative intended for oral use.

ACTIVITY AND RESISTANCE

- **Good activity** ($\text{MIC} \leq 1 \mu\text{g/mL}$) against many Gram-positive and Gram-negative bacteria (including *Pasteurella* and *Bordetella bronchiseptica*), against the majority of anaerobic bacteria as well as against *Borrelia* sp, rickettsiae, chlamydiae and some mycoplasmata.
- **Moderate activity** against some Gram-negative intestinal bacteria such as *klebsiella* sp. and *enterobacter* sp.
- **Unsatisfactory activity** against *Pseudomonas* sp. and *Proteus* sp.

Acquired resistance in bacteria species such as *E. coli* and *S. pseudintermedius* is widespread but is still unusual in, for example, *Pasteurella* sp.

Where the measurement of antibiotic susceptibility is concerned, tetracycline (oxitetracyclin) is the group representative.

PHARMACOKINETICS AND DYNAMICS

The half-life is around 8-10 hours in dogs and around six hours in cats. Doxycycline is only partially metabolised and 25% is excreted via the kidneys in its active form. Excretion is principally via the intestines (not via the bile) in its inactive form. In the event of reduced renal function, there is an increase in the excretion of chelate-bound doxycycline via the faeces.

The tissue distribution is good (see above). Doxycycline crosses easily over biological membranes. The volume of distribution in dogs is about 1.5 L/kg.

The bioavailability when the substance is administered orally is about 50%. The simultaneous intake of food does not affect the bioavailability. The maximum plasma concentration (4 - 4.5 µg/mL) is reached within four hours following oral administration (10 mg/kg).

The plasma protein binding is high and has been reported to be around 80% in dogs and cats. This is, however, of limited importance since the means of transport into the bacterial cell is active.

The effect of doxycycline is bacteriostatic and is thought to depend on both the duration of time that the concentration is greater than MIC.

COMMENT

Nausea and vomiting are common side effects. In order to reduce the risk of vomiting, doxycycline can be given together with food without the bioavailability being affected to any great extent. This is because the tendency to form metal-chelate complexes is less for doxycycline than for oxitetracyclin. The use of tetracyclines in young animals during the period when the mineralization of the teeth is under formation can result in enamel hypoplasia and tooth discolouration. Tetracyclines are also stored in the skeleton of growing individuals.

Tetracyclines, mostly doxycycline, also have anti-inflammatory and immunosuppressive effects. This can mean that treatment results can be misinterpreted, i.e. that symptom improvement, such as an improved general condition and normal body temperature, can also mean that a bacterial infection is not actually responsible but that the condition can have an immunological background.

TRIMETHOPRIM – SULPHONAMIDE

Mechanism of action. These two substances block bacterial folic acid synthesis in two consecutive steps. The effect of each substance alone is bacteriostatic but in combination they act synergistically and the effect, with an optimal relationship between the substances, is instead bactericidal.

Activity. The combination of trimethoprim and a sulphonamide has good activity against Gram-negative bacteria such as *E. coli* and *Pasteurella* sp. and good to moderate activity against Gram-positive bacteria such as staphylococci. Trimethoprim-sulphonamide also have activity against certain protozoa such as *Toxoplasma* and coccidia.

The effect of trimethoprim on susceptible bacteria is counteracted by thymidine. In a corresponding fashion, the occurrence of PABA inhibits the effect of the sulphonamides. Both thymidine and PABA can occur in damaged tissue, especially in combination with suppuration. The effect of trimethoprim-sulphonamides can therefore be less than expected in some situations, especially in the case of anaerobic purulent processes such as abscesses. PABA can also be released from procaine in plasma (procaine is an ester in which PABA is a component) and therefore the simultaneous treatment with procaine penicillin should be avoided.

