The Swedish Veterinary Association's Guidelines for the clinical use of antibiotics in the treatment of horses

ABBREVIATIONS

ESBL	Extended spectrum beta-lactamase, including plasmid-borne AmpC
MIC	Minimum inhibitory concentration
MRL	Maximum residue level
MRSA	methicillin resistant *Staphylococcus aureus*
NSAID	Non-steroidal anti-inflammatory drug
PK/PD	Pharmacokinetic/pharmacodynamic

1. ANTIBIOTICS POLICY

The purpose of this document is to provide guidelines for antibiotic use in horses. It is based on Swedish conditions and viewpoints. It should not be regarded as a "cheat sheet" but a reference guide to be adjusted to your own practice. It is Good Veterinary Practice to follow the general principles on which this document is based.

As is indicated here the "right choice" regarding antibiotics treatment is sometimes to refrain and instead wait or choose another treatment.
In many cases, antibiotics 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. Advising 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 based on 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.

These guidelines complement Swedish legislation that requires all veterinary practitioners to have a hygiene plan (SJVFS 2013:14, K112), restricts the use of quinolones and 4th generation cephalosporins to exceptional cases where susceptibility testing demonstrates an absolute need, and bans veterinary use of certain antimicrobial substances (SJVFS 2013:42, D9).

> **According to the Swedish Veterinary Association's/Swedish Veterinary Society's general antibiotic policy, antibiotic treatment is normally only motivated if both 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 this infection, in all likelihood, will not resolve without the support of antibiotic treatment**

If there are equivalent methods of treatment when antibiotics are not used, they should be the chosen course of therapy. It is of fundamental importance that antibiotics should only be used when absolutely necessary and that infections whenever possible, should be counteracted by 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 be motivated in a few specific situations 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.

When possible, the infectious agent should be identified by laboratory examination. This is especially important in cases of therapy failure, relapse and on other occasions when antibiotic resistance can be

suspected. Samples should always be taken from infections that arise post-operatively, even if antibiotics treatment is not being considered. Correct technique in taking and handling samples are very important in order to get the most relevant test result.

The risk of antibiotic resistance should always be taken into consideration when choosing an antibiotic (SJVFS 2012:32; "D9"). This means that the antibiotic and the route of administration is chosen with the aim to affect the animal's normal bacterial flora as little as possible (so-called narrow-spectrum antibiotics). In Sweden the most common infectious agents in horses are usually (in cases of beta-haemolytic streptococci) or often (staphylococci, *Actinobacillus*) sensitive to penicillin.

With this in mind, local treatment can in fact be preferable when correctly implemented, 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, current regulations (SJVFS 2012:32; "D9") should be adhered to and antibiotics not approved for animal use and that have particular importance in treating human patients, such as mupirocin and substances from classes such as the carbapenems, and glycopeptides should not be prescribed at all. Third or fourth generation cephalosporins and fluoroquinolones 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 based.

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 6

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2. THE PERIOPERATIVE USE OF ANTIBIOTICS

INTRODUCTION

The expression perioperative use of antibiotics refers to antibiotics that are administered before, during and after a surgical procedure without signs of infection in the surgery area. Prophylactic use of antibiotics cannot replace good aseptic, good surgery techniques and good operating rooms routines. In most cases of elective surgery with clean wounds antibiotics are unnecessary anyway.

The aim of perioperative use of antibiotics is to prevent, or at least reduce the incidence of, post-operative wound infections, which can occur either through exogenous contamination (from for example staff, instruments or airborne) or endogen contamination (from the animal's own skin or tissues).

Drawbacks of perioperative use of antibiotics can include the risk of reduced attention to good surgery techniques and aseptic, side effects from the substance, infection by multiresistant bacteria, and increased costs. Unnecessary and in other ways superfluous use of perioperative antibiotics is not only ineffective but can have a negative effect on the patient and increase the risk of antibiotic resistance.

Prophylactic antibiotics should be given directly before or during surgery. The most common mistake is to administer antibiotics postoperatively instead of preoperatively, to give antibiotics in cases with clean wound without implants, and to continue too long, that is more than 24 hours post-surgery.

Careful handling of tissues, short duration of the surgery, as few sutures as possible and very careful debridement are other examples of routines that reduce the risk of post-surgery wound infection. The depth and duration of anaesthesia is also important for the outcome of surgery. Short duration of surgery and a light general anaesthesia, preferably with the addition of local anaesthetics (nerve blocks preferably) and analgesics will reduce the risk of post-surgery infection, as they contribute to good circulation. Surgery on critically ill patients increase the risk of post-surgery infection, as is the case in older patients.

In cases that have an ongoing infection in the planned surgery area it should if possible first be treated and resolved before surgery.

CLASSIFICATION OF 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. There is a classification of surgical wounds that is an aid in evaluating the necessity for prophylactic or therapeutic antibiotic treatment.

CLEAN WOUNDS

Clean wounds occur during surgery with optimum conditions and primary closure. 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 unless implants (screws, plates) are used, the area is very traumatized or the surgery time is expected to be very long. In human surgery the risk of infection in this type of wounds is usually less than 1 percent. In veterinary medicine there are only a limited number of studies made, but in for example elective arthroscopy the risk seems to be about equal with those numbers. In one study concerning elective arthroscopy of 932 joints in 682 horses 39 percent of the horses were given preoperative antibiotics, there was no difference between the treated and untreated groups regarding the risk of post-operative septic arthritis. The risk of infection in that study was 1 percent, but increased to 1,5 percent when only those available for thorough follow-up were included.

CLEAN-CONTAMINATED WOUNDS

Clean-contaminated wounds occur in cases of minor discontinuation of the aseptic environment occurs and following procedures where luminal organs are entered but where any leakage of luminal contents is minimal. The use of prophylactic antibiotic treatment can be justifiable. Antibiotics should preferably be administered before the opening of viscera.

CONTAMINATED WOUNDS

Contaminated wounds occur when there is a longer break in the surgery aseptic, when there is inflammation in the incision area, or in cases of more major leakage from the viscera. Fresh (less than 4-6

hour) traumatic wounds are also included in this category. In humans the incidence of infection in this type of wounds is 10-17 percent. This group also includes acute colic surgery in horses. There are studies reporting an incidence of postoperative infection of up to 40 percent.

DIRTY WOUNDS

The category dirty wounds include traumatic wounds older than 4-6 hours, traumatic wounds older than two hours with a lot of devitalised tissue, wounds with foreign bodies or faecal contamination, surgery wounds with a lot of exudate or in cases of perforated luminal organs. Then perioperative antibiotic therapy is valid.

ANTIMICROBIAL PROPHYLAXIS IN SURGERY

INDICATION

In equine surgery perioperative use of antibiotics should be restrictive. In general, prophylactic preoperative antibiotic use is indicated in all cases of clean-contaminated or contaminated wounds, in surgery with implants or prosthesis, and in situations where an infection could be life-threatening.

Open uncovered castrations in the field can under certain circumstances be regarded as a clean-contaminated wound. Perioperative antibiotics is not indicated in the normal case, but under certain circumstances such as an inexperienced surgeon, problems during surgery or a difficult patient, antibiotics can be considered.

In human medicine correct prophylactic use of antibiotics is defined as a single dose before surgery, and up to an additional two doses within 24 hours of the end of surgery in high risk patients, and when implants are used, and not giving antibiotics in cases of clean wounds. If the risk of infection is believed to be 5 percent or higher this is an indication to give prophylactic antibiotics in surgery cases. Human studies have not been able to demonstrate any decrease in the incidence of postoperative wound infections after perioperative antibiotic use in surgery of non-complicated soft tissue surgery. Careful debriding was the probable explanation to why there was no difference between the patients given or not given prophylactic antibiotics.

There are equine studies regarding horses describing no difference in the risk of infection after celiotomy with or without preoperative treatment with antibiotics (penicillin and gentamicin). Use of perioperative antibiotics is however common in abdominal surgery and can be useful if an enterotomy is necessary.

Further indications for preoperative antibiotic use can be high risk patients, for example those with additional disease, undernourished or possibly patients on cortisone treatment. Preoperative antibiotic use is in general not indicated in cases of clean incision wounds, such as closed castration, periosteal lifting, desmotomy of the deep flexor tendon or a biopsy.

There are studies of clean wound surgery in dogs and cats showing an increase in risk of infection if the prophylactic treatment was not done correctly, that is primarily was continued for too long, compared to with no prophylactic treatment.

Prophylactic use of antibiotics is not recommended in cases of clean orthopaedic surgery. Exceptions to the rule would be if the surgery is expected to be of long duration, if major dissection is needed or if an implant is used.

Regarding surgery with unclean wounds antibiotic treatment could be seen as therapeutic rather than prophylactic. International literature often recommends broad-spectrum antibiotics for 24-48 hours, and then changing to a narrower spectra substance based on results from tests taken during surgery. The current recommendation in Sweden is instead to treat simple traumatic wounds and infected wounds in a patient with normal status locally and completely without antibiotics. The value of a bacteriology test should be evaluated case by case depending on why the wound is classified as unclean.

DOSAGE AND TIMING

For prophylactic antibiotic treatment to have effect it is very important to administer the antibiotic just before the start of surgery in order to reduce the risk of infection, or else give no antibiotics. Human studies show a fivefold higher risk of infection if antibiotics were administered 2-24 hours before or more than 3 hours after surgery, compared to if given 0-2 hours before incision. Studies have also shown that prophylactic antibiotic treatment is most effective if administered within an hour after inoculation with bacteria and inefficient if delayed until three to four hours after bacteria reached the wound.

The aim of prophylactic antibiotic use is to maintain a high tissue concentration during surgery and briefly afterwards, to prevent any contamination from resulting in an infection. It is important to choose a

substance that is active against the type of bacteria that are most common in post-surgical wound infections. In equines beta haemolytic streptococci and staphylococci (mainly S. *aureus)* are common.

In prophylactic use intravenous injection should be the primary choice, with the injection made a minimum of 30 minutes but not more than 60 minutes before the incision, and preferably at the same time as the induction of anaesthesia. If penicillin procaine is given intra muscularly it should be administered one to two hours before incision. The prophylactic dosage should be the same as the therapeutic.

The half time for sodium penicillin is under one hour and for Gentamicin 3 hours. This means that in surgery of long duration a second dosage penicillin should be given during surgery. The recommendation is to repeat the dosage after two halftimes, so two hours for penicillin and six hours for Gentamicin.

CHOICE OF ANTIBIOTICS

In prophylactic use bactericidal antibiotics are preferred.

Penicillin is active against most bacteria that are equine pathogens and should therefore be the first choice. Based on literature ampicillin is also recommended in equine orthopaedic surgery. Ampicillin is however not approved for equine use in Sweden, except for foals and then as tablets. In abdominal surgery in Sweden a combination of penicillin and Gentamicin is normally used pre-surgery. Gentamicin should not be administered during anaesthesia as it can amplify the respiratory impairment from certain anaesthetics. Trimethoprim-sulpha is also contraindicated perioperatively if an α2 receptor agonist is used for premedication.

International literature usually recommends broad spectra antibiotics for prophylactic use, but this is not the primary choice in Sweden.

PROPHYLACTIC DURATION

Perioperative use of antibiotics should end within 24 hours of surgery. As a rule, one to three injections during 24 hours after the end of surgery is sufficient. There are many studies in humans when the positive effect of antibiotics does not increase if it is given as a single dose before surgery or several times the first 24 hours post-surgery. Similar studies in small animals show the same results.

When treating traumatic wounds longer antibiotic use than during the actual procedure is probably unnecessary, provided that very careful surgical debridement with removal of foreign material and necrotic tissue is done.

In orthopaedic surgery the perioperative treatment usually continues until any vacuum drainage has been removed, as the risk of retrograde infection has then decreased.

If the substance has been administered for therapeutic aims the treatment duration should be until signs of infection has disappeared.

3. GUIDELINES FOR TREATMENT

WOUNDS

INTRODUCTION

There are huge variations in opinions on treatment, medication, bandaging and suturing techniques in treating wounds in horses. Many substances for wound treatment are marketed to horse owners, but some of them are even dangerous. The clinician who improves his knowledge and uses his understanding of the wound healing process, combined with the absolutely necessary knowledge in anatomy, will be best prepared for dealing with wounds.

New research is appearing about modern wound treatment in companion animals. There are many new findings about wound treatment which facilitates a marked reduction in antibiotic use, using antibiotics more rationally and knowing in which cases it is unnecessary or even inhibits wound healing. Using modern interactive or bioactive dressings can result in promoted wound healing, which will result in shorter healing times and less risk of formation of proud flesh.

Infection delays wound healing, but faulty or excessive use of antibiotics can also have a negative effect on wound healing.

In most cases of local infection in wounds with secondary healing it is sufficient to use only topical anti-bacterial treatment with bioactive dressings, not containing antibiotics.

INITIAL EVALUATION AND TREATMENT PLAN

First evaluate the whole patient, rather than deal with a major bleeding wound without first examining the whole horse. Solid understanding of anatomy is very important in order to make a correct evaluation of possible risks for other damaged tissues apart from skin and subcutis. In addition to the examination of the wound it is sometimes also necessary to do imaging to check for any fractures, foreign bodies etc, and to check for any possible perforation synovial structures. If how the wound occurred is known this can be of major help in the initial evaluation the patient. The main principle in treatment planning for a horse with a traumatic wound is to try closing the wound. Remember that a wound that is not sutured will roughly double in size after two weeks compared to when fresh. It normally pays to invest time, effort and money in doing a thorough early effort with wound cleaning, debridement and treatment with bioactive dressings, as the healing time can be markedly reduced and the end result improved.

There are only two reasons not to try and do at least primary closure of a wound and that is infection or lack of tissue.

There are however several reasons to careful consideration; for example, in case of obvious oedema, wounds older than 8 hours, a deep wound, open joint, contamination etc. It is important to tell the horse owner that wounds often break up after suturing, but it is worth trying anyway, even if it is not done as primary suturing but delayed.

ANTIBIOTICS

Simple wounds

Are lesions that do not involve structures beneath the skin and subcutis. In these cases, the recommendation is to not give any antibiotics.

Most important to minimize the risk of infection is always to do a careful debridement of the wound, as soon as possible. Antibiotics cannot replace debridement of the wound. Wounds less than six hours old will after correct debridement be classified as a clean wound. If use of antibiotics is deemed indicated, it can be done very briefly, that is one injection before wound treatment or a maximum of 24 hours duration.

In wounds with a high risk of infection, that is big, superficial trauma with major tissue involvement, heavy contamination or in cases of impaired circulation, antibiotics are often indicated.

In complicated wounds, that is acute, traumatic wounds that involve more structures than just skin and subcutis, the recommendation is to administer intravenous antibiotics as soon as possible (preferably even before any referral). When antibiotics is given only penicillin should be given, even if there of course will normally be a mixed bacterial flora on the wound surface and the recommendation in many other countries is to give a combination of for example penicillin and Gentamicin or other combinations of broad-spectrum antibiotics. The exception is synovial cavity perforating wounds (see separate chapter). How long antibiotics should be given must be considered case by case, and it is important to consider the size and depth of the wound. The general principle is that antibiotics should be used only with clinical indication and with as short duration as possible. Local antibiotics should not be used at all, as most products kill leukocytes and fibroblasts, which are needed locally in the wound.

Equine wounds that have been contaminated and therefore are at immediate risk of infection should not be treated by systemic antibiotics. If the horse has general symptoms, lymphangitis, osteomyelitis or if synovial structures are involved systemic treatment can be relevant (see separate sections). In cases of only local infection, even if there is a sequester, damaged tendon or bare cortical bone antibiotics should not be given. A patient whose wound is infected, bone oedema or granulation tissue that does not look healthy, will not benefit from systemic antibiotics treatment. Perfusion is normally poor in a chronic wound area. These wounds should instead be treated locally during 1-2 weeks with antimicrobial dressings, that do not contain antibiotics. If a sutured wound ruptures, any ongoing antibiotics treatment can be discontinued immediately, as the wound is accessible for continued local treatment.

In antibiotics treatment of horses with acute traumatic wounds a general guideline is 1-3 days of treatment. In certain cases, the treatment could be extended to five days but there are no set guidelines on which to base decisions on. If there is an established infection in the tissue with generalized symptoms the systemic treatment must continue until the clinical signs of infection have disappeared.

WOUND TREATMENT

WOUND CLEANING

Very contaminated wounds can be rinsed by water hose with tepid water before clipping of hairs. Before debridement the wound should be protected by hydrogel or moist dressings with saline while the wound area is clipped. The dressings or hydrogel is then removed in connection with the wound cleaning. The wound is then flushed with considerable amounts of saline solution. The flushing can be done with a 20-30 ml (or even better 60 ml) syringe with a pink (1,2 x 40 mm) needle, provided the contents are pushed out with force. The wound should not be rubbed with dressings at all. Wound cleaning done in this manner will reduce the number of bacteria in the wound, and also reduce contamination with earth and other dirt. In the next step the skin area around the wound is disinfected ahead of debridement and suturing (normal sterile cleaning).

SURGICAL DEBRIDEMENT

Debridement of the wound should be done irrespective of whether the wound should be sutured by primary or secondary intention or left to heal. Debridement removes dirt and bacteria. Flushing of the wound is done again (in the same manner as above), and surgical debridation of tissue is done across the whole wound with the aid of a scalpel, not scissors. Loose tears of any damaged tendon are removed, and bare bone be cureted across the whole surface. Large, partly loose skin flaps should be left, unless it is absolutely certain that they will become necrotized.

SUTURING TECHNIQUES

Suturing of skin should be done by monofilament material. Make sure circulation stays as intact as possible, that is do not use continuous suturing, do not pull the sutures too hard and use strong enough thread that do not cut. Use as little suturing material as possible deep in the wound and if needed use drainage or a tampon with direct pressure application. Suture as much as possible of the wound, even if the whole wound cannot be closed due to loss of tissue.

MOIST WOUND HEALING

A considerable number of studies in many species have demonstrated that a moist wound environment will result in a better and faster wound healing than a dry environment. This is a radical re-evaluation of previous theories that wounds should be dry and aired.