Resistance mechanisms. Resistance is acquired against trimethoprim and sulphonamide separately. Acquired, transferable antibiotic resistance against sulphonamides is widespread and is caused either by a reduced uptake of the agent by the bacteria or by an alteration of the enzyme involved in folic acid synthesis in a way that makes it insensitive to the sulphonamides. Also resistance against trimethoprim is commonly transferable and is usually due to the formation of an insensitive enzyme, as for the sulphonamides. Resistance against the combination of trimethoprim and a sulphonamide is not unusual in Sweden in, for example, *E. coli* from dogs.

Pharmacokinetics and dynamics. The majority of sulphonamides are absorbed quickly and to a large extent following oral administration. The degree of plasma protein binding, volume of distribution and half-life vary between the different sulphonamide substances.

The effect of the substances individually is bacteriostatic but they, in combination, work synergistically and the effect, with an optimal relationship between the substances, becomes bactericidal. The effect is dependent on the time that the concentration is greater than MIC (time-dependent).

TRIMETHOPRIM-SULPHADIAZINE

Trimethoprim-sulphadiazine (QJ01E W10) is a combination that is authorised for oral administration to dogs and for parenteral use in other animal species. The ratio between trimethoprim and sulphadiazine is 1:5.

ACTIVITY AND RESISTANCE

- **Good activity** ($MIC \leq 1 + 19 \mu\text{g/mL}$, trimethoprim-sulphonamide) against many Gram-negative bacteria such as *Enterobacteriaceae* and *Pasteurella* sp.
- **Good to moderate activity** against Gram-positive bacteria such as staphylococci and streptococci. The activity can be **good to moderate** also against anaerobic bacteria *in vitro* but is thought to be insufficient *in vivo*.
- **Unsatisfactory activity** ($MIC > 8 + 144 \mu\text{g/mL}$) against *Pseudomonas* sp. and Mycoplasma.

For information on the resistance, see the introductory section.

PHARMACOKINETICS AND DYNAMICS

Following oral administration, the two components are absorbed to a high degree. The half-life in dogs after oral administration is about 10 hours for sulphadiazine (SDZ) and about two and a half hours for trimethoprim (TMP).

The medium serum concentration in dogs (24 hours after the last dose) following oral administration over a period of five days (5 mg TMP/kg and 25 MG SDZ/kg x 1) is about 50 µg/mL for SDZ and around for TMP 0.7 µg/mL.

Trimethoprim has a considerably larger volume of distribution than sulphadiazine. The volume of distribution for trimethoprim in dogs is 1.6 L/kg. Trimethoprim crosses over to the prostate.

Trimethoprim and sulphadiazine are partially metabolised in the liver but are excreted in their active form in the urine.

The effect of each of the two substances is bacteriostatic, yet in combination they work synergistically and the effect, in optimal conditions, is bactericidal. The effect is dependent on the time that the concentration is greater than MIC (time-dependent).

COMMENT

Side effects that have been reported are, for example, changes in the blood picture (thrombocytopenia and leukopenia), allergic reactions (fever, urticaria), keratoconjunctivitis sicca (mostly in collie dogs) and renal injury (crystalluria). A number of reports have been made, mostly concerning Doberman Pinschers, describing undesirable and serious reactions such as aseptic polyarthritis, polymyositis and skin reactions. The side effects are mostly related to the sulpha component of the preparation. Trimethoprim is believed to be an atoxic substance.

OTHER ANTIBACTERIAL SUBSTANCES

FUSIDIC ACID

Fusidic acid (J01X C01, QD06A X01, QD07C C01, QD09A A02, QS01A A13) is a lipophilic substance consisting of a steroid skeleton. Fusidic acid exerts its effect by inhibiting the binding of the bacterial tRNA to the ribosomes (the 30S subunit) and this in turn results in the inhibition of protein synthesis.

Only formulations intended for local treatment of infections of the skin, eyes and ears are authorised for use on animals in Sweden.

ACTIVITY AND RESISTANCE

- **Good activity** (MIC \leq 0.5 µg/mL) against staphylococci, clostridia and corynebacteria.
- **Moderate activity** (MIC 1 – 8 µg/mL) against streptococci.
- **No activity** against Gram-negative bacteria.

Resistance is acquired by means of a genetic mutation whereupon a factor involved in the synthesis of proteins is altered. Such mutations can arise and be selected during ongoing treatment. The resistance mechanism is unique and does not entail cross-resistance against other agents.

Resistance occurs in *S. pseudintermedius* and can be assumed to be relatively common in coagulase-negative staphylococci.

PHARMACOKINETICS AND DYNAMICS

Passage over biological membranes is good and fusidic acid distributes itself well amongst the different tissues, and is even taken up through intact skin. Fusidic acid can also cross the cornea and gain entry into the eye itself. The substance is lipophilic.

NITROFURANTOIN

Nitrofurantoin (J01X E01) is a nitrofuran derivative intended for oral use and is not, at the time of writing, authorised in Sweden for use on animals. The mechanism of action is incompletely understood but different degradation products would appear to inhibit various bacterial enzymes. The bacterial DNA can also be damaged.

ACTIVITY AND RESISTANCE

The activity is highest in an acidic pH (<5.5).

- **Good activity** (MIC \leq 32 $\mu\text{g/mL}$) against many Gram-negative bacteria such as *E. coli* as well as against staphylococci and enterococci.
- **Unsatisfactory activity** against *Proteus* sp. and *Pseudomonas* sp.

The selection of drug-resistant clones during the course of treatment itself is unusual. Resistance occurs but is very unusual in e.g. *E. coli* in dogs in Sweden.

PHARMACOKINETICS AND DYNAMICS

Nitrofurantoin is absorbed quickly following oral administration. The half-life in dogs is around 30 minutes. Elimination via the kidneys (filtration and secretion) is so effective that therapeutic concentrations are not maintained in the blood and tissues, using a normal dose in a patient with normal renal function. The concentration in the urine is, however, high and therapeutic concentrations in the urine can be arrived at extremely quickly (within 30 min) following the substance's administration.

Nitrofurantoin is metabolised in the liver to only a small degree. Around 40-50% of the agent is excreted in the urine in its unchanged form. The degree of protein binding is 20-60%.

The effect is usually bacteriostatic.

COMMENT

Nitrofurantoin can act antagonistically in combination with fluoroquinolones.

The substance's toxicity and pharmacokinetic characteristics mean that it is only really used for the treatment of urinary tract infections. The substance should not be used in a patient with reduced renal function due to the risk of toxic effects; the concentration in the urine is also less and the effect of treatment is consequently worse.

Gastrointestinal disturbances such as vomiting, diarrhoea, bleeding and liver injury have been reported.

Nitrofurantoin has a broad spectrum yet its fast absorption combined with its fast elimination via the kidneys means that the risk of any effect on the normal bacterial flora in the intestine is small.

CHLORAMPHENICOL

Chloramphenicol (J01B A01, QS01A A01) is an aromatic nitro compound intended for parenteral or local use. Only substances for local application are authorised for use on animals in Sweden. Chloramphenicol inhibits bacterial protein synthesis by binding to the ribosomal 50S-subunits.

ACTIVITY AND RESISTANCE

- **Good activity** ($MIC \leq 8 \mu\text{g/mL}$) against the majority of Gram-positive and Gram-negative aerobic and anaerobic bacteria.
- **Unsatisfactory activity** against *Pseudomonas* sp.

Resistance is usually transferable and is caused by the bacterial production of chloramphenicol-inactivating enzymes. Resistance occurs in, for example, *E. coli* and *S. pseudintermedius* in dogs in Sweden.

PHARMACOKINETICS AND DYNAMICS

The volume of distribution is large at about 2 L/kg. The half-life is around one and a half hours in dogs and four to eight hours in cats.