Wounds should be treated as biologically mild as possible, that is keeping the environment moist. A moist wound environment results in less pain, as free nerve endings are embedded in physiological solution, there are fewer wound infections as the natural defence mechanisms of the tissue is promoted, and there is less dry tissue that can harbour microorganisms. Frequent bandage changes should be avoided as they cool down the wound, damage newly formed epithelial cells and interfere with for example macrophage activity. A moist wound surface will in addition keep the dressing moist, which will reduce damage when changing or removing bandages. The wound should be kept moist, but the degree of moisture should be controlled so that it is not too high and that excretions cause maceration of wound edges and the surrounding skin.

Moist wound healing is obtained with the aid of modern interactive or bioactive dressings. Bioactive dressings refer to dressings that deliver or stimulate substances that are active in the healing cascade. The dressings control the wound environment while passive dressings absorb moisture and block the wound. Many modern dressings are designed to create a moist wound environment, which results in wound exudate and growth factors staying in contact with the wound, promoting autolytic debridement and faster wound healing. Through correct wound treatment, when necessary processes are supported and inhibitory factors removed presence of bacteria in the wound will normally not delay healing.

When treating wounds with secondary healing we want to stimulate the *initial inflammation*. This is done through a substantial debridement, use of bioactive dressings, not too frequent bandage changes and no or little use of NSAID. Later in the process when the wound is filled by granulation we want to inhibit the inflammation by using a different kind of dressing (foam).

If there is proud flesh it should be cut away. Do not use any astringent substances, such as Lotagen. Lotagen (metacresolsulfon acid and formalin) is a caustic substance with antibacterial effect but will in addition damage surrounding tissue and should not be used. Proud flesh is often a result of infection, so local antibacterial treatment should be started after excision of surplus proud flesh has been done, and the wound covered by an antibacterial dressing for 1-2 weeks. Local corticosteroids can sometimes help against formation of proud flesh. In cases of repeated forming of proud flesh, a silicon dressing is recommended.

BANDAGING

Bandages can be divided into three different layers; the primary or the contact layer, the medium secondary layer and the outer tertiary layer.

The purpose of the bandage is to provide pressure to reduce cavities, reduce oedema and bleeding, immobilise and protect the wound, support surrounding tissue and create the moist wound environment that promote healing. Immobilisation of a wound has great influence both for wound healing and for preventing infection. Immobilisation of extremities can be achieved by plaster, Robert Jones bandages with splints, or other substantial bandages.

PRIMARY LAYER

The primary layer is in direct contact with the wound and its aim can be debridement, to administer drugs or remove exudate to the secondary layer. The primary layer should minimize pain and prevent superfluous loss of moisture. This part of the bandage can be adherent or non-adherent, occluding (tight fit) or semi occluding. Adherent dressings are used if debridement is wanted. Semi-occlusive dressings allow air to pass in and exudate to pass out through the dressing, while the occluding dressing is also non-permeable to air and used when non-exuding wounds need to keep all moisture in the wound.

In veterinary medicine semi-occluding dressings are normally used. In horses, fully occluding dressings have a negative effect on wound healing as they are too tight and cause excessive formation of granulating tissue (this has been shown with occluding hydrocolloid dressings, however there is now also semi-occlusive hydrocolloids developed for humans). Non-adherent dressings can be used as the primary layer if there is no necrotic tissue left in the wound. They maintain moisture in the wound.

The primary sutured wound is less sensitive to which type of contact layer is used. The most important factor is that the wound is not stuck on the dressing. Also, in primary suturing of wounds a moist environment is preferable. Today there are thousands of different interactive or bioactive dressings

available as primary layers and new ones are constantly being developed. Below is a check sheet for different types of dressings based on their contents, as a guide to choosing the right dressing for the right stage in wound healing. There is not one single dressing that can be used during the whole healing process, but they have differing effects. It is therefore necessary to learn and understand the wound healing process and based on that be able to judge at what stage a certain wound is and what you want to happen next in the wound, in order to choose the right dressing.

Hydrogels

The purpose of hydrogels is to create a moist wound environment for dry wounds. When a hydrogel dressing is placed on a necrotic wound it acts as a barrier that prevents moisture from the necrosis to pass into the air. Moisture accumulates which results in the necrosis dissolving.

Equine wounds are often so moist that extra moisture is not needed, and hydrogels are then not necessary. Rather they can cause delayed healing in horses if used for more than 2 days. If they are used, you should change to a different dressing as soon as granulation is appearing in the wound.

Hydrogel contains water, a polymer (often cellulose or starch) and propylene glycol. Debridement increases as the collagenase production is stimulated, hydrogel aids moisture and protects exposed tissue. Hydrogel is a good first aid for horse owners to have at home. They can be used to protect wounds while clipping the wound area and can also be used for a day or two until suppuration has started. Hydrogel decreases the inflammation, and therefore should only be used for a short time on a completely fresh wound that is still dry. The alternative is an alginate dressing, made moist with saline solution.

Alginate

Alginates are so far the best type of dressing for wound treatment in horses. Alginates are extracted from seaweed and consist of non-woven fibres of calcium- or sodium calcium alginate. When the dressing comes into contact with the wound exudate there is an ion exchange between the calcium in the dressing and sodium in the exudate, which results in the fibres swelling into a gel like mass. They can be used underneath hydrocolloid- or foam dressings on very liquid wounds.

Alginates debride the wound, stimulate the initial inflammation response (stimulating macrophages) and the formation of granulation tissue and improves healing. Alginates are very hydrophilic, that is have good absorbency. Give a good local protection against infection. Should be used until the wound has filled out with granulation tissue.

Hydrogenated polymer, foam

Foam dressings can be used for basically all wounds, also sutured. They absorb exudate and are available in many different forms and thicknesses, that can be chosen based on the expected amount of exudate and how the wound looks.

Foam dressings is the best choice when the wound has been filled with granulation tissue, when contraction and epithelisation is wanted. Available with and without a sticky surface.

Antimicrobial dressings

There are many versions of antimicrobial dressings. They can contain active activated carbon, silver polyhexanide, medical honey, hypertonic saline solution, iodine, or absorb bacteria passively. In human medicine the most common types are iodine-, silver -, honey and polyhexanide dressings.

Antimicrobial dressings are used for infected wounds, on proud flesh extirpation, as a preparation of the wound area before graft surgery, or if the wound is covered by bio film. Can also be used on wounds with a critical degree of colonisation or that are regarded at high risk of becoming infected.

Should not be used more than 1-2 weeks (Resistance can develop, at least regarding silver.) See further under the headline wound infection.

Gauze like dressings

Gauze like dressings consist of impregnated gauze covered by a perforated polyester film.

Gauze like dressings are only used for sutured wounds, normally surgery wounds. They prevent adhesion between the wound and the dressing. Permeable and therefore denatures the wound.

Silicon

In veterinary medicine silicon dressings are primarily used to treat proud flesh in horses, but the primary function is preventing keloids and the formation of hypertrophic scars in humans, by closing micro-vessels. The dressing is expensive but can be washed and reused at the next change of dressings. The dressing can also be stretched to cover a larger area. Is seldom needed if the wound has been correctly handled from the start, as it will then be very little proud flesh.

Film dressings

For clean wounds which need epithelialization but do not suppurate, which basically all equine wounds do. Therefore, not very relevant for horses. Film dressings consist of polyurethane and resembles plastic but are permeable dressings where microorganisms can pass through. Available in spray form. Should be used on pink, healthy tissue. One drawback is that hardly any exudate is absorbed. Can be used as protection when a bandage is not used.

Hydrocolloids

Should not be used in equine wound care, as they form an occluding layer and stimulate the formation of proud flesh. They consist of gelatine and pectin from carboxyl methylcellulose. New semi-occluding hydrocolloids are being developed and can become an alternative in the future.

SECONDARY LAYER

The middle layer in a bandage is an absorbing layer which removes and stores exudate, bacteria and enzymes away from the wound surface. This layer should be thick enough to absorb the fluid which is created before the next change of bandage and is part of the immobilisation of the wound. The most common material used for the secondary layer is cotton wool. Many wounds are so moist that the selected primary dressing cannot hold all the fluid. It is important that the surrounding skin is not macerated by excessive wound secretion. This often means that a dressing with a high degree of absorption must be put on top of the primary layer before cotton is added. There are a lot of dressings with the sole purpose to absorb moisture, but for large wounds a baby nappy or ladies' sanitary pad is also an option.

TERTIARY LAYER

The outermost, tertiary, layer of the bandage has the main purpose of keeping it together. It usually consists of gauze, and adhesive tape of different kinds, but different kinds of splints can also be for extra strength.

AFTERCARE

Post-surgery wound treatment has the aim to promote healing and should be specifically designed for each wound. Wounds should be evaluated at every change of bandages in order to decide about any adjustments needed of the treatment. It is at the same time important not to change bandages too frequently. Preferably the bandage should not be changed more often than every fifth day, if it fits well and there are no signs of complications, but an interval of 3-7 days is possible. During secondary healing profuse secretion from the wound is common, also when no infection is present. During the healing period wound cleaning should be restricted to minimize disturbance of the healing process. The skin surrounding the wound must however be cleaned at every change of bandages. Skin areas not covered by the bandage but where wound secretions gather, should be protected by creams such as Vaseline, to prevent dermatitis. Do not disturb a granulating wound with local treatment before delayed healing has been ascertained. It will take a certain time before the tissue defect has filled out, also in cases of normal healing processes. Box rest until when sutures have been removed is normally recommended, to reduce the risk of wound rupture.

WOUND INFECTIONS

Most wounds are not infected, although all wounds contain bacteria. The normal bacterial flora can protect against colonisation of more aggressive bacteria and stimulate wound healing. This means that all bacteria in a wound do not need to be eliminated. The clinical symptoms in a wound will increase with the number of bacteria present and how long they have been present. Whether the wound is contaminated, colonized, critically colonized or infected governs the degree of symptoms, but how much tissue is damaged, and the blood supply also plays an important part in the process of whether a wound gets infected or not. When the balance between bacteria and the host's ability to counteract infection is affected, a wound infection can occur.

Wound healing and infection cause similar inflammatory reactions. This poses a challenge when evaluating if a wound is infected or not. Wounds that heal with difficulty often look yellow and smudgy, which can easily be interpreted as an infection. But the yellow substance is fibrin and debris, not pus. Delayed wound healing is usually due to bacterial growth in the wound, especially in the form of biofilm. Biofilm is a slime consisting of extra cellular polymer substances where bacteria is often assembled and bound. Biofilm is now a focus in a lot of wound research. It is suspected that most of the wound bacteria are bound in the biofilm and that it causes a chronic inflammation in the wound, which inhibits healing. Considerable research efforts have focused on identifying substances that can eliminate biofilm and the bacteria present there.

Debridement has an important part in the process of removing biofilm. Some substances that have been shown to have effect on different ingredients in biofilm is: Polyhexanide, iodine, medical honey, EDTA, acetylsalicylic acid and others, as well as treatment with fly larvae. Often the choice of treatment is a combination of thorough mechanical cleaning plus local topical substances to break up the biofilm.

The symptoms of a wound infection are the classic signs of inflammation, that is redness, swelling, heat and pain in the surrounding tissue. (Bad) smell can also be a sign of infection, and pain in the area of a wound which did not hurt previously is a sign of infection. If bacteria from a slow healing wound are analysed some 10 different species can sometimes be identified. Bacterial culture is often not very helpful in deciding the treatment but based on the increase of for example MRSA it can be appropriate to do an initial culture in cases of slow healing wounds. Wound infections are usually caused by beta-haemolytic streptococci or staphylococcus, but other bacteria such as *Coliforms* and *Pseudomonas* also occur.

The condition of the tissue, as a result of for example surgery techniques and wound treatment, is the most important underlying factor deciding if a wound becomes infected or not. The risk of infection is normally much lower in cases of a cut with bleeding, even borders and minimal tissue damage, compared to in a crush trauma. Certain wounds should always be regarded and treated as primary infected, for example bite wounds and shot wounds caused by high energy projectiles. An infected wound can be sutured after the wound has cleaned (delayed primary suture) or when it is covered with clean granulation tissue (secondary suture) to reduce the substance defect and decrease healing time.

TREATMENT

An infected wound cannot become a clean wound through surgical techniques. The treatment should instead be based on supporting the body's biological defence mechanisms.

In most cases of local infection in wounds with secondary healing it is sufficient to use only topical antibacterial treatment with bioactive dressings, not containing antibiotics. The treatment should be based on a clinical evaluation of the patient, possibly in combination with laboratory tests. In principle antibiotic use should be restrictive, due to the risk of selection of resistant bacteria (for example MRSA). Regional perfusion with antibiotics can be appropriate.

The use of bioactive dressings containing iodine is a standard treatment in cases of *Pseudomonas* infection in slow healing leg wounds in humans. As *Pseudomonas* wounds excrete a lot of pus, hydrofibre and alginate dressings can be used**.** Dressings containing silver can also be used in wound infections. They have topical effect on a number of bacteria, especially *Pseudomonas* and *S. aureus*.

Local treatment with antibiotics should be avoided, but wound cleaning should be thorough and if there is heavy colonisation or presence of biofilm the wound can be treated with for example polyhexanide, as a gel or a moist dressing, applied for at least 15-20 minutes. Especially in humane medicine there has been a change in attitude to the use of antiseptic solutions in wounds. One main reason is the aim to prevent antibiotics resistance, but also as a number of modern, non cell-toxic substances are now available on the market. In cases of infected wounds local treatment is increasingly common. The most relevant substances include honey, iodine, silver polyhexanide.

Silver dressings
Silver has been used for a long time in wound treatment, especially in humans, and is an ingredient in several types of dressings, but should only be used with clear indications and the treatment should be as short as possible. It should be noted that The Swedish Institute for Medical Evaluation (SBU) has declared that in human medicine silver dressings should only be used in the framework of controlled studies or with other systematic analyses and reporting of the effect.

Ionized silver has antibacterial effect against many bacteria. Modern silver dressings have a slow secretion of silver and lack many of the drawbacks that older silver preparations had. In addition, silver has anti-inflammatory effects and downregulates metalloproteases in slow healing wounds.   Reports of resistance development exist. Silver is available in several different bioactive dressings, sometimes combined with alginates or foam.

Iodine dressings
Iodine has been used for wound treatment for more than 150 years. Modern iodine dressings lack the drawbacks that previous versions had. Iodine has antibacterial effect against Gram-positive and Gram-negative bacteria. No development of resistance has been reported. Individuals with thyroid problems or large wounds should not be treated with iodine.

Polyhexanide (PHMB)
Polyhexanide impregnated dressings are relatively new in Sweden but has been used in human medicine in the rest of Europe during quite a long time. Polyhexanide is cytotoxic for bacteria including MRSA. No

resistance has been reported. Polyhexanide appears to have good ability to clean up contaminated wounds. It is available as flushing liquid, gel or a dressing. Dressings prepared with antiseptic substances can be used preventively in wounds with very high risk of infection but should not be a standard dressing for all wounds.

Medical honey

Medical honey has become increasingly important in modern wound treatment in humans. Honey has been used in wound treatment since pre-historic times and its antibacterial properties are well documented. Honey dressings have a debriding effect, removes odours and creates a moist environment in the wound. There are no reports of development of resistance.

Medical honey (Manukka honey from bees who has lived in a Manukka tree environment in Australia and New Zeeland) has an antibacterial effect due to several factors a lowering of the pH, but also immunomodulating properties. Honey also acts anti-inflammatory, has an osmotic effect and stimulates granulation and epithelization. The drawback is that honey can become occluding. Medical honey products should include a UMF (Unique Manuka Factor) value, which should be about 10-12 to secure the effect. Medical honey is available in a tube and in different types of dressings.

VASCULAR DISEASE

THROMBOPHLEBITIS

AETIOLOGY, GENERAL

Thrombophlebitis is an inflammation of the vessel wall of a vein, with or without infection and with or without a concurrent thrombus. The cause is often an irritation of the inside of the vessel wall by a catheter. Patients suffering infections, for example horses with diarrhoea, are more at risk of developing thrombophlebitis compared to healthy individuals. To prevent thrombophlebitis hygiene when placing a cannula is important. This requires hair removal with clippers that are cleaned and washed with surgical spirits between each patient, sterile wash of the skin and cannula insertion by a person who disinfects his/her hands and wear sterile gloves. Modern cannula materials make it possible to administer treatment longer without a change of cannula, as polyurethane is less of an irritant than materials used previously.

TREATMENT

Treatment of thrombophlebitis consist of local application on the skin with an NSAID-substance, possibly in combination with a systemic treatment with acetylsalicylic acid to hinder further thrombus formation. In cases of septic thrombophlebitis antibiotics, primarily penicillin, should be administered after the cannula has been removed and the tip saved for bacterial culture. The damaged vein should not be used for any injections until the thrombophlebitis has healed. If one of the jugular veins is heavily damaged the healthy jugular should not be used for a permanent cannula, as bilateral thrombophlebitis can cause oedema of the whole head due to lack of circulation. Surgery is very seldom necessary as the vein will eventually find a new route or develop collaterals.

LYMPHANGITIS

AETIOLOGY, General

The protein rich interstitial fluid in cases of lymphoedema is a good bacterial substrate. The entry route for bacteria (usually streptococci) is often a small skin wound on a leg. The infection spreads in the tissue along the lymphatic system. The horse will be acutely lame (hindlegs are more likely to be affected) and be clearly sore also at a very light touching of the swollen, oedemic area, and develop a fever. It is not unusual that the horse's general condition is also affected. If the infection proceeds abscesses can form in the damaged tissue or more phlegmon-like changes occur. In rare cases sepsis can occur.

Lymphangitis must be regarded separately from lymph oedema, which is a swelling in a body part due to reduced function in the lymphatic system. Secondary lymph oedema can be caused by impaired lymphatic circulation. Lymph oedema in the distal extremities of the horse are common. They are normally painless and disappear with work but can be obvious if the horse has been standing still all night without moving. Horses who due to injury are subject to lengthy box rest can easily get swollen legs, especially around the fetlocks, and should therefore wear leg bandages to reduce the oedema.

TREATMENT

Treatment consist of a revision of any wounds, cooling the legs by hosing them with cold water, massage- preferably in combination with the water hosing, aluminium acetotartrate bandage, rest with short walks by hand, NSAID (sometimes also glucocorticoids), systemic treatment with penicillin (in case of insufficient effect, broad spectra antibiotics are necessary). Possible abscesses should be incised. Repeated lymphangitis can result in the condition becoming chronic.

Treatment of lymph oedema is primarily increased exercise and secondly bandaging.

BACTERIAL SKIN DISEASE

Bacterial skin disease refers to conditions beyond wound infections and abscesses.

AETIOLOGY, GENERAL

The normal skin, hair and the normal microbial flora consist an effective barrier against infections, carrying both mechanical, chemical and immunological properties. Insult of the skin's protective barrier can however result in bacterial colonisation and infection. The emulsion of fat, sebum and sweat which are present on the cornified layer of the skin (*Stratum corneum*) pose both a physical and chemical barrier and contain for example fatty acids, ceramides, cholesterol, salts and proteins with antibacterial properties. Disruption of barrier integrity allows for proliferation and invasion of potential pathogens present on the skin. An intact protective barrier and hygienic routines in general will hinder the establishment of an infection.

A large number of factors can cause defects in the skin barrier. The most common for horses is friction, from tack, and maceration, due to moisture dissolving the protective barrier. Excessive washing and hosing of the skin results in a less dense *Stratum corneum* and the emulsion is reduced or disappears. Skin trauma of any kind, including micro-trauma, insect bites or itching, can also pave the way for microorganisms.

SUPERFICIAL PYODERMA

Superficial pyoderma/bacterial folliculitis is the most common type of bacterial skin infection and is primarily caused by some kind of insult of the protective barrier. This in turn paves the way for establishing a colonisation/infection by microorganisms. In superficial pyoderma the infection is confined to the epidermal layer and the hair follicles. There is often a mixed flora of bacteria, usually dominated by different species of Staphylococci, especially *Staphylococcus aureus*. Other agents are for example *Proteus* spp, *E. coli*, streptococci and *Pseudomonas* spp. This type of pyodermas most commonly occur on the horse's distal legs and is one of the most common causes of mud fever. Pyoderma can also evolve secondarily to almost any type of dermatosis, affecting the skin, resulting in defects of the skin's protective barrier.

DEEP PYODERMA

Deep pyoderma is a much less common form. In those cases, the infection has reached the dermis by breaking through the skin's basal membrane or by burst of the hair follicles. Clinically deep pyoderma presents with swelling, phlegmon, abscesses or draining fistula. In these cases, the infectious agent is usually also Staphylococci, but other types of bacteria occur. One particular form of deep pyoderma is so-called botryomycosis. These cases involve deep, nodular bacterial granuloma, normally associated with staphylococci. *Corynebacterium pseudotuberculosis* can also cause deep abscesses with fistula and diffuse cellulitis in horses but is very uncommon in Sweden.

DERMATOPHILOSIS

Dermatophilosis, also called rain scald or streptotrichosis, is caused by *Dermatophilus congolensis,* an actinomycete. The microorganism requires moisture and to become infectious, and also here a defect in the skin barrier is a prerequisite for infection. In a damp environment the microorganism releases flagellated zoospores. These can then cause infection if the animal's skin barrier is compromised, for example because the skin has been moist for some time. Outbreaks of the disease is therefore often seen after rainy periods. The microorganism can then survive in the environment several years and be a source of re-infection. Horses do not develop immunity to the bacteria after infection. Dermatophilosis can infect also other species, primarily cattle and sheep. As humans can occasionally be infected, dermatophilosis should be regarded as a zoonosis.

DIAGNOSIS

GENERAL

The clinical picture in superficial pyoderma is dominated by varying degrees of encrusted papules or crusty lesions with a more or less erythematous base. These clinical signs are however not pathognomonic for bacterial skin infections but can also be seen in a number of other conditions. An adequate investigation is therefore necessary for diagnosis.

The best way to confirm or exclude a bacterial infection is by a cytological analysis of samples taken from the skin. Tools needed are glass slides and the possibility to stain the sample, for example with Hemacolor or Diff Quick, immersion oil and a microscope

If crusts are present, remove the crus with a sterile skin scalpel. The glass slide can then be pressed against the moist underlying skin surface (impression smear). Alternatively, a cotton tip or the skin scalpel blade can be used to collect some of the surface material which then is spread on to the glass. If there is purulent exudate this can be spread on to the slide. In case of nodular lesions - take a fine needle aspirate and express the material to the glass. Let it dry. After staining the slide is examined by the microscope, with immersion oil under x 100. The cytological picture will quickly reveal whether bacteria are present, if there are coccoid or rod-shaped bacteria and if they occur intracellularly in neutrophils and/or macrophages. In addition, the cytology samples will give an idea about the number of bacteria and if there is a uniform or mixed bacterial flora. In dermatophilosis the typical branched chains of the coccoid bacteria can be demonstrated.

A culture sample with susceptibility testing is recommended in case a bacterial infection is demonstrated by microscopy and has been none responsive to empirical treatment or recurrent. A culture should also always be taken in cases where systemic treatment with antibiotics is considered. Samples for the culture can be taken with a culture swab or fine needle aspirate depending on the type of lesion. A biopsy, taken in a sterile manner and then placed in a sterile beaker with a few drops of sterile NaCl can also be sent for culture.

Biopsies can be used for culture (see above) but also histopathological analysis, which verify the diagnosis of bacterial infection. Histopathology is however more invasive, costly and time-consuming method compared to cytology. If a biopsy is taken from crusty areas, pay attention to include the crust in the vial sent to the pathologist. In dermatophilosis the diagnostic changes (typical bacterial chains) often are present in the crust itself.

SUPERFICIAL PYODERMA

Superficial pyoderma often occurs on the distal leg and areas subject to friction, for example the saddle area and where other tack is present. The coat will not be smooth and even in affected areas. Instead hairs will stand on end and papules and crusts can be palpated. The crust can fall off and leave a hairless area with erythematous (reddish) and scaly borders. The area can get increasingly larger, and underneath the crusts the skin can be erosive and moist or suppurative. Pain and oedema can also be noticeable factors in the clinical picture. In infections in the distal leg the scabs tend to be thick and adherent with erosions and exudate underneath. This in contrast to infections affecting other parts of the horse's body where crusts often are thinner and easy to epilate and without visible erosions and exudate underneath.

DEEP PYODERMA

Deep pyoderma cause phlegmons, draining fistula and nodules.

DERMATOPHILOSIS

Areas which get and stay damp over time (the back, legs) are predisposed for dermatophilosis. The coat hairs will become matted together and crusts can be palpated. These crusts are often quite thick, and the horse shows sign of pain if crusts are removed. During an active infection greenish pus is often present on the under surface of the crust. During healing the crusts are lost, revealing focal or multifocal alopecia., similar to superficial pyoderma/folliculitis.

HANDLING AND TREATMENT

Of prime importance for a successful treatment result is an understanding of the mechanism behind the development of pyodermas. The bacterial infection is secondary to a compromised protective barrier and once the infection is resolved the primary cause must be addressed. "Mud fever" with a bacterial infection

can primarily be caused by both lack of hygiene/grooming, or excessive cleaning and washing, constantly wet legs, (macerated protective barrier) due to muddy paddocks, *Chorioptes* infection, photo sensitivity, vasculitis etc, etc. Environmental factors which damage the protective barrier lead to secondary infections. Cytology then often show a rich, mixed flora of bacteria. If there is an outbreak of mud fever with several cases together an analysis of the environment and stable routines is needed to identify possible predisposing factors such as excessive grooming that cause trauma or maceration in the skin, excess of water, for example in muddy fields and from cleaning procedures macerating the skin. If the primary cause is not addressed the horse will have recurrent pyodermas and not recover in spite of repeated antibiotic treatment, also after bacterial culture. Horses who will be out in wet, muddy paddocks might need a protective layer of fat on the skin, to maceration. In all handling of patients, prudent hygiene routines should be adopted to minimize the risk of spreading infectious organisms. This is especially important with horses with pyoderma. MRSA has been demonstrated in horses, primarily in the nasal mucosa but also in wound infections, post-operative infections and also in rare cases pyoderma.

SUPERFICIAL PYODERMA

In superficial pyoderma the infection can usually be controlled with daily topical treatment only. What is most important is that the treatment reaches the site of infection, underneath any crusts. Many horses can be sensitive to the touch of affected areas and NSAID can sometimes be useful in order to allow appropriate treatment.

Scabs should preferably not be torn off, as that causes pain and increased inflammatory reaction. Instead they can be moistened prior to the use of antibacterial shampoo. Salicylic acid has keratolytic properties and can be used for example by applying salicylic acid vaseline at 2 % and leave it on for

½-1 hour before washing the affected area.

Antibacterial shampoos, containing for example chlorhexidine 2-4 %, benzoyl peroxide 2,5-3 % or ethyl lactate should be allowed 10-15 min before rinsing it off to be efficacious. Dry with towels afterwards.

After washing an antibacterial leave on product can be used. Examples of substances without antibiotics that can be used is for example alcogels, medical honey, 1 % hydrogen peroxide cream and 0,4 % stannous fluoride. In cases when topical antibiotics are judged to be necessary, premier tier is fusidic acid, as the substance often is effective against staphylococci and usually not used for systemic treatment of horses. Mupirocin should not be used as this substance is a key substance for elimination of MRSA in humans, and therefore should be reserved for this purpose. Also avoid the use of topical trimethoprim-sulpha. Staphylococci are often sensitive to trimethoprim-sulpha, but as the choice of oral antibiotics for horses is extremely limited this combination should be protected so that infections can be effectively treated with this substance also in the future. Topical use of penicillin (for example mammary tubes) should also be avoided as penicillin is a potent hapten that can induce contact allergy when used topically.

Topical corticosteroids might be needed to control any remaining inflammatory reaction when the infection is in remission. When the infection is controlled a remaining inflammatory reaction in the tissue can negatively affect the skin barrier, thus carrying a risk of re-infection. A short-term topical treatment with corticosteroids, for example hydrocortisone aceponate, hydrocortisone or betamethasone is often effective. Corticosteroids do though inhibit the phagocytic capacity of neutrophils and macrophages and can therefore have unwanted effects during an ongoing infection. Ear drops for treatment of infectious otitis externa in dogs contain both antibiotics, corticosteroids and antifungal substances, which should be considered. Corticosteroids can also induce cutaneous atrophy over time. The risk of inducing cutaneous atrophy, which is irreversible initially but later turns permanent, increases with the length of treatment and the strength (potency) of the corticosteroid used.

Systemic treatment with antibiotics is only indicated if an infection has been diagnosed and does not heal with topical treatment (antibacterial nursing as described above) or if a more deep-seated infection or lymphangitis has developed. Systemic treatment should always be based on results from bacterial culture and susceptibility testing.

DEEP PYODERMA

In cases of deep pyoderma systemic treatment with antibiotics should be considered, based on bacterial culture and susceptibility testing, and be continued until the infection is cured, which can take two or several weeks. In cases of botryomycosis surgical treatment is usually needed, and in some challenging cases also in combination with antibiotic treatment.

An analysis to identify and address the underlying, primary cause should always be made in case of recurring or deep pyodermas.

DERMATOPHILOSIS

Dermatophilosis is effectively treated by bactericidal washing (benzoyl peroxide 2,5-3% or chlorhexidine 2-4%) daily or every second day until the infection has healed. Any crusts should be collected and destroyed, as they contain large amounts of the bacteria. In cases when topical treatment is not feasible systemic penicillin or trimethoprim-sulpha is usually effective, even if resistance to trimethoprim-sulpha has been reported. Systemic treatment with antibiotics against dermatophilosis should be continued for 3-5 days.

SYNOVIAL AND OSSEOUS INFECTIONS

INFECTION AND/OR PERFORATION OF SYNOVIAL STRUCTURES

AETIOLOGY, GENERAL

Infections in synovial structures (septic arthritis, bursitis and tenosynovitis) in horses are a potential threat to the horse's athletic career and even its life. If infection is established the joint cartilage and intraarticular structures may be damaged and even destroyed. The inflammatory process releases a cascade of catabolic interleukins, enzymes and free radicals which add to the damage caused by the infecting organism. Cartilage damage in the adult horse is basically irreversible. In the best possible case the hyaline cartilage is replaced by functional scar tissue (fibrous cartilage). Consequently, a joint infection should be treated with urgency and efficiency. Bacterial infections are by far the most common.

Joint infections can occur in three different ways:

Hematogenous infection
Foals with inadequate transfer of maternal antibodies have a highly increased risk of developing bacteraemia and hematogenous joint infections (and infections of tendon sheaths and bursae). Pathogenic bacteria can invade the blood circulation from the gastrointestinal tract, the umbilicus and the lungs. Inoculation of the joint will be classified in relation to the site of infection; synovia and synovial membranes (S-type; the foal is usually less than one week old), the subchondral bone (E-type; the foal is usually several weeks old) or the growth plate itself (P-type; foals a few weeks to several months old). Clinical signs are fever, joint effusion, periarticular swelling, and lameness.

All types of bacteria seen in neonatal sepsis can also cause septic arthritis/bursitis/tenosynovitis; for example, *Enterobacteriaceae* (*E. coli*, *Klebsiella* and *Salmonella* spp), *Actinobacillus* spp, *Pasteurella* spp, *Streptococcus* spp, *Staphylococcus* spp and also *Rhodococcus equi* in older foals.

Hematogenously spread agents causing joint infection or infection of tendon sheaths and bursa are unusual in adult horses but may occur.

Joint infections after penetrating wounds and infections in periarticular structures
Wounds penetrating to a joint / tendon sheath / bursa can cause synovial infections. Infected wounds and infected structures in the vicinity of a synovial structure may result in a secondary synovial infection. In all cases of wounds close to a joint, tendon sheath or bursa any possible penetration of the synovial structure and any contamination and infection should be checked for and excluded.

A horse with established synovial infection will usually show clinical signs like marked lameness (even at walk), marked effusion (of the affected synovial structure), diffuse swelling around the synovial structure, and in most cases a raise in temperature (sub febrile to febrile). If the joint capsule/ tendon sheath or bursa wall is open and can drain freely the horse will often show no or low-grade lameness, no effusion and little change of temperature. In this type of situation, it is not uncommon that the horse owner underestimates the seriousness of a wound and treats the horse at home without veterinary involvement. Days or weeks later, when the wound is healing and the drainage is closed, the horse will show the clinical signs of a synovial infection.

Common causes are bacteria from the skin and environment, for example *Streptococcus* spp, *Staphylococcus* spp*, Enterobacteriaceae, Pseudomonas* spp and anaerobic bacteria.

Iatrogenic infection
Iatrogenic inoculation of bacteria can occur after surgical procedures such as arthrotomy and arthroscopy/tenoscopy/bursoscopy or synoviocentesis (puncture/injection of synovial cavity). Clinical signs of an iatrogenic infection can occur several days or weeks after the procedure performed. With surgical site infections, clinical signs usually appear once the sutures have been removed. Clinical signs will be distension of the synovial structure, diffuse swelling (possibly focal at the site of an infected endoscopy portal), lameness and possibly fever.

It is not unusual that the clinical signs are less obvious than in septic synovitis after trauma, as previous treatment with steroids and/or concurrent treatment with NSAIDs will reduce the clinical signs. Especially iatrogenic synovial sepsis following steroid treatment may have an insidious onset and may be neglected by the owner and treating veterinarian for days.

A joint infection after arthroscopy is a rare complication, most will be related to infections related to the surgical portals and suture removals, primary joint infections are very rare. No significant prophylactic effect of perioperative antibiotics in connection with equine or human arthroscopy have been shown.

Perioperative antibiotic treatment can be considered for procedures that involve implants, biomedical preparations (for example stem cells or transplants), when multiple joints are operated during the same anaesthetic, or when surgery time is prolonged > 90 minutes).

Joint infections after a correctly performed intraarticular injection is highly unusual. A retrospective study at the Helsingborg Equine Hospital showed that out of 14124 i.a. injections during 5138 patient visits the incidence of iatrogenic joint infections was 0,075 percent, with all substances included. There was no case of joint infection when only a local anaesthetic had been administered. The analysis however showed a significantly increased risk of infection after treatments combining glucocorticoids (steroids) and polysulphated glucosaminoglycans.

Prophylactic antibiotic treatment in connection with intra articular joint treatments is not considered proper veterinary practice in Sweden. Diagnostic local joint anaesthetics and i.a. treatment should only be performed with strictly aseptic techniques. Prophylactic antibiotics use is not an alternative to strict aseptic techniques.

Avoid the combination of a steroid and polysulphated glucosaminoglycans.

Staphylococcus aureus is the most common (> 30 percent) bacteria in cases of iatrogenic synovial infections, both after synovial injections and surgery. Other bacteria involved in synovial infections include *Staphylococcus* spp, *Streptococcus* spp, *Enterobacteriaceae* and *Pseudomonas spp.*

DIAGNOSIS

An infection in synovial structures should be considered in cases with the following clinical signs and case history: lameness, joint effusion, periarticular swelling, fever, wounds close to a synovial structure and/or previous treatment/surgery in the area.

It is very important that the veterinarian has a detailed understanding of equine anatomy when evaluating wounds. When a synovial infection can be suspected the diagnosis should be verified and correct treatment started immediately.

Synoviocentesis should be performed under strict aseptic conditions in horses with a suspected synovial infection. The synovial fluid should be evaluated by ocular inspection, cytological analysis and a total protein count should be performed. Part of the sample should be submitted for bacterial culture in dedicated enrichment media (aerobic and anaerobic). Horses with wounds located near a synovial structure should be evaluated by distension of the joint/tendon sheath/bursa to demonstrate possible communication with the wound, and intrasynovial antibiotics should be administered at the end of the procedure. An aminoglycoside is first choice.

Synoviocentesis in a horse with a suspected synovial infection should preferably be performed under sedation. An inflammation of synovial and adjacent structures makes the horse hypersensitive to touch and manipulation of the joint (for example if the leg is lifted during the procedure). If the synovial membrane is inflamed or the joint (tendon sheath/bursa is filled with fibrin, it can be difficult to get enough synovia for cytology and bacterial culture. It might be necessary to repeat the sampling several times until a sufficient amount of synovial fluid has been collected (preferably 4-6 ml).

Normal synovia is clear, light yellow and viscous. If the synovial fluid is thin, opaque, yellow or reddish brown, this strongly indicates an infection with a high cell count.

Normal joint fluid has a cell count of $\leq 0,5 \times 10^9$ cells/L. Infected synovia commonly has a cell count of $>20 \times 10^9$ cells/L, however the cell count can vary greatly depending on when in the process the synovial sample is collected. Situations when the cell count can be low in spite of an infection is for example if the synovial structure has drainage, has a large accumulation of fibrin and cells, or in cases of chronic *Staphylococcus* infection (cell counts of $5-10 \times 10^9$ cells/L). If the horse is displaying clinical signs of a synovial infection and the sample is not contaminated by blood, synovial infection also should still be considered even with a cell count at $5-10 \times 10^9$ cells/L. The number of neutrophil granulocytes in the synovia is usually <10 percent. In case of a joint infection it rises to ≥85 percent, with varying toxic changes. The amount of protein in the synovia can be measured by a refractometer; the normal value is 8-25 g/L, with an infection

the protein value rises to 40-80 g/L. In chronic infections the cell count can be low, but the protein content high ≥55 g/L.

In wounds, bleeding due to penetration can cause synovia to be mixed with blood. To make an estimate of what portion of the cell count that derives from the blood the following formula can be used (relevant if the contamination is from pure blood):

(Haematocrit, synovia)/ (Haematocrit, blood) = (No. of leukocytes, synovia)/ (No. of leukocytes, blood)

It is important early on to try and determine what type of bacteria that has caused the infection. If the horse does not respond to the chosen antibiotic treatment is important to have determined what organism has caused the infection, and any possible antibiotic resistance. Joint fluid should be collected and transferred to blood culture bottles (both aerobic and anaerobic). The culture method enriches low bacterial counts. To avoid contamination and misleading culture results proper aseptic sampling should be used. Culture of samples where synovial fluid has been transferred to a swab for transport to the laboratory has insufficient sensitivity. The reported frequency of positive culture results from synovia varies between 30 and 79 percent. The chance of getting a positive culture result varies with the type of patient, inclusion criteria and the method of culture.

Radiography is an important diagnostic aid for demonstrating intraarticular gas shadows, to exclude any possible intraarticular fractures and any possible foreign bodies. Radiography should be performed before synoviocentesis. Contrast radiography can demonstrate possible communication between the wound and any synovial structure. Ultrasound can be very valuable and demonstrate an inflamed synovial membrane, intraarticular fibrin and accumulations of cells, cartilage defects, fractures and fissures, foreign bodies and any communication with a wound. In chronic infections osteomyelitis can be demonstrated with radiography (in foals already within 7-10 days), and in an early stage with CT and/or MRI.

Distension of a synovial cavities can be performed for diagnostic purposes in horses where you want to test for any possible communication between a wound and a synovial structure. The volume depends on what anatomic structure you want to examine. Expect to use a volume 3-5 times higher than the volume you would use for a diagnostic anaesthesia. If you have excluded any intraarticular fracture it can be easier to perform the distension if a regional nerve block is first performed to provide local anaesthesia, or alternatively to first distend the synovial cavity with mepivacaine 2% followed by isotonic saline (NaCl). High intraarticular pressure is painful and the horse can show violent reactions. If spontaneous communication between the synovial structure and the wound is not demonstrated the leg should be flexed and extended, alternative the horse can be led for a few steps before a suspected communication is excluded. Please observe that it is not unusual that communication with a wound is found, when the wound is debrided under general anaesthesia, even if pre-surgery distension tests were negative.

Synoviocentesis should be followed by intrasynovial treatment with a concentration dependent antibiotic with bactericide effect; an aminoglycoside is a natural choice.

TREATMENT

An infection of a synovial structure is a potential threat against the horse's athletic function and treatment should commence before the result of a bacterial culture is available. Surgery is usually needed for successful results. When a joint infection is suspected the veterinarian in the field should contact a referral clinic to handle the case, before treatment commences.   The decision if antibiotics treatment should be started immediately or not is taken in consultation with the referral clinic. As a positive bacterial culture can be very valuable later on both systemic and local antibiotics should not be administered until synovia has been obtained for culture. The exception can be acute wounds, where it can be suspected that antibiotics given at an early stage can prevent infection.

In iatrogenic infections and infections of older wounds, the infection will be established and immediate initiation of antibiotic therapy will have little effect on the outcome compared to the value of having a result from bacterial culture. Antibiotic treatment can be delayed for some hours until synovia has been obtained for culture.

In fresh (less than six hours) perforating wounds with minimal contamination a synovial infection can potentially be prevented; the bacterial flora is often a mixed flora and it is not obvious that the bacteria which is isolated corresponds to which organism that might later cause an infection. If the horse is being transported far (more than 4 hours) to a clinic/equine hospital before synovia can be cultured the wound should be cleaned, covered with a sterile bandage for the transport and given local and systemic antibiotic.

A retrospective study of wound cases at the Helsingborg Equine Hospital the time from when the wound occurred until arrival at the hospital was more important for the culture result than whether antibiotics

therapy was started before referral. In positive culture results there was a significant association with the horse having had clinical signs for at least 24 hours. Antibiotic therapy before sampling/referral did not affect the results. However, a bacterial culture should be performed before starting antibiotic therapy.

Broad spectrum systemic antibiotic therapy against both Gram positive, Gram-negative and anaerobic bacteria is indicated in order to fight the pathogen as quickly as possible. Once a positive culture result is available the therapy should be adjusted so that the choice of antibiotics is appropriate based on the organism and pattern of resistance. If a culture result is negative and the infection does not respond to treatment, a new surgical procedure should be performed (arthroscopy/tenoscopy/bursoscopy) for sampling and debridement of infected tissue. Change in antibiotics strategy can be considered, for example change of substance or route of administration, however it is not unusual that an infected synovial cavity requires more than one surgical debridement and lavage before significant improvement is seen. If clinical signs persist another surgical intervention should be considered before changing antibiotics, unless a bacterial culture shows otherwise.

In cases of infection of synovial structures, it is seen as important that an antibiotic with bactericidal effect is used. To reduce the damaging effect of the immune system on the joint, the pathogen should be fought with minimum "assistance" from the immune system. Surgical lavage is used to remove both bacteria, catabolic enzymes and phagocytic cells from the joint.

International studies have shown that the combination of penicillin and gentamicin has effect on >85 percent of pathogens isolated form infected joints. This has been confirmed in Sweden in a large retrospective study of cases at the Helsingborg Equine Hospital. (Synovial culture from 259 horses with suspected/confirmed joint infection).

Both penicillin and gentamicin achieve sufficiently high concentrations in joints during systemic treatment. The combination of penicillin and gentamicin is therefore recommended as the primary choice in initial systemic therapy of equine synovial infection in Sweden. The systemic treatment can be combined with local therapy with an aminoglycoside, primarily gentamicin.

For systemic treatment of foals with hematogenic synovial sepsis please note the section on foals and neonatal septicaemia.

Local therapy with aminoglycosides has been shown to be very valuable. Experimental and clinical studies have shown that you can achieve concentrations 5-100 times what is achieved with systemic administration. Local administration methods include intrasynovial injections, regional intravenous perfusion, regional osseous perfusion, administration via a "constant rate infusion" catheter, placed intrasynovially, implantation of various antibiotic impregnated material (e.g. gentamicin impregnated PMMA-pearls). In intrasynovial injection with Gentamicin the dose is 100-500 mg.

In regional IV perfusion the gentamicin dose is up to 500mg. The solution should be diluted so that the concentration of gentamicin does not exceed 5 percent. Higher concentrations are tissue irritant and may cause thrombophlebitis. In local treatment it is also important to pay attention to the total systemic dosage of the chosen aminoglycosides so that it does not exceed the recommended amount. This is especially important with foals.

Joint infections and wounds that penetrate joints and other synovial structures require surgery in order to maximize the chances of successful healing without reduced athletic function. Diagnostic and surgical endoscopy offers visualization and cleaning of intrasynovial lesions and focus for persistent infections such as cartilage defects, pannus, accumulation of fibrin and cells, necrotic and contaminated tissue and foreign objects. Wounds entering a synovial cavity can be visualized by endoscopy. The endoscopy is done after standard cleaning of the wound and endoscopic intrasynovial debridement can be performed. Endoscopy is also very valuable in iatrogenic infections after injections. Cartilage defects, pannus and accumulation of fibrin and cells are common in these cases and require surgical intervention. Endoscopic debridement reduces the demands on the immune system to fight the infection.

Synovial infections can be treated by repeated needle lavage, however there is a risk that a focus for infection is missed. If the horse does not respond to treatment diagnostic and surgical endoscopy is recommended. In chronic infections that are difficult to treat arthrotomy and drainage through the arthrotomy wound can be valuable.

It is recommended to continue treatment until at least three days after clinical signs have ceased and synovia cytology values have been normalized.

INFECTIOUS OSTEITIS - OSTEOMYELITIS

AETIOLOGY, GENERAL

Bone inflammation (osteitis) is in general seen in association with inflammation of both the periosteum (periostitis) and bone marrow (osteomyelitis). Common pathogens are *Enterobacteriaceae,* beta haemolytic streptococci, staphylococci and pseudomonas spp.

Infected wounds with bare bone can be one cause of secondary osteomyelitis. Osteomyelitis caused by hematogenous spread of bacteria in animals is unusual, except in foals. A purulent osteomyelitis will in generally result in a more or less widespread necrosis in the affected bone. The necrosis can be separate from surrounding tissue and finally become loose, creating a sequestrum. This can result in a fistula, as the sequestrum acts as a foreign body.

If the infection in the bone is not limited, as occurs with a sequestrum, the infection will spread in the bone and widespread necrosis will form. In the acute phase radiographs rarely detect any visible changes. They will show only after about a week as lysis of the bone. Initial radiographs are always valuable to evaluate changes over time.

DIAGNOSIS

In acute osteomyelitis the patient will have fever and moderate to severe pain, and the horse may be non-weight bearing lame. A sample for bacterial culture should be taken from the infection site before systemic treatment is commenced.

HANDLING AND TREATMENT

Sequestrae can be resorbed by the body or require surgical removal, but only rarely cause any serious symptoms in the animal, and seldom require antibiotic treatment.

In acute osteomyelitis systemic antibiotics must be administered for a long time. If the infection has spread from a septic joint in a foal aggressive surgery with arthroscopy and cleaning of the infected joint plus curettage of the infected subchondral bone is necessary. There can also be a fracture fragment which must be removed if the infection is to heal.

Penicillin is the primary choice in septic processes involving the skeleton and may be combined with gentamicin if coverage of Gram-negative bacteria is considered necessary.

RESPIRATORY TRACT INFECTIONS

AIRWAY INFECTIONS SUMMARY

Respiratory disease is probably the most common cause of antibiotics treatment in horses, in spite of a lack of scientific documentation of the efficacy. Equine airway infections are mainly caused by viruses, but the underlying cause of symptoms can be difficult to diagnose. Therefore, it can be difficult to determine if any possible bacterial infection is primary or secondary. In the early stages of a bacterial upper respiratory tract infection it can also be a challenge to give a prognosis on whether the horse will be able to fight the infection. Choosing treatment and recommendations for prevention of respiratory disease in race- and sport horses is a major challenge for equine vets.

Decisions on further examinations and testing is based on the clinical history and results from the clinical exam. In cases other than acute uncomplicated upper respiratory tract infection a thorough endoscopy exam of the pharynx, nasal cavity and guttural pouches will provide guidance for further diagnostics.

Samples for viral testing can be taken from specific areas, for example from nasal discharges (viral swab), nasal wash, from the pharynx with a longer testing swab, or by saline lavage. PCR-analysis for detection of virus in a nasal swab test in early stages of disease is a good alternative to serological diagnostics of antibodies, as serology can only be performed after the acute phase. Blood analysis can be used especially in diagnostics of bacterial airway infections (haematology, acute phase proteins). Samples from the nasal cavity is usually contaminated by the normal flora and there is a considerable risk of over-interpreting the result or missing pathogens. If bacterial respiratory disease is suspected general sampling from the trachea or guttural pouches is recommended.

The upper respiratory tracts contain a normal flora which contain a large number of different bacterial species. Bacteria can normally also be isolated from the trachea. For example, many healthy horses have colonisation of *Streptococcus zooepidemicus,* which is a common cause of infection. The clinical relevance of bacterial findings in the airways can therefore be difficult to judge. It is important that any findings are evaluated together with all other information from clinical exams and test results from for example haematology and cytology.

With both tracheal aspirate and lung rinsing sampling it is very important to observe standardised testing methods and timing. These samples are primarily collected for cytology and microbial analysis. The test results are markedly affected by sampling techniques (volume and type of liquid used), the timing of sampling in relation to transport and/or lab work, the time elapsed between sampling and analysis and sample handling and analytic methods in the appointed laboratory. Tracheal aspirates or transtracheal aspirates are primarily used for bacterial culture, as secretions from the entire respiratory system accumulate in the trachea. In order to avoid contamination protected testing catheters can be used.

Further diagnostic options for investigating lung disease are for example x-rays, ultra sound, arterial blood gas analysis, scintigraphy, biopsies and different lung function testing.

A majority of airway infections that do require antibiotic treatment are caused by streptococci, which is why benzyl penicillin is often a suitable choice. Based on the oral preparation and withdrawal aspects horse owners often prefer trimethoprim sulphonamide. Trimethoprim sulphonamide is however in these cases a poorer choice from a bacterial viewpoint and as oral antibiotics available for equine are extremely limited, this substance should be preserved for those cases when it is correctly indicated.

UPPER RESPIRATORY TRACT INFECTIONS

AETIOLOGY, SUMMARY

Infections in the upper respiratory tracts including the trachea is a common cause of antibiotic treatment in horses. The diagnosis is based on clinical symptoms (poor performance and coughing) plus endoscopy (secretions from the throat or trachea, signs of pharyngitis). Horses become less susceptible with age, probably due to a combination of age-related immunity and immunity against pathogens in the environment. Bacteria associated with infections of the upper respiratory tract are primarily opportunistic species including *S. zooepidermicus*, *S. pneumoniae, A. equuli* and *Pasteurella spp*.

DIAGNOSIS

A diagnosis of bacterial upper respiratory tract infection is based on the case history and clinical symptoms (poor performance and coughing), plus endoscopy (secretions from the throat or trachea, signs of pharyngitis) plus bacteriological testing and resistance testing. If a throat infection is suspected samples can also be taken by a nasal wash or sampling with a longer swab. If a bacterial infection of the trachea is suspected the diagnosis can be confirmed through cytology. There are however contradicting views on interpretation of results. Tracheal aspirate is used for bacteriological culture when a tracheal infection is suspected. To avoid contamination protected swab catheters can be used, if the sample is taken by endoscopy, alternatively the sample can be taken through transtracheal aspiration. The culture result should be interpreted with caution, as the lower respiratory tract is regularly exposed to bacteria from the upper respiratory tract, which can then be isolated in the trachea in spite of no infection being present. Inflammation of the trachea can result in secondary colonisation of bacteria from the throat due to poor mucociliary clearance, without any primary or secondary bacterial infection being present. The overall clinical picture (case history and clinical exam) together with results of diagnostic tests pose the basis for treatment decisions.

HANDLING AND TREATMENT

Results from bacteriological testing should be interpreted in the light of the horse's symptoms. Many horses can have signs of bacterial colonisation in the trachea, without needing antibiotics treatment. Antibiotics treatment is relevant in specific cases of disease outbreaks and confirmed bacterial infection that does not resolve on its own. Basically, streptococci infections are the most common and benzyl penicillin is a suitable empirical choice.

INFLAMMATORY AIRWAY DISEASE

AETIOLOGY, SUMMARY

Inflammatory Airway Disease (IAD) is a term for a number of conditions involving inflammation of the upper airways of unknown or varying causes (bacteria, virus and environmental factors) primarily in young racehorses. Horses become less susceptible with age, probably due to a combination of age-related immunity and immunity against pathogens in the training environment.

DIAGNOSIS

A number of diagnostic tests may be needed to determine the aetiology behind the inflammation. The diagnosis is based on the case history and clinical symptoms (poor performance and coughing), endoscopy findings (secretions from the throat or trachea, signs of pharyngitis), bacteriological sampling and resistance testing (see the section on upper respiratory tract infections) plus cytological analysis of lung wash samples (possibly also tracheal aspirate).

HANDLING AND TREATMENT

The overall clinical picture (case history and clinical exam findings) together with the results of diagnostic tests guide the treatment options. If test results point to a bacterial cause of IAD the treatment principles are the same as for upper respiratory tract bacterial infections. In addition, the treatment regimen should address underlying factors, for example environmental factors, possibly in combination with inhalation treatment in cases of non-infectious inflammation.

GUTTURAL POUCH INFLAMMATION AND INFECTION

AETIOLOGY

Both bacterial and viral infections can cause inflammation of the guttural pouch mucous membrane. Accumulation of mucopurulent/purulent mucus in the guttural pouches can be observed secondary to airway infections, especially in young horses. *Streptococcus equi* (strangles) is a common cause of accumulation of mucus and pus, associated with abscesses in the retropharyngeal lymph nodes.

DIAGNOSIS

Clinical symptoms of guttural pouch infections are an intermittent, often unilateral, purulent/mucopurulent nasal discharge, swelling in the parotic region and in severe cases difficulties breathing and swallowing, plus low head carriage with a stretched neck. Guttural pouch infection is diagnosed by endoscopy and should include bacteriological testing to exclude *S. equi* infection (for strangles diagnosis see below). X-rays can be used if the endoscopy exam fails.

HANDLING AND TREATMENT

Local treatment of the guttural pouches is performed by removing the accumulated secretions in the guttural pouches through lavage, or in severe cases, surgical drainage, for example of heavy pus or presence of chondroids in *S. equi* infection. Systemic antibiotics treatment is indicated after sampling and resistance testing. As in other airway infections penicillin is the empirical choice awaiting bacteriological culture results. In cases with a considerable accumulation of chondroids in the guttural pouch, surgical drainage can be considered.

SINUSITIS

Infection or inflammation of the guttural pouches is sometimes a complication to upper airways infections. Usually the sinusitis is unilateral. Sinusitis can be primarily bacterial or fungal but may also be secondary to dental problems, trauma, cysts, ethmoidal hematoma or sinonasal neoplasia.

AETIOLOGY

Several bacteria can be involved. One common agent is *Streptococcus zooepidemicus*, alone or often in combination with aerobic or anaerobic bacteria (especially with secondary sinusitis). Culture results can therefore be difficult to interpret.

DIAGNOSIS

The clinical symptoms are purulent nasal discharge (often unilateral), sometimes enlarged submandibular lymph nodes and sometimes in chronical cases, swellings across the sinuses or exophthalmos. Endoscopy shows a purulent flow from the opening of middle nasal meatus. The percussion tone can be unchanged across the affected sinus. A complete oral exam should be performed to exclude dental problems as the primary cause. X-rays can be used for the same purpose and to evaluate the volume and localisation of exudate in the sinuses. Sinuscopy of the affected sinus is a sensitive examination method that ensures optimum sampling for bacteriological culture and resistance testing. Imaging such as MRT and CT can be used, especially to diagnose the aetiology of secondary sinusitis.

HANDLING AND TREATMENT

Penicillin is the empirical primary choice when treating acute primary bacterial sinusitis. However, the diagnosis is usually made in a more chronical phase, (> 2 months duration), when surgical drainage and lavage is usually necessary. During surgery a bacteriological sample is also taken. In secondary sinusitis it is important to treat the primary cause, as antibiotics treatment in general only provide temporary relief if the primary cause has not been removed.

PNEUMONIA AND PLEUROPNEUMONIA

Pneumonia and pleuropneumonia are relatively uncommon in adult horses. Pneumonia is more common in foals. Pneumonia and pleuropneumonia in adult horses is often caused by opportunistic bacteria and associated with stress, for example after long transports that weaken the defence mechanisms of the respiratory tract, and as a complication to equine influenza. Pleuropneumonia in horses is a serious condition that in quite often is life threating and in general requires equine hospital care.

AETIOLOGY

Several bacteria can be involved in equine pneumonia. *S. zooepidemicus* alone or in combination with other aerobic or anaerobic bacteria is common. In foals *Rhodococcus equi* can cause pneumonia (see separate section on foals).

DIAGNOSIS

The clinical symptoms vary markedly. In general pleuropneumonia has an acute and serious disease course. The horse can suffer severe malaise and show varying degrees of anorexia, fever, affected breathing (increased lung sounds) and nasal discharge. Horses with pleuropneumonia show more serious symptoms related to pain from the thorax: elbow abduction, pain response with pressure between the ribs/sternum, silent breathing sounds at auscultation/percussion ventrally over the lung field, that indicate fluids in the thorax and possibly ventral oedema. Some horses show colic like symptoms and have difficulties moving.

The diagnosis is made with the help of the case history, clinical symptoms, endoscopy, haematology, x-ray exam, ultrasound exam, and bacteriological tests (tracheal aspirate/aspirate from thorax in cases of pleuritis). The bacteriological tests should include both anaerobic and aerobic bacteria.

HANDLING AND TREATMENT

In general streptococci infections are most common in horses. For horses including older foals with mild pneumonia and without general malaise benzylpenicillin is usually sufficient. It is very important that the horse owner receives thorough instructions about monitoring the horse's condition, including by regular temperature checks, and follow-up contacts with the veterinarian.

Pleuropneumonia is often life threatening and the treatment is started on empirical grounds. In pleuropneumonia and severe pneumonia intravenous treatment with benzylpenicillin and gentamicin can be motivated awaiting test results. International literature also suggests use of metronidazole in serious infections, as they could involve some anaerobic bacteria such as *Bacteroides fragilis.* It is not clear to what extent penicillin resistant *B. fragilis* occur in Sweden.

In pleuritis/pleuropneumonia surgical drainage of the thorax may be necessary. The patient should in addition receive supportive care, intensive if needed.

ASPIRATION PNEUMONIA

AETIOLOGY, SUMMARY

Aspiration pneumonia can occur as a complication to choking and some throat surgery, and in some throat diseases. The symptoms after aspiration vary, partly associated with the volume and type of substance that

have entered the lungs. Aspiration often causes pneumonia and/or abscess formation in the lung. The upper airways contain a mixed flora and several agents are often involved. *S. zooepidemicus* in combination with other Gram positive and Gram negative aerobic or anaerobic bacteria are commonly involved.

DIAGNOSIS

The diagnosis is made based on case history, clinical symptoms (the same as in bacterial pneumonia), endoscopy, haematology, x-rays, ultrasound and bacterial culture of tracheal aspirate, and in pleuritis aspirate from the thorax.

The bacteriological testing should include both anaerobic and aerobic bacteria. Interpretation of culture results are challenging as bacteria that occur naturally in the upper airways and in feed contaminate the lower airways in connection with aspiration. The culture results should therefore be interpreted with caution.

HANDLING AND TREATMENT

Many cases of choking do not result in aspiration pneumonia and do not require initial antibiotics treatment. Once the blockage is resolved it is however very important that the horse owner monitors the horse carefully, including by temperature checks, and have follow up contacts with the vet. In some cases, antibiotics treatment can be considered before signs of infection. The choice of treatment should consider the horse's symptoms and how serious the suspicion of aspiration is. If the suspected aspiration is believed to be mild benzylpenicillin is regarded as sufficient. If the infection is manifest it is treated based on results from bacteriological culture. As the condition is serious, treatment with benzylpenicillin and gentamicin can start awaiting the result of bacteriological culture, and the horse will require intensive and/or supportive care.

International literature also suggest treatment with metronidazole as certain anaerobes such as *Bacteroides fragilis* might be involved. It is unclear to what extent penicillin resistant *B. fragilis* occur in Sweden.

STRANGLES

SUMMARY

Strangles is a bacterial airway infection caused by *Streptococcus equi* subspecies *equi.* The disease is notifiable by Swedish law, at the first suspicion of infection (SJVFS 2012:24; "K4"). In its classic form (often young stock and other horses without previous immunity) the symptoms are fever, malaise, difficulties swallowing, coughing and a nasal discharge that quickly becomes purulent. After a few days' swellings and abscesses appear in the submandibular lymph nodes. Retropharyngeal lymph nodes are often affected and might rupture into the guttural pouches. The disease can cause serious complications such as constrictions in the upper airways (restricted breathing and throat function), purpura haemorrhagica, bastard strangles or immune mediated myositis. Horses that undergo tracheotomies also are at risk for pneumonia/pleuropneumonia. The disease can also have much milder symptoms, for example only a nasal discharge or coughing without a high fever. After recovery some horses will carry the bacteria in the guttural pouch for lengthy periods, so called silent carriers. They pose a challenge to vets both from a diagnostic viewpoint, and regarding treatment and preventing the spread of infection.

DIAGNOSIS

The diagnosis is made based on clinical symptoms and test results. Bacterial culture and/or PCR-diagnostics is used to confirm a suspected strangles infection. If samples are taken in a field situation without an endoscope a throat lavage or nasal swab samples, with special swabs with nylon fluff and transport medium that have higher sensitivity than traditional bacterial swabs. Sampling from an abscess is also possible. Samples from the guttural pouch is taken with the help of an endoscope. A negative nasal swab test does not exclude an infection as it offers poorer sensitivity than samples from the throat or guttural pouches. *S. equi* can remain in the guttural pouches for long periods after the horse seems to have recovered from the infection. Identification of such carriers is a challenge. They can be identified through repeated sampling from the guttural pouch or throat lavage. Serological diagnostics might be useful to demonstrate previous exposure, for example if bastard strangles or purpura haemorrhagica is suspected, but cannot be used for diagnosis in the acute phase and probably not either to identify possible carriers.

HANDLING AND TREATMENT

The prime focus with strangles cases is to prevent spread of the disease. An affected horse should be placed in isolation, if that is possible. SVA (www.sva.se) offers rules and guidelines on preventing a spread of the disease, and handling of the infection in an affected yard.

Whether to treat strangles with antibiotics or not is a debated subject. In most cases the horse will recover without antibiotics, but with supportive treatment, possibly in combination with surgical drainage of abscesses. If antibiotics treatment is deemed necessary it should commence at an early stage of the disease, before any abscesses have formed, and the horse must be isolated from suspected carriers to avoid reinfection. Horses treated early on in the disease process do not develop immunity and there is a risk of reinfection. In severe cases with complications antibiotics can be indicated (throat swelling, bastard strangles, infections of the guttural pouches, persistent fever etcetera). In cases of silent carriers where the bacteria persist in spite of lengthy convalescence antibiotics treatment can be indicated to contain spread of the disease. This should include an investigation of all horses in the stable. Literature describes a combination of local and systemic treatment in cases of a chronic guttural pouch infection. When antibiotics treatment is indicated penicillin is the primary choice.

NEONATAL DISEASE

GENERAL

There are important differences between neonatal foals and adult horses that have to be considered when determining antimicrobial therapy. New-born foals have a larger proportion of extracellular fluid in the body, which results in a larger volume of distribution. This means that the dosage of certain medications has to be increased in foals in order to achieve therapeutic concentrations. At the same time clearance can be reduced, which also affects the calculations of the maintenance dose. It is important that the veterinarian in charge is aware and informed about how the dosage of the chosen antibiotic should be adjusted based on the age of the foal, as dosages for adult horses cannot always be extrapolated to foals. One example is gentamicin, where studies have shown that foals younger than two weeks of age require a higher dose but with an increased dose interval compared to the recommendation for adult horses in order to reduce the risk of kidney injury.

Other parameters such as increased oral bioavailability and a more penetrable blood-brain barrier in young foals can be an aspect in the choice of antibiotics. For septic foals or when there are other reasons to suspect a reduced absorption from the gastrointestinal canal, parenteral administration is preferable.

NEONATAL SEPTICAEMIA

AETIOLOGY, GENERAL

Septicaemia is the single largest cause of mortality in foals up to seven days of age. Foals are born immunocompetent but without protective levels of antibodies, which is why colostrum intake shortly after birth is of importance to prevent life threatening infections. In the absence of this protection, bacteria that are part of the normal flora can cause sepsis. Apart from controlling early colostrum intake, cleaning the mare and the surroundings in connection with foaling can help prevent infections in the foal.

Routine prophylactic antimicrobial treatment of the new-born foal is not a substitute for good hygiene and colostrum intake, and not accepted practice in Sweden. Such use of antibiotics has not been shown to be effective in preventing infections.

DIAGNOSTICS

Blood culture is the "gold standard" for diagnosis of septicaemia, but false negative culture results are common and there is a lag period before results can be obtained. Infections are usually caused by Gram negative bacteria (in one Swedish study primarily *E. coli* and *Actinobacillus* spp), but infections with Gram positive bacteria appear to be increasing and mixed infections occur. A preliminary diagnosis of sepsis is made based on clinical findings, haematology, analysis of acute phase proteins and serology for antibody levels in combination with the clinical history.

HANDLING AND treatment

Due to the disease process in SIRS (systemic inflammatory response syndrome), where circulatory shock and organ dysfunction can occur quickly, it is not an option to wait for bacterial culture results before

antibiotic treatment is commenced. When sepsis is suspected in a neonatal foal, treatment with a broad-spectrum antimicrobial should be initiated immediately, prior to obtaining culture results. An analysis of blood culture results from SVA between 1988 and 2005 show that penicillin and trimethoprim-sulpha in combination has a good effect *in vitro* in most cases of neonatal sepsis. This means that this combination is often a suitable treatment alternative in Sweden. International literature often recommends penicillin in combination with an aminoglycoside, as in other countries *E. coli,* which is a common pathogen, often show resistance against trimethoprim-sulpha.

The infectious agents and their resistance patterns probably vary between stud farms and regions. It is therefore important to routinely take blood samples for bacterial culture if septicaemia is suspected in a foal and keep records of the results. This will provide guidelines for the most appropriate choice of antibiotics in future patients awaiting culture results.

The length of treatment varies from case to case due to causative agents and the response to treatment. Dosages might need to be adjusted during treatment, considering the growth of the foal. Treatment should not cease until clinical parameters have returned to normal. Analysis of serum amyloid A may be useful as this acute phase protein has a short half-life and is quickly normalized after an inflammatory process has subsided.

PNEUMONIA CAUSED BY RHODOCOCCUS EQUI

AETIOLOGY, GENERAL

In neonatal foals pneumonia usually occur in connection with general septicaemia. For treatment of pneumonia in older foals not infected by *R. equi,* please refer to the section on airways.

R. equi is ubiquitous in the environment and both virulent and avirulent strains occur. Even if the bacteria are sensitive to many antibiotics *in vitro*, this is not applicable in *in vivo* as it survives and proliferates inside macrophages. This requires treatment with substances capable of intracellular penetration. Virulent strains cause formation of granulomas and abscesses, especially in the lungs but also elsewhere in the body. Clinical signs usually occur at between 1 to 6 months of age, but it has not been determined how long the incubation period is for natural infection or why some stud farms have endemic problems while others only have sporadic cases. Subclinical infection in foals is common and many of these cases recover completely without any treatment, in spite of having lung abscesses.

DIAGNOSIS

Diagnosis of *R.equi* is made based on x-rays or ultrasound showing the presence of lung abscesses, in combination with a positive culture from tracheal aspirate plus clinical signs of pneumonia. In individuals from farms with an endemic *R equi* problem a preliminary diagnosis can be made based on clinical signs in combination with the presence of lung abscesses. However, bacterial culture and resistance testing are still recommended in these cases, with the aim of surveillance of the potential development of antimicrobial resistance.

HANDLING AND TREATMENT

An important aspect of pneumonia caused by *R. equi* is that the infected foal should be isolated in order to prevent spreading of the infection.

Based on current knowledge a macrolide combination with rifampicin is the primary choice of treatment. Studies comparing the clinical effect of macrolides only versus macrolide and rifampicin in combination are lacking. Prospective randomised studies of which macrolide (Erythromycin, azithromycin or clarithromycin) which is most effective are also lacking. Tulathromycin, which is approved for treatment of cattle and pigs have a relatively low MIC for *R. equi.* The effect can therefore be expected to be poorer than with the previously mentioned substances. Rifampicin should never be used as the sole antibiotic due to its high risk of resistance development during ongoing treatment. The absorption of macrolides with oral administration is markedly reduced with concurrent treatment with rifampicin.

As antimicrobial-induced colitis in the mare has been reported in Sweden when foals have been treated with erythromycin, a combination of rifampicin and gentamicin is sometimes used. *R.equi* is often sensitive *in vitro to* both these substances, but gentamicin has poor penetration into abscesses, , has poorer activity at low pH and no activity in an anaerobic environment. It is therefore uncertain if the concentration and activity of gentamicin at the infection site is sufficient for satisfactory effect. It is not known if this combination potentially increases the risk of development of resistance during ongoing treatment.

As rifampicin and macrolides are used to treat tuberculosis and other severe infections such as invasive MRSA in humans it is important that these substances are not used except when not absolutely necessary. In addition, one possible side effect is that the mare develops acute colitis, which can be fatal. These antibiotics should therefore not be used unless a diagnosis of *R. equi* infection has been thoroughly confirmed.

Preventive treatment of foals with *R. equi* is not in accordance with good antimicrobial stewardship. Treating foals with subclinical infections and lung abscesses at stud farms where *R. equi* is endemic and where foals are screened for *R. equi* has not shown a positive effect compared to placebo. Such foals should therefore not be treated with antibiotics, but should instead be carefully monitored and treated only if developing clinical signs of infection.

Once started; treatment should continue until there are no more clinical signs of infection. Lung radiographs and analysis of plasma fibrinogen can be valuable for evaluation of the response to treatment. Usually treatment is required for more than a month, and the dosages must be continuously adjusted to the weight of the growing foal.

FOAL ENTERITIS

AETIOLOGY, GENERAL

The primary differential diagnoses in neonatal foal diarrhoea is sepsis, foal heat diarrhoea, nutritionally caused diarrhoea, rotavirus infection, clostridia and salmonella. Positive blood culture often occurs in foals with diarrhoea, not just the foals that develop diarrhoea secondary to general sepsis. This is probably caused by a weakened gastrointestinal mucosal barrier, resulting in secondary translocation of bacteria.

DIAGNOSIS

Obtaining a diagnosis for neonatal foal diarrhoea is described elsewhere. Faecal culture without a specific query about growth of for example salmonella or clostridia is not relevant. Foals are not affected by *E. coli* diarrhoea, unless it is associated with general septicaemia. When septicaemia is suspected samples for blood culture should be collected before any antimicrobial treatment is initiated.

HANDLING AND TREATMENT

Foals that do not have signs of severe infection, for example severe malaise or blood profile changes, should in general not be treated with antibiotics. If the foal has signs of general infection associated with diarrhoea antibiotic treatment should however be considered, partly due to the risk of sepsis but also due to the risk of secondary bacterial translocation. Antibody titers should be analysed in foals with malaise and if the tests show a lack or partial lack (4-8 g/L) of IgG antimicrobial treatment can also be indicated. The same applies if the foal is transported to an equine clinic for supportive treatment, as the foal will then be subjected to agents in the new environment that the dam has not produced antibodies against in her colostrum. Please note the section above about sepsis and choice of antibiotics. Treatment times should then be considerably shorter, and the antibiotic treatment can cease when the diarrhoea improves, if no signs of secondary septicaemia or other localised infections have occurred.

REPRODUCTION SYSTEM

In horse breeding *Taylorella equigenitalis* (CEM), *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* are regarded as the primary pathogenic bacteria causing venereal disease. Swedish law requires all stallions used for AI to be tested for CEM. The annual number of stallions that have been CEM positive at testing has varied, (0-7 cases per year 2003-2013).

For *P. aeruginosa* and *K. pneumoniae* the pathogenicity is dependent on which variation of the bacteria (strain/capsule) that causes the infection. In addition, the potentially pathogenic bacteria ("opportunists") *S. equi subspecies zooepidemicus* (beta-haemolytic) and *E. coli* are usually the cause of endometritis in mares.

ANTIBIOTIC USE IN EQUINE REPRODUCTION

AI stations and studs in general have a large turnover of antibiotics as semen extenders contain antibiotics, mares with endometritis are treated with antibiotics and many foals are treated against infections. It is of great importance that routines at AI stations and stud farms follow general medical hygiene principles.

ARTIFICIAL INSEMINATION

In Sweden, almost all Warmblood and Standardbred breeding is by artificial insemination. In AI antibiotics are routinely used in diluents for stallion semen. The reason is that stallion semen normally contains bacteria due to contamination by naturally occurring bacteria from the outer genitalia during semen collection, and that semen itself is an excellent growth substrate for bacteria. Adding antibiotics prevents proliferation of these bacteria. There is limited knowledge about how much of these antibiotics are resorbed after deposition in the uterus and about the possible risk of any resistance development. There are also no studies on the possible environmental impact of semen extenders which end up on the ground after insemination. AI with frozen semen results in smaller amounts of semen extenders released than with fresh semen as the backflow then is a lot smaller.

Several different antibiotics are used in diluents, for example benzylpenicillin (Na or K), streptomycin and gentamicin. Stallions with specific bacteria in their semen should not be used in breeding without undergoing a thorough investigation, and then require permission from Jordbruksverket (Swedish Board of Agriculture).

During the breeding season the extended semen should be regularly tested by bacterial culture, preferably every 14 days. There should not be any bacterial growth in the extended semen.

DISPOSAL OF UNUSED SEMEN EXTENDERS

Do not pour unused extenders/extended semen in the drain. Treatment plants cannot process it. Therefore, it important that AI stations have careful antimicrobial strategies in place in order to minimize the risk of resistance development. The following guidelines for handling of unused extenders/extended semen should be followed:

- Certain types of antibiotics (for example ampicillin, penicillin, gentamicin, neomycin, streptomycin, amphotericin B) can be inactivated in an autoclave or by ordinary boiling before being poured down the drain
- Another alternative is putting the unused diluent in a plastic bag or glass container which is then handled combustible waste.
- Some antibiotics are difficult to inactivate and must be handled as chemical waste.

COLONISATION OF THE STALLION'S OUTER GENITALIA

AETIOLOGY, GENERAL

Healthy stallions usually have a normal nonpathogentic bacterial flora on the outer genitalia (penis, preputium, fossa urethralis, distal part of the urethra). If bacterial culture is done on the semen /ejaculate it is very unusual to find no bacterial growth, as the semen is contaminated at collection. If the normal flora is disturbed for some reason potentially pathogenic bacteria may proliferate. In these cases, the stallion does not have an infection, but colonisation of bacteria on the outer genitalia. Bacteria that can affect mares, that the stallion is used for during these circumstances, are primarily *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and beta-haemolytic streptococci (CEM, *Taylorella equigenitalis*, is discussed separately, see below). In rare cases the bacteria can ascend up through the urethra to the seminal vesicles and cause an infection, seminovesiculitis.

HANDLING AND TREATMENT

Systemic treatment of the stallion is not recommended in such cases. Instead outer genitalia should be treated locally by cleaning the penis with a mild soap solution with a low pH. Experimental studies have shown that using disinfection and local antibiotics can disturb the normal flora and thereby promote proliferation of potential pathogens. Local treatment with antibiotics can be considered in individual cases, but only after bacterial culture and resistance testing. Sexual rest with no coverings is also effective to restore the normal flora on stallion genitalia.

INFECTIONS IN THE STALLION'S INTERNAL GENITALIA

AETIOLOGY, GENERAL

Infections of the internal genitalia (urethritis, prostatitis, seminovesiculitis, infections in the bulbourethral glands) are unusual in stallions.

The most common bacteria isolated in connection with seminovesiculitis are *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, but also *Streptococcus* spp. and *Staphylococcus* spp.

DIAGNOSIS

The diagnosis is made based on clinical findings and bacteriological and cytological testing of the semen. Symptoms often seen are blood in the ejaculate and high counts of neutrophils in the ejaculate. Infected stallions usually do not show general malaise. Endoscopy can be used to determine the location of the infection in the internal sexual organs. A thorough description of the technique is available in the Manual of Equine Reproduction (Blanchard TL et al., 2003, 2th ed. pp 150-152).

Bacterial culture and resistance testing should always be performed.

HANDLING AND TREATMENT

Infections in internal genitalia can be difficult to treat due to the challenge for antibiotics to penetrate to the infection site. The choice of antibiotics should be determined based on resistance testing results. Systemic treatment with antibiotics can be combined with local treatment of for example the seminal vesicles. Local treatment is preferably done with the aid of endoscopy, in order to locate the entrance to the seminal vesicles. Lavage with saline and local deposition of antibiotics is recommended. Treatment results do vary.

ORCHITIS

AETIOLOGY, GENERAL

The most common causes of orchitis are physical trauma (for example a kick), hematogenous spread or through a scrotum wound. Several different bacteria have been reported internationally in connection with orchitis: *Streptococcus equi, Streptococcus zooepidemicus,* and less frequently Salmonella *abortus equi* and *Klebsiella pneumonia*e.

DIAGNOSIS

The diagnosis is made based on the case history, clinical findings that can also include lameness, careful palpation of the testicles, and ultrasound. If a semen sample can be taken and tested the result often shows a high count of leukocytes and bacteria in the ejaculate. Bacterial culture and resistance testing should always be performed in these cases.

HANDLING AND TREATMENT

Treatment of an acute orchitis should commence as soon as possible to try and prevent testicle degeneration. The local increase in temperature in the testicle can damage the seminiferous epithelium and can also have a negative effect on the other testicle. The following treatment is recommended in cases of acute trauma without an infection: cooling of the testicle with ice cold water, and NSAID treatment. Unilateral castration at an early stage is also an alternative. If an infection is suspected in the testicle the stallion should be treated with systemic antibiotics. Culture and susceptibility testing are time consuming, which means that treatment sometimes have to start before results are available. A combination of penicillin and trimethoprim-sulphonamide is possible, to address both gram positive and gram-negative bacteria. The dosage recommended by pharmaceutical companies for trimethoprim-sulphonamide is controversial. Pharmaceutical companies recommend a dosage interval of 12-24 hours, but it has been reported that the recommended dosage should rather be administered every 12 hours and that oral paste is preferable to IV treatments, due to better kinetics. This should especially be taken into account when the infection is caused by bacteria with relatively high MIC-values.

The prognosis regarding the fertility of the affected testicle is guarded, and poor if the condition becomes chronic.

CONTAGIOUS EQUINE METRITIS (CEM)

AETIOLOGY, GENERAL

CEM (contagious equine metritis) is a notifiable disease and suspected cases must be dealt with in accordance with the Swedish Agricultural Board's regulations (SJVFS 2012:24;" K4") about notifiable diseases. CEM is categorized as a venereal disease and is mainly spread in connection with coverings and AI.

Government regulations on AI with equines (SJVFS 2015:1" M4") requires stallions used for AI to be tested annually for CEM. Individual breed societies may have their own rules on testing, also for stallions used for natural covering and not AI. Everyone involved in reproduction work has the responsibility to follow these rules.

CEM is caused by the bacteria *Taylorella equigenitalis.* In mares the infection causes an acute endometritis. Symptoms usually occur 2-10 days after covering/AI as a vaginal discharge. The discharge can vary, from very heavy to so light it produces no outward symptoms. Shortened heat intervals often occur in infected mares. The acute endometritis causes a temporary but marked reduction in fertility. There is no proof of it causing foetal death or chronic reduced fertility.

Infected stallions are carriers without showing any symptoms. Mares can also be carriers without symptoms.

DIAGNOSIS

The clinical symptoms in CEM cannot be distinguished from infections caused by other bacteria. When CEM is suspected it is therefore necessary to do sampling and specifically ask for CEM testing. The sampling must be done by a veterinarian and the samples sent to a laboratory with official accreditation. Please note that for CEM diagnosis samples must be collected from several sites in the same individual and reach the lab within 48 hours of testing. The bacteria are difficult to culture and require a special transport medium (Amies charcoal medium). CEM test kits including the correct transport medium can be ordered from SVA.

HANDLING AND TREATMENT

CEM is possible to treat. Infected horses are isolated, treated and then tested again based on a treatment plan. The suggested choices of antibiotics for local treatment or general treatment should be compared with results from resistance testing.

Culture and resistance testing take longer than for many other bacteria and consequently you might be faced with the decision to start treatment before test results are available. Penicillin is available fas intramammary formulation (with streptomycin) and for injection. Gentamicin is available for injection. For local treatment Gentamicin can be ordered as an extempore preparation, as gentamicin cream is currently not marketed in Sweden. Pharmacies can mix 0,3 % gentamicin drops with Essex cream to a concentration of 0,1 %.

Disinfect your hands and use gloves when cleansing and treating a CEM infected case, changing gloves between cleansing and treatment.

For a thorough description of how the treatment should be done in stallions and mares respectively, please see Appendix 1.

PROPHYLAXIS

CEM is highly contagious. Good breeding hygiene is highly important in all handling of mares, stallions and semen in order to prevent any spread of the disease. One important routine is using disposable gloves when handling the reproduction organs of mares and stallions and discarding them after each individual. Thorough cleaning and disinfection of equipment and the phantom is another important rule. Examining mares including performing a gynaecological exam ahead of coverings or AI can help identify suspected carriers.

PSEUDOMONAS- AND KLEBSIELLA INFECTIONS

AETIOLOGY, GENERAL

A venereal infection can be suspected if several mares that have been covered or inseminated by the same stallion display symptoms such as not pregnant, discharges or shortened heat intervals. Some mares may be infected but display no clinical symptoms. An infected stallion is often a carrier without showing symptoms. The exception is if the stallion has an infection in the internal genitalia, when semen sometimes can contain blood and neutrophils.

DIAGNOSIS

The diagnosis is made based on clinical symptoms and bacterial culture. Samples for bacteriological testing and resistance testing should be taken from all mares covered by the stallion and from the stallion himself

(fossa urethralis, urethra and the ejaculate). A cytological analysis of the semen should also be made to test the possible presence of inflammatory cells.

HANDLING AND TREATMENT

If a venereal infection is suspected or has been diagnosed the stallion should immediately stop covering until an adequate treatment has been given. During an ongoing breeding season one alternative can be to" treat" the semen with a suitable extender containing adequate antibiotics. Treatment recommendations for stallions are described under "Seminovesiculitis and bacteria on stallions' external genitalia". Treatment recommendations for mares are described under "Endometritis".

Good hygiene when handling breeding mares and stallions are of great importance in order to prevent spread of any infections.

ENDOMETRITIS

AETIOLOGY, GENERAL

Endometritis is a common cause of subfertility and infertility in mares. In contrast to metritis (after foaling) mares with endometritis do not show general malaise. In cases of pyometra mares also normally do not show general malaise, even if their uterus contains several litres of purulent exudate. The most common agents isolated in endometritis cases are *E. coli* and *S. equi, subgrupp zooepidemicus*. Other important causes are *Pseudomonas aeruginosa* (non-venereal) and *Klebsiella pneumoniae*. Anaerobic bacteria can also occur but are probably unusual.

Fungal infections can also occur in the uterus but are relatively rare.

DIAGNOSIS

If endometritis is suspected samples for bacteriological testing (including resistance testing) can be taken from the uterus with a guarded swab. The bacteriological analysis could be combined with cytological samples from the uterus in order to reduce the risk of false positives/false negative. It is important to adhere to a sampling technique that is hygienically correct, due to the great risk of contamination at testing. At stud farms where bacterial infections can be spread directly or indirectly, resistance testing of bacteriological samples should be done regularly. The results should be monitored in order to have early warning of any treatment related spread of multi-resistant bacteria.

Note that the resistance situation varies between countries and probably also between regions and stud farms.

HANDLING AND TREATMENT

Depending on which bacteria that is isolated the mare can either be treated locally, systemically or both. The individual case determines which route of administration is chosen. With, for example chronical endometritis and metritis, systemic treatment is preferable.

LOCAL UTERINE TREATMENT

Treatment is started by a uterine lavage, using physiological saline solution and continuing the lavage until the liquid turns clear, plus oxytocin (i.m.). As the mare does not suffer general malaise in endometritis antibiotics need not be administered until results from the bacteriological culture is ready. In mild cases of endometritis, the saline lavage together with oxytocin may be sufficient. The local uterine treatment can be performed daily for 1-5 days and should be performed during the mare's heat, and not later than 1-2 days post ovulation. The duration of treatment depends on the severity of the case and the cause.

The uterine mucous membrane in mares is very sensitive to different substances. Medication used locally in the mare uterus should be water soluble and not cause precipitations. Oil based preparations are irritant and can cause the formation of uterine adherences. Examples of antibiotics that are therefore contraindicated for use in the uterus is tetracycline, chloramphenicol, enrofloxacin and ampicillin. Please note that ampicillin is mentioned in international literature as an alternative to local treatment, but that refers to other preparations than what is available in Sweden.

Antibiotics are selected based on culture results and resistance testing.

1) Penicillin (Na or K-salts): 3 g (5 million units) in a 100 ml sterile water solution. Penicillin is the choice in streptococcus infections.
2) Gentamicin sulphate: 1000-2000 mg buffered with 5 % sodium bicarbonate solution, 1,5 times the volume of gentamicin sulphate. The solution is diluted with 100-200 ml sterile water or physiological

saline solution. The reason for the buffering is that gentamicin sulphate has a low PH, which can cause irritation in the uterine mucous membrane.

Dihydrostreptomycin is used on empirical grounds in Sweden as relevant studies are lacking. The resistance situation is less favourable. Local treatment with other antibiotics, for example neomycin, ticarcillin, ampicillin and ceftiofur are described in international literature. These antibiotics should only be used with great restraint and only when resistance testing have shown that there are no alternatives. None of these antibiotics are approved for equine use in Sweden.

SYSTEMIC TREATMENT

If systemic treatment is given it should be performed daily for 3-5 days and during the mare's heat. The antibiotics should be selected based on resistance testing results. Penicillin is the primary choice in streptococci infections. In infections with Gram negative bacteria trimethoprim-sulfa can be used in most cases.

PREVENTIVE TREATMENT

Some mares have recurrent endometritis due to conformational problems in the vulva/rectum area, for example poor closing of the labia lips, which causes ”air sucking”. This defect results in air and faeces entering the vagina and intestinal bacteria and fungus can then cause vaginitis/endometritis. By closing the upper part of the vulva by a so-called Caslick's operation the problem can be at least partly prevented.

ABORTIONS

AETIOLOGY, GENERAL

In only about half of equine abortions cases a clear aetiological diagnosis can be made. The most common infectious cause of equine abortion are virus infections (EHV-1) but bacterial and fungal infections also occur. The most common bacteria isolated are beta-haemolytic streptococci, *E. coli, Pseudomonas* spp., *Staphylococcus aureus* and *Enterobacter* spp. Leptospira has also been described as a sporadic cause of abortions in mares.

The most common non-infectious cause of equine abortion is twin pregnancies.

DIAGNOSIS

In order to improve the conditions for a diagnosis the following should be included in the investigation: a careful case history, clinical exam of the mare, exam of the foetus and foetal membranes. Samples for microbiological analysis from the foetus and foetal membranes should be sent for diagnosis. There are tests available where several different viruses are analysed in parallel. For a complete investigation the foetus and foetal membranes must be sent in for a post mortem.

HANDLING AND TREATMENT

Treatment is usually not given after an abortion, as the damage is already done. If a bacterial infection of the uterus is suspected the choice of treatment is determined based on the results from the post mortem, bacterial culture and resistance testing.

MASTITIS

AETIOLOGY, GENERAL

The incidence of mastitis in mares is relatively low. If it occurs it is mainly in adult mares during lactation and up to two months after weaning, but it can also affect mares who have never been pregnant. The most common bacteria found in mastitis is *Streptococcus zooepidemicus*, but other species have also been isolated. This corresponds well to results from bacterial culture of mares' milk at SVA when *S. zooepidemicus* was isolated from about 40 % and staphylococcus (*S. aureus* or coagulase negative staphylococcus) in 9 % of the cases. About 40 % of the samples were negative or had a mixed flora.

DIAGNOSIS

The diagnosis is made based on symptoms, that include a warm, swollen, tender udder, ventral oedema and fever. Sometimes a mild hind-leg lameness can also be detected, on the same side as the affected udder part

A milk sample should always be taken for bacterial culture and resistance testing. Careful hygiene is important at sampling to avoid contamination from the mare or from the tester's hands. Cytological testing can also be done and often show a high count of neutrophils.

HANDLING AND TREATMENT

Treatment consist of a combination of frequent milking and systemic antibiotics treatment. Penicillin is the primary choice and can be administered straight away awaiting the culture results and resistance testing. Treatment with NSAID can be indicated to reduce the fever, pain and inflammatory reaction. If the mare is not pregnant treatment with oxytocin is recommended. If the culture result is negative the antibiotics treatment should be stopped, but the rest of the treatment with frequent milking, oxytocin and NSAID remains indicated.

PLACENTAL RETENTION

AETIOLOGY, GENERAL

The placenta will usually pass within 30 minutes (up to 2-3 hours) after foaling. If the placenta has not passed after 3-4 hours, it is classified as retained. The effects of a retained placenta may be none but also life threatening with metritis, septicaemia or toxaemia, laminitis and death. Streptococci is normally the dominating bacteria in the uterus in cases of retained placenta but other Gram-negative bacteria, that can produce endotoxins, such as *E. coli*, may be more important.

DIAGNOSIS

A diagnosis of retained placenta is easy to make and normally bacterial samples are seldom taken. In some cases, bacteriological culture and resistance testing should be done.

HANDLING AND TREATMENT

Different treatments for retained placenta have been described. Treatment with oxytocin is the most common. The primary recommendation is a slow (lasting about 1 hour) IV infusion of oxytocin in 1 litre of saline solution, or injections of a small dose (10 -20 IU) of oxytocin that is repeated as needed. Having the mare move about (exercise) is also positive. Another alternative, less frequently used, is to fill the allantochorion (if it is intact) with about 10-12 litres of sterile physiological saline at body temperature and thereby stimulate the passing of the placenta. This treatment can be combined with oxytocin injections.

If the mare is showing general malaise and there is a danger of metritis and laminitis antibiotics and NSAID should be administered. In such cases it is probably Gram-negative bacteria that may cause most damage (endotoxin production). Trimethoprim-sulpha can then be the primary choice.

URINARY TRACT

Urinary tract disease is unusual in equine medicine and bacterial infections are rare.

AETIOLOGY, GENERAL

Bacterial infections in the urinary tracts are almost always caused by ascending infections. Mares are at greater risk due to a shorter urethra. Other predisposing factors are bladder atony, lengthy recumbency, complications after obstetric manipulation and catheterisation, plus very occasionally late stage pregnancy. Strangely horses with urinary stones do not seem to be at increased risk of cystitis.

When a pathogen has colonised a distal urethra, a speedy proliferation can pave the way for bacteria to invade also the proximal urethra and bladder, which lack protective bacterial normal flora. Agents isolated from the equine urinary tract include *E. coli, Klebsiella, Proteus, Enterobacter, Streptococcus* and *Staphylococcus* spp, *Pseudomonas aeruginosa,* and rarely, *Corynebacterium renale*. In addition, secondary *Candida* infections have been reported in foals treated with broad spectra antibiotics. Isolates of more than one agent are unusual.

DIAGNOSIS

Routine urine tests can aid diagnosis in urinary tract infections where pyuria (more than five leukocytes per area at 100 x enlargement) indicate infection. Urine samples, especially from mares who foaled recently, can however contain a lot of leukocytes in spite of no infection being present.

Samples for bacterial culture should always be collected by catheterisation. For analysis the culture needs to be performed semi-quantitatively, which is why it is necessary to deliver urine in a sterile container, a swab is not sufficient. For the test result to be clinically significant the sample must include a minimum of 10^5 bacteria/mL. In a suspected pyelonephritis culture of urine samples collected from the ureters with the help of an endoscope.

HANDLING AND TREATMENT

Most bacterial equine urinary tract infections are secondary to predisposing factors, and these should be diagnosed and addressed while the infection itself is treated. The few studies that have been published conclude that equine urinary tract infections are not difficult to cure, if the predisposing factors are removed.

The choice of treatment should be based on results from bacterial culture and resistance testing. For *E. coli* and other coliforms, a combination of trimethoprim and sulphonamides are usually indicated.

Infections that have been present for some time should be treated for at least 10 days. In pyelonephritis lengthy treatments are required. The exact length is determined by clinical exams and repeated urine culture and cytology demonstrating the absence of active infection.

OTHER

The coccidia *Klossiella equi* is often found at autopsy, but at present there are no indications that it has any clinical importance.

TICK-BORNE BACTERIAL INFECTIONS

Among tick borne infections in Sweden there is only Equine anaplasmosis (also known as Equine Granulocytic Erlichiosis) which is scientifically accepted as affecting equids. Borrelia is also discussed here, as many horses are infected and carry antibodies against borreliosis. There is, therefore, often discussions whether borreliosis might have caused clinical symptoms and if so, they should be treated. In Sweden the tick *Ixodes ricinus* is the primary vector of these agents. If other tick species get established in the country other agents might also affect horses.

EQUINE ANAPLASMOSIS

AETIOLOGY, GENERAL

Equine anaplasmosis (previously called ehrlichiosis) is a tickborne infection caused by the bacteria *Anaplasma phagocytophilum*. In horses it mainly is subclinical but can also cause acute symptoms. In a 2001 study 17 percent of horses in Sweden had antibodies against the infectious agent. Cattle and sheep can also get acute symptoms, called tick-borne fever (TBF). Humans, dogs and rarely also cats can also fall ill.

DIAGNOSIS

A preliminary diagnosis of acute equine anaplasmosis can be performed based on clinical symptoms; high fever, malaise, anorexia, swollen legs, ataxia and reluctance to move, and increased heart rate and breathing. Thrombocytopenia and lymphopenia is common and also mild anaemia and icterus can be seen. It is very common with subclinical infections in horses, associated with anti-body formation.

The diagnosis is confirmed by demonstrating the bacteria in serum by PCR or microscope in the acute phase, or by a positive paired serum sample, when specific antibodies are found. An alternative diagnosis to acute equine anaplasmosis is acute virus infections, that can cause similar symptoms.

So-called chronic Equine anaplasmosis/ehrlichios is not a scientifically proven diagnosis and lack generally accepted diagnostic criteria. In experimentally infected horses not treated with antibiotics the bacteria have been shown to be persistent, but not to cause any symptoms. A notable percentage of Swedish horses have a positive antibody titre, without any symptoms. There is no proof of increased titres against anaplasma at two or more occasions would be associated with ongoing disease. Further there is no scientific proof that

the antibiotics treatment would affect either the serum titre or possible clinical signs of chronic Equine anaplasmosis.

HANDLING AND TREATMENT

Acute equine anaplasmosis will heal by itself over time, but the horse than be severely affected for several days. A prompt start of the treatment most likely results in a shorter disease process. Empirical experience from clinicians show that NSAIDs often pose a suitable choice of treatment in the acute phase awaiting diagnosis, often with a good effect on clinical symptoms. If the result of NSAID treatment is that the fever subsides and the horse starts eating again NSAID can therefore often be sufficient.

Tetracyclines is currently regarded as the most suitable substance against anaplasma, in cases where antibiotics are considered. The risk of side effects in horses should be considered, and horses subject to stress should not be treated. Oral treatment with tetracyclines is not suitable for horses, for several reasons including increased risk of colitis due to poor bioavailability. In Sweden no preparations containing tetracycline are approved for horses.

In the literature oxytetracycline is suggested for horses, but then as a slow IV injection due to the high risk of side effects in horses, for example acute cardiac symptoms. Studies describing the optimum duration of treatment of anaplasmosis in horses is lacking. Most horses with acute equine anaplasmosis respond quickly to treatment and are often free of symptoms within 24-48 hours, which indicates that three days of treatment should be sufficient.

The benefits of a longer treatment have to balance the risks. If a small number of horses get recurrent fever longer treatment can be considered on a case by case basis.

Monitor the horse's condition and stop the treatment immediately in case of any early signs of gastrointestinal disturbance, such as reduced appetite, fever and loose droppings.

If targeted therapy in acute equine anaplasmosis do not result in a prompt resolution of symptoms the diagnosis should be re-evaluated.

There is no scientific basis for antibiotics treatment of "chronic anaplasmosis/ehrlichiosis" in horses. Please observe that tetracycline treatment can result in clinical improvement of lameness from non-infectious causes, due to the antiinflammatory effect of tetracyclines and its effect on orthopedic tissue. This can result in reduction of joint swelling and pain (shown in rheumatoid arthritis) and prevent the breakdown of collagen in cartilage and connective tissue. This is not associated with the antimicrobial effect and can therefore be misleading when interpreting the treatment results and confirmation of the diagnosis. The risk of antibiotic resistance mean that it is not acceptable to use antibiotics for other uses than antimicrobial, as there will be other alternatives.

BORRELIOSIS

AETIOLOGY, GENERAL

The Borrelia burgdorferi-group causes a tick-borne infection that is usually subclinical in horses. Studies in Sweden has shown a prevalence of antibodies of 17 percent. In for example the United States, borreliosis is more often caused by *B. burgdorferi* itself and can then cause so called Lyme disease. The borrelia bacteria can also infect humans, cats and dogs.

DIAGNOSIS

The diagnosis "clinical borreliosis" has not been scientifically confirmed in horses. In studies with experimentally infected horses, disease or pathological changes have not been demonstrated, although the infective agent could be isolated. You can therefore not specify what symptoms can be expected or how a possible case could be confirmed. Descriptions of equine borreliosis in literature lack necessary information in order to connect described symptoms to borreliosis, and diagnostic criteria are lacking.

No association between exposure to the agent (seropositivity) and symptoms have been found either and many healthy horses are seropositive.

Clinical signs described in literature as symptoms of equine borreliosis include arthritis, lameness, muscle soreness, frontal uveitis, encephalitis, abortion, foal mortality, low grade fever and malaise. It is however not confirmed cases of borreliosis and all symptoms can have other causes.

Antibody titres are not sufficient for a diagnosis, as studies show that many horses have antibodies against borrelia without any symptoms. Demonstrating the bacteria by PCR or bacterial culture from organs that

appear affected should be one criterion, together with a thorough investigation to exclude any possible alternative diagnosis.

If borreliosis cannot be excluded as a diagnosis and the horse is treated with antibiotics, it should respond to treatment, otherwise the diagnosis should be revalued. Please not that in treatment with tetracyclines their anti-inflammatory effect and effect on connective tissues can result in a clinical improvement (please also note re Equine anaplasmosis), which can cause confusion in the interpretation of treatment results and evaluation of the diagnosis.

HANDLING AND TREATMENT

As there are no set diagnostic criteria for equine borreliosis there is also no scientific basis for antibiotics treatment in suspected cases.

If a treatment seem warranted penicillin can be considered in uncomplicated suspected cases, as this is the recommendation in human cases. In addition, penicillin is relatively well tolerated by horses.

CENTRAL NERVOUS SYSTEM

BACTERIAL MENINGITIS

AETIOLOGY

It is relatively unusual with infections caused by bacteria or protozoans in the horse's central nervous system. Bacterial meningitis is seldom reported in adult horses, and in cases of brain abscesses the infection focus is limited.

In brain abscesses that are not locally defined or disease involving the central vestibular system *S. equi* has been reported. Occasional cases of otitis media associated with a paralysis of the facial nerve and a tilted head carriage has been associated with the presence of bacteria (*Actinobacillus, Salmonella, Enterobacter, Pseudomonas, Streptococcus, Staphylococcus*) or even fungal infections (*Aspergillus*), possibly originating from the guttural pouches.

Foals can suffer from bacterial meningitis, often secondary to septicaemia (see the section on foal diseases). The treatment is then focused on the septicaemia rather than the meningitis.

DIAGNOSIS

Samples for bacterial culture can consist of cerebrospinal fluid, samples from the middle ear if there are signs of otitis media, and blood if there are symptoms of bacteraemia or septicaemia. The exception is cases of fulminant meningitis in foals, where samples of the cerebrospinal fluid is usually negative at bacterial culture, probably as the infection is closed off in an abscess.

In a localized infection like otitis media a needle aspirate is taken through the ear drum under anaesthesia. Clinical cases of otitis media have been diagnosed at the Swedish University of Agricultural Sciences, but culture of samples taken with a needle aspirate have not been performed. It is however reasonable to presume that the infectious agents mentioned above are relevant also in horses in Sweden. In the absence of bacterial culture summaries of resistance data in these agents should guide the choice of treatment.

HANDLING AND TREATMENT

The Central Nervous System (CNS) is largely demarcated from the immune system through the blood-brain barrier. The immune system of the CNS is therefore limited in scope, with a low number of white blood cells, low concentration of antibodies and complement factors. Sometimes the expression "immunological vacuum" is used. This means that bacteria have time to multiply before the blood-brain barrier becomes so inflamed that defence cells and proteins pass over to the CNS.

Antibiotics used in CNS cases should therefore have two properties:

1. Ability to penetrate the blood-brain barrier
2. Bactericide effect as there are so few defence cells present to support the antibiotic effect.

PROPERTIES OF ANTIBIOTICS RELATED TO THE BLOOD-BRAIN BARRIER

A.Substances that pass into the CNS also when no inflammation is present in the meninges

1. Combinations of trimethoprim and sulphadiazine or sulphametoxazole: Trimethoprim has a good penetration of the blood-brain barrier and this also applies to some sulphonamides. The combination

has a bactericidal effect, according to some authors. Trimethoprim-sulphadiazine is therefore a suitable primary choice in suspected bacterial infections in the CNS in situations when bacteria have not been isolated and resistance testing not been done.

2. Chloramphenicol: Chloramphenicol may absolutely not be administered to horses who might enter the food chain. A drawback with chloramphenicol is that the substance does not have bactericidal effect, which has a negative effect in the CNS.

B. Substances with penetration into the CNS when the meninges are inflamed

This group includes penicillins, including amino-penicillins. Penicillins probably have no advantage compared to trimethoprim-sulpha from a therapeutic point of view. Ceftiofur have poor permeability across non-inflamed meninges, but third generation cephalosporins can have more favourable properties (for example cefotaxime).

C. Substances with only limited penetration into the CNS also with inflamed meninges

This category includes first generation cephalosporins and all aminoglycosides. Substances from these groups are therefore only an alternative when bacterial culture and resistance testing has shown that other alternatives cannot be expected to be effective. If aminoglycosides are selected, they should be administered both systemically and intrathecally. With this background it is seldom indicated to use an aminoglycoside in CNS disease.

OTITIS MEDIA-INTERNA/TEMPOROHYOID OSTEOARTHROPATHY

Compared to the prevalence in other species otitis media-interna is unusual in horses. Clinical signs are those associated with peripheral vestibular syndrome, with tilted head carriage, walking in circles and ataxia. The syndrome is not always associated with bacterial infections, but agents such as *Streptococcus* spp, *Staphylococcus* spp and *Aspergillus* spp have been reported. Infection of the middle ear is believed to be caused either by hematogenous spread or encroachment from infections in the nasopharynx or guttural pouches. A confirmed diagnosis requires lavage of the middle ear through tympanocentesis (which is seldom performed) or secondary indicators such as culture of exudate from the ear, guttural pouch or nasopharynx. If there is diagnostic evidence of a bacterial infection trimethoprim-sulphadiazine combined with anti-inflammatory medication (flunixin meglumine) is the primary choice, based on clinical experience.

EYE DISEASES

INTRODUCTION

In eye cases a thorough examination and taking samples for testing is important to be able to detect an ongoing bacterial infection or risks of a secondary infection, in order to avoid unnecessary antibiotics treatment.

The choice of antibiotics for eye treatment can be empirical or specific. Empirical treatment should only be used in mild ocular infections when laboratory tests do not seem necessary. In cases of therapy failure, a relapse and infections that might threaten the patient's vision, bacterial culture and resistance testing should always be performed if sampling is possible. In Sweden eye infections are often caused by Gram positive bacteria but infections with Gram negative bacteria, parasites and viruses also occur. Fungal infections are more uncommon.

ADMINISTRATION OF MEDICATION

There are several methods to administer medication when treating eye disease; topical, subconjunctival, intraocular or systemic. Local treatment is in most cases sufficient for disease in the front segment of the eye. More deep-seated problems in many cases require systemic treatment in addition.

TOPICAL ADMINISTRATION

When treating conditions in the conjunctiva, cornea and tear canal openings the routine treatment is topical administration. The bioavailability of a topically administered substance is low. Some of the applied substance will disappear with the tear film and at every blink of the eye. Medication that is administered topically must penetrate the cornea epithelia and stroma to reach the eye, and the concentration gradient drives the diffusion. The tear film is impermeable for lipid soluble substances. In addition, the cornea epithelium is a barrier against water soluble substances while the stroma blocks lipid soluble substances. Consequently, a substance needs to be both water and lipid soluble in order to pass the cornea.

With the right choice of substance and correct dosage intervals therapeutic concentrations will in many cases be achieved at the infection site. Most antibiotics that are used topically are available as commercial eye preparations. When needed a solution for IV injection can be mixed with a tear substitute for the right concentration.

In general eye drops are preferable to creams as they will act less as an irritant and usually have better penetration. The drawback is that eye drops need to be administered more often, usually at least 5-6 times per day, while creams and gels can be administered less frequently. This is due to their longer contact time, that is that they remain longer on the eye surface. Creams and gels are easier to apply in a horse eye but are contraindicated in cases when there is a risk of the substance entering the front eye chamber, as this can result in a very severe intraocular irritation. When frequent treatments are needed it can be suitable to put in a subpalpebral catheter. In some cases, it is necessary, if the horse is unruly due to pain or other causes. Subpalpebral catheters do require careful supervision in order to not cause damage, and is primarily meant for clinical settings, but can be applied also in the field in exceptional cases when the alternative would be no treatment. It is important to underline that daily veterinary supervision is necessary.

If the horse is treated with different topical substances at least 2-5 minutes must pass between each dose. It is also recommended that drops are given before creams in cases when more than one substance is given. Very frequent applications can be negative as it might cause local toxicity or decreased epithelisation Intramammary tubes cannot be recommended for topical administration as there are no pharmaceutical studies to support for example suitable dosage intervals, cornea penetration or expected therapeutic concentrations. The possible toxicity of the preparation should also be considered.

SUBCONJUNCTIVAL INJECTION

Therapeutic concentrations can be achieved in the front segment via subconjunctival injection. This mode of administration can be indicated if very high concentrations in tissues are required and can be combined with topical treatment. Treatment can be given every 12 to 24 hours but should not be repeated excessively due to the risk of local irritation in the conjunctiva. Parenteral solutions of chloramphenicol and tetracycline are poorly tolerated when administered in this manner and should be avoided. This administration is also less suitable if the treatment might have to be stopped earlier than planned. Subconjunctival injection should therefore only be used after careful consideration and the injection should be given by a person with good ophthalmological knowledge. For dosage and choice of substances please see handbooks.

INTRAVITREAL INJECTION

Intravitreal injection can be combined with systemic treatment, for example endophthalmitis in humans, but is seldom used in veterinary ophthalmology. It requires special equipment and expertise.

SYSTEMIC TREATMENT

Systemic treatment is primarily necessary in case of an intraocular infection or risk thereof. In order for an antibiotic that is administered systemically to have effect it must have lipid soluble properties. Low degree of protein binding and low molecular weight will also facilitate the passage. Groups such as beta-lactam antibiotics and aminoglycosides normally have low degree of penetration to the eye's inner structures, but during an active inflammation the barrier function is weakened, and substances that normally would not penetrate the barrier can be indicated for use. Systemic treatment can be valid in cases of cellulitis, infections in the eyelid or tear canal, the eye's deeper segments and optic nerve, or sometimes in addition to local treatment in diseases in the front segment of the eye.

BLEPHARITIS

Inflammation in the eyelid, blepharitis is unusual as a primary problem in horses but are usually secondary to a trauma or infection. The most common cause of blepharitis in horses is a bacterial infection (for example staphylococci) after a penetrating trauma. A less common cause is a primary bacterial infection (*Moraxella* spp and *Listeria monocytogenes* have been described), as is fungi and parasitic infections. Blepharitis can also be immune mediated, caused by local or systemic allergic disease or overexposure to sunlight. Diagnosis of blepharitis includes culture including resistance testing and if necessary, cytology. The treatment is adapted to the aetiology and/or test results. Biopsies can be considered in chronical cases that do not respond to treatment.

In cases of an acute wound the damage is surgically repaired after cautious debridement and careful lavage. As the eye lids have a strong blood supply wounds normally heal quickly without complications, but antibiotics therapy should be considered in cases of extensive damage. Penicillin is the first choice for systemic treatment. If there is a risk of secondary bacterial conjunctivitis topical treatment with fusidic acid can be used.

ORBITAL CELLULITIS

Orbital cellulitis refers to an infection in the connective tissue around the orbit, which quickly can lead to damage in the eyeball and the optic nerve. Symptoms occur suddenly and include for example a bulging eyeball, tear flow, bulging third eyelid, oedema of the conjunctiva (chemosis), pain and fever. The aetiology of orbital cellulitis includes for example perforation of a foreign body, direct trauma, tooth problems or hematogenic infection. A thorough examination is necessary in order to try determining the aetiology and exclude further damage such as for example a fractured orbit. An ultrasound and/or x-ray exam can aid the diagnosis. The treatment is high doses of broad spectra, systemic antibiotics (penicillin and Gentamicin) and topical treatment (for example chloramphenicol or ciprofloxacin) plus systemic NSAIDs. The possible underlying factor should of course also be addressed. In horses it is relatively uncommon with a retrobulbar abscess but if this occurs it should be drained and samples for aerobic and anaerobic bacterial testing be taken.

CONJUNCTIVITIS

In cases with symptoms of conjunctivitis there is often a predisposing condition. A careful eye examination is therefore important in order to locate and treat the primary cause. Possible aetiologies are for example a foreign body, trichiasis, anatomical eyelid defects, local irritation due to sunlight, dust, smoke, hypersensitivity reactions but other diseases can also be a factor, for example corneal trauma, uveitis or glaucoma. Virus and parasitic infections are also common aetiologies in equine conjunctivitis.

In acute conjunctivitis local cleaning of the eye (and preferably also the tear canals) with saline solution once or a few times, in combination with treatment of the primary cause is usually sufficient. A fly mask can provide useful protection during the summer months in order to reduce local irritation and disturbances of the normal bacterial flora due to flies and other insects. Bibrochatol is a substance with antiseptic effect that can be used in cases of mild conjunctivitis. If topical antibiotics are needed the first-line choice is fusidic acid as different types of staphylococci and streptococci are common in acute bacterial conjunctivitis. As MRL values are not available for fusidic acid treatment results in a lifelong slaughter ban. Bacterial culture including resistance testing and cytology analysis samples from the conjunctiva should be performed on all eyes with chronic conjunctivitis, lack of treatment effect or recurrent cases. The subsequent treatment should be based on test results.

DACRYOCYSTITIS/CANALICULITIS

Dacryocystitis/canaliculitis is an inflammation of the lacrimal gland or tear canal. Can be caused by for example conjunctivitis encroachment to the tear canal, or trauma, a foreign body, encroachment from a tooth infection. In cases with mucopurulent lacrimation bacterial culture and resistance testing plus possibly cytological analysis should be performed on eye wash liquid. After sampling the eye should be profusely irrigated with saline solution with the horse sedated, followed by topical treatment with antibiotics drops (the choice of antibiotics should preferably be based on the test results but if the patient is very uncomfortable the treatment should commence with substances active against streptococci and staphylococcus, for example fusidic acid). The irrigation might need to be repeated several times for a satisfactory result and systemic treatment (directed therapy based on test results) can be necessary in more serious cases. Possible predisposing causes should be addressed if possible.

KERATITIS

Most non-ulcerating keratitis, with the exception of stromal abscesses, are not caused by bacteria but have a mechanical or immunological aetiology. Treatment does therefore normally not include antibiotics, except if the clinical picture or test results indicate otherwise. Horses can also get keratitis caused by herpesvirus. With keratitis a complete examination of the eye is recommended to look for the primary cause such as a foreign body or similar. Cytological and microbial testing can be done. A biopsy might be considered in certain cases to aid the diagnosis but can only be performed by a specialist. The primary cause should be addressed if possible. Treatment is started with anti-inflammatory medication and preferably tear substitutes. Some cases of keratitis with an immunological background may respond to treatment with ciclosporin, others respond better to treatment with topical corticosteroids or NSAID. It is important to remember that in other cases these substances can be contraindicated, and a careful examination of the eye is needed to ascertain a correct diagnosis and treatment.

Stromal abscesses in the cornea is usually difficult to treat and can result in reduced vision if not treated correctly. A secondary abscess can form after healing of a small or larger ulcer on the cornea or after micropuncture and injection of bacteria or a foreign body penetrating the cornea epithelia. The symptoms usually include for example blepharospasm, tear flow, different degrees of uveitis and varying degrees of vessel in-growth in the cornea plus focal white and/or yellow demarcated stromal infiltrates surrounded by oedema. Single or multiple abscesses may develop. Fluorescein colouring is usually negative but can also be positive adjacent to the lesion. Aggressive medical treatment can be tested initially, unless the evaluation is that urgent surgery is needed in order to save the animal's vision (for example in cases of a deep abscess and/or risk of rupture in the eye). If clinical improvement is not seen within 48-72 hours after medical treatment commenced the abscess should be drained surgically.

A subpalpebral catheter is recommended to make intensive medication easier. Very frequent doses of antibiotics with good penetrating effect in the cornea is necessary, for example chloramphenicol or ciprofloxacin, that initially is administered every hour to get sufficient therapeutic concentration. Gentamicin is not suitable as the substance has poor ability to penetrate intact cornea. Debridement of cornea epithelia across the lesion can facilitate the passage of medication. Systemic treatment with broad spectrum antibiotics (penicillin and Gentamicin) is indicated in these cases as the condition is difficult to and potentially can threaten the horse's vision. Usually vessel ingrowth develops in the cornea which facilitates for systemic medication to reach its destination. The secondary uveitis is treated with topical atropine and systemic NSAID.

ULCERATING KERATITIS

AETIOLOGY AND DIAGNOSIS

Corneal ulcers are usually caused by trauma and seldom primarily by bacteria. Secondary infections are however very common and therefore prophylactic treatment with topical antibiotics are always indicated. When an ulcer occurs, the equine cornea run the risk of being destroyed by collagenolysis, which is often associated with infections by *Pseudomonas* or beta-haemolytic streptococci. Chronic corneal wounds with poor healing ability in the cornea epithelia (so called "indolent ulcers" or "boxer ulcers") occur in horses and also in dogs.

Corneal ulcers are classified based on their depth, that should be examined during the examination of the eye. In case of a corneal ulcer you should always look for any possible foreign body or other primary cause.

HANDLING AND TREATMENT

In superficial, uncomplicated corneal ulcers without signs of infection or meltdown topical antibiotics treatment is used as a preventive measure during the healing period as secondary infections are a very common complication. A suitable first-hand choice based on Swedish conditions is fusidic acid, one alternative is chloramphenicol. It is important to note that both these substances require lifetime exception from slaughter for human consumption. If the owner wants to avoid this, other substances are available. Ciprofloxacin is included on the EU so-called "equine list" and can be used with six months withdrawal time for slaughter. The length of treatment is adapted to the rate of wound healing. The treatment should continue for a few days after the corneal wound has epithelized and a fluorescein test is negative.

Chronic, indolent ulcer demand mechanical debridement of loose epithelial edges in order to heal. The procedure often needs to be repeated, and sometimes also keratotomy will be necessary. Topical antibiotics are selected based on test results from cytological and bacterial samples. Often fusidic acid is sufficient in combination with tear substitutes.

With deep, progressive or perforating corneal ulcers and symptoms of meltdown bacterial and cytological tests should always be performed. These cases should be referred in order to be examined and treated by specialists.

With deep stromal ulcers with risk of perforation, and in cases of perforation, the treatment should include broad-spectrum antibiotic drops with good penetrating effect. Chloramphenicol, Gentamicin or ciprofloxacin are suitable, depending on the degree of meltdown. Treatment should commence straight away, but the choice of antibiotics be adjusted later based on cytology and culture results including resistance testing. Please note that creams are not suitable in cases of deep ulcers or perforation, as the cream can cause a severe intraocular irritation. In addition, systemic treatment is indicated (penicillin and Gentamicin) in order to have a chance to save the eye with chirurgical means.

In meltdown cases a cytology sample is taken from the edge of the ulcer for fast and directed antibiotics therapy. The cytological testing is complemented by bacterial culture and resistance testing. If cytological sampling is not possible in the acute phase intensive topical treatment is started immediately with a broad-spectrum substance with effect on *Pseudomonas*. Awaiting test results suitable substances for topical treatment are Gentamicin or ciprofloxacin, combined with anticollagenase treatment (serum plus Na-EDTA or acetylcysteine). The topical treatment should be combined with systemic treatment (penicillin and Gentamicin) due to the risk of perforation.

Treatment length is adjusted based on the clinical development. The frequency of treatment can be reduced slightly when the meltdown has stopped, and further when the ulcer shows signs of healing. Topical treatment with antibiotics continues until the ulcer has epithelized fully.

It is important to consider the risk of uveitis in cases of corneal ulcers in horses. It should be treated with systemic NSAIDs plus atropine (please note the risk of colic as a side effect).

UVEITIS

AETIOLOGY AND DIAGNOSIS

Equine uveitis is usually not primarily caused by bacteria, unless the cornea is perforated. Certain infectious diseases such as strangles, *Rhodococcus equi*-infection, Brucellosis, Leptosirosis and other can however cause uveitis. A careful clinical examination and an eye exam is important in order to try and understand the aetiology. Symptoms that can be seen in uveitis is for example blepharospasm, miosis, cells and proteins in the chamber fluid, ciliary injection, conjunctival hyperaemia, cornea oedema, hypopyon, swollen iris etcetera. An ophthalmological examination can be needed to examine the rear eye segment, possibly supplemented by an ultrasound exam, if a satisfactory ophthalmological examination is not possible. The horse might also need to be investigated for any general infection, with the necessary exams and tests.

HANDLING AND TREATMENT

In a case of uveitis, the underlying cause must be found and treated. The treatment of the uveitis itself is systemic NSAIDs, topical atropine plus topical anti-inflammatory treatment. Meanwhile please abstain from topical anti-inflammatory treatment if the cornea is damaged and/or there are signs of local bacterial infection such as purulent eye flow. Topical antibiotics should be administered if the horse has purulent eye flow and/or a corneal ulcer (treatment of corneal ulcers is described elsewhere) but can in some case also be indicated for prophylactic use. Systemic antibiotics should always be used if the patient has been diagnosed with other diseases where this is indicated. The choice of antibiotics is determined by the primary disease

4. GENERAL ADVICE ON CHOICE OF ANTIBIOTICS

Antibacterial substances differ from other medication in several aspects:

- They are normally prescribed for a limited time, which means that each new prescription requires a new evaluation of the choice of substance.
- They should preferably have no effect on the animal being treated but only on the bacteria – any effects in the animal are then side effects.
- Resistance can occur in bacteria, which reduces the efficacy of the antibacterial substance.

When selecting an (anti-bacterial) substance the aim should be to prescribe medication approved for equine use, in line with the so-called cascade principle (Please read the Jordbruksverket/Agricultural Board SJVFS 2012:32; "D9", second chapter).

Antibacterial substances have a central role in treating patients, whether human or animals. Antibacterial substances can reduce and cure symptoms but also cause problems. When a veterinarian (or doctor) is prescribing antibiotics a number of aspects must be considered, including if antibacterial treatment is in fact necessary given the condition. There are many conditions when other treatment is possible and use of antibiotics can be avoided. One main advantage if antibiotic treatment is avoided is reducing the risk of antibiotic resistance. Another advantage is to avoid the possible side effects from antibiotic treatment, including gastrointestinal disturbances.

Is an antibacterial substance necessary in the current situation? This question should always be asked! In many cases the reply should be "let's wait", and the horse owner asked to for example take the horse's temperature daily to determine if an infection is present. In other cases, antibacterial treatment is required but the treatment period can be kept short.

CHOICE OF ANTIBIOTICS

In order to make the best possible choice of antibiotics in a treatment situation where antibiotics are deemed necessary it is important to have a thorough understanding of the substances in question. The choice should be based on several aspects including pharmacokinetics, risk of side effects, possible interactions with other medication, activity against different microorganisms, risk of resistance and an understanding of the underlying mechanisms, and if the effect is bacteriostatic or bactericidal. Patients with impaired immune system should if possible be treated with bactericide substances. Sometimes the preparation and mode of administration can determine the choice.

When prescribing substances for indications other than what they are approved for, or if the substance is not approved for horses, the demands on the veterinarian's understanding of these factors are especially high.

Bacteria sensitivity

Bacteria sensitivity for different substances are measured as Minimum Inhibitory Concentration (MIC) expressed in µg/mL or mg/L. To have effect *in vivo* higher concentrations than that are often necessary, because the antimicrobial substances to a varying degree bind to different tissue components, for example plasma proteins.

Resistance testing

When choosing an antibiotic resistance testing is becoming a more and more important aid. The methods must be standardized and quality control very rigorous. A faulty test can give misleading results. In routine diagnostics resistance testing is usually done with the help of dilution or diffusion methods. Irrespective of the method a preselected substance is usually used to represent a whole class of antibiotics.

To facilitate the interpretation a system is used where the result is classified as sensitive (S) when the MIC is below a certain value, or resistant (R) if the result is higher than a certain threshold value. For certain antibiotics an intermediate category is also used (I). The criteria have been developed for general treatment where the MIC value in question is related to the concentration in plasma of the antimicrobial substance at

normal dosage. If a bacterial strain is categorized as resistant this usually means that treatment with an antibiotic from that group will fail. In cases of local treatment very high concentrations can occur at the infection site, and then also antibiotics classified as resistant can have sufficient inhibitory effect for successful treatment. Sensitive bacteria should in principle have an inhibitory effect during treatment, but the testing is of course done in a standardized laboratory setting and the result of a treatment is influenced by many other factors than the substance, such as at what stage of infection the treatment started, the location of the infection site, the individual animal's own immune system, and so forth. A bacterial strain which is classified as intermediate can be treated if the infection is located to tissue where very high concentrations of the antibiotic occur. One important example is ampicillin and the urinary tract.

Pharmacokinetics and dynamics

Pharmacokinetics describe how different antibiotics are metabolized and distributed in the body. It can vary between species and between individuals. The term distribution volume is used to describe the distribution of the substances in the body, expressed as L/kilo. If the distribution volume is <0,5 L/kilo this means that the substance probably distributes itself in the extracellular space (where also most pathogens are located). A large distribution volume (>1 L/kg) reflects that the antimicrobial substance is likely to pass biological membranes and distribute well in body tissues. This often means high intra cellular concentrations. A large distribution volume therefore means that tissue concentrations will be high, but it is only the concentration of the substance not bound by tissue that can wield its effect on the microorganism, and therefore the free concentration in plasma is the best marker of potential effect.

For certain antibiotics, for example beta lactams and macrolides, the result of the treatment is dependent on how long the antibiotic concentration at the infection site is above the MIC. How high the concentration is in relation to the MIC is less important, as long as it is higher than the minimum inhibitory concentration. For other categories of antibiotics, such as fluoroquinolones and aminoglycosides, the killing effect is in contrast dependent on the concentration of the antimicrobial substance; the higher the concentration the better the effect. These antibiotics are called concentration dependent.

Combining the substances pharmacokinetics and pharmacodynamics provides a so-called PK/PD index. These indexes describe which connections between pharmacokinetics and dynamics that have the greatest influence of the effect and is used for example when dosages for a substance are evaluated. The PK/PD-index are: T>MIC (the duration or time when the antibiotics concentration is above the MIC, so time dependent); C_{max}/MIC (the highest concentration (C_{max}) that is achieved in relation to the MIC, so concentration dependent) and AUC/MIC (the area under the concentration curve in relation to the MIC, concentration dependent but to some extent also time dependent).

Combination therapy

Antibiotics that have different effects can act together and have an improved synergy effect. Other combinations can have the opposite result in that the substances counteract each other (antagonistic effect). The interaction between different antibiotics can be very complex. Therefore, only well documented combinations should be used.

Treatment length

What variables that determine treatment length has not been fully researched. Clinical experience of how different types of infections respond to treatment is essential to determine how long a treatment is needed. Chronic infections usually require considerably longer treatment than what is the case for acute infections. One basic rule is that treatment in acute uncomplicated infections should continue until one-two days after symptoms disappeared.

INFORMATION TO HORSE OWNERS

One important factor to ensure a successful treatment is that the person owning, or otherwise responsible, for the horse has a full understanding of why the treatment is done and how the medication should be used. Antibacterial substances can provide a quick improvement of symptoms, tempting the owner to stop the treatment early. This is unsuitable as treatments that end prematurely can result in a relapse.

For a treatment to be successful it is also important that the owner is capable of administering the medication in a correct way. Oral administration is normally the easiest option but can be associated with other challenges. One example is that oral medication is frequently associated with inadvertent cases of

banned medication. If the owner/person responsible lacks experience in administering medication it is therefore recommended to give a practical demonstration. In cases when the substance is given intramuscularly is of vital importance that the veterinarian gives careful instructions to the owner or person responsible how and at where the injection should be made. If the owner has previously had problems administering medication it is particularly important to give practical advice and try and help the owner to resolve his/her specific problems in giving the horse the prescribed substance.

When prescribing antibacterial substances, it is also important to inform the owner about potential side effects. In addition, it is to be recommended to ask whether