The substance's large ability to cross biological membranes (it is a small lipophilic molecule), combined with its low degree of protein binding, means that effective concentrations of chloramphenicol are reached in the majority of tissues including the central nervous system.

In dogs, only about 20% is excreted in its unchanged form in the urine by means of glomerular filtration. The remainder is metabolised and conjugated principally with glucuronic acid in the liver. Cats have a less of an ability to conjugate the substance with glucuronic acid and excrete about 25% of the dose in its unchanged form via the urine.

The effect is usually bacteriostatic.

COMMENT

Chloramphenicol also has an affinity to the mitochondrial ribosomes in fast-growing mammalian cells (e.g. in the bone marrow) and this can lead to bone marrow depression. Dose-dependent reversible bone marrow depression and anorexia, vomiting and diarrhoea are all side effects that have been reported following systemic administration.

Chloramphenicol blocks the mechanism that transports aminoglycosides into the bacteria cell; these substances should therefore not be administered simultaneously.

METRONIDAZOLE

Metronidazole (J01X D01, P01A B01) is a nitroimidazole intended for parenteral or oral administration. Other substances in the same class are, for example, ronidazole and dimetridazole. Nitroimidazoles are, at the time of writing, not authorised for use in animals in Sweden.

The mechanism of effect for metronidazole is incompletely understood. In anaerobic bacteria, the nitroimidazoles are reduced and the resultant metabolites cause breakages within the bacterial DNA and consequently inhibit nucleic acid synthesis.

ACTIVITY AND RESISTANCE

- **Good activity** ($MIC \leq 8 \mu\text{g/mL}$) against the majority of anaerobic bacteria.

- **Unsatisfactory activity** against *Actinomyces* sp. Normally, the activity is insufficient against aerobic bacteria. There can, however, be a limited effect against aerobic bacteria found in an anaerobic environment.

Resistance is unusual and is thought to be caused by a reduced production of active metabolites.

PHARMACOKINETICS AND DYNAMICS

Metronidazole is absorbed relatively quickly following oral administration. The half-life in dogs is around eight hours. The bioavailability in dogs is high but varies from patient to patient. Metronidazole is relatively lipophilic and is distributed quickly to the majority of tissues, even bones and the central nervous system. The substance is metabolised by the liver and is excreted via the urine and faeces. The degree of protein binding in humans is less than 20%.

Nitroimidazoles also have a cidal effect on protozoa such as *Giardia* spp. The effect is bactericidal.

COMMENT

Metronidazole has certain amount of activity against intestinal protozoa. Metronidazole should not be prescribed during pregnancy as the substance can cause chromosomal damage. Hepatotoxicity and dose-dependent central nervous system disturbances have been reported in both dogs and cats.

POLYMYXIN B

Polymyxin B (QS01A A20) is available in combination with neomycin and is intended for local application (eyedrops).

Polymyxins are alkaline cyclic decapeptides. Polymyxin B is a mixture of different polymyxins. These substances are surface-active agents and affect the phospholipids of the cell membrane; resulting in an increased cell permeability. Another polymyxin is, for example, colistin which is used in many countries for the local treatment of diarrhoea in pigs.

ACTIVITY AND RESISTANCE

- **Good activity** against the majority of Gram-negative bacteria including *Pseudomonas* spp.
- **Unsatisfactory activity** against Gram-positive bacteria and *Proteus* spp.

Acquired resistance is unusual but occurs in *Pseudomonas* spp.

PHARMACOKINETICS AND DYNAMICS

The passage over biological membranes is insignificant. Negligible amounts of the substance are absorbed when it is administered locally.

The effect is bactericidal.

COMMENT

Polymyxins are tolerated well when applied locally but are very toxic when administered systemically.

During recent years, and despite their toxicity, polymyxins are increasingly used for the systemic treatment of humans suffering from life-threatening infections with Gram-negative bacteria that are resistant against other antibiotics, including cephalosporins and carbapenems.

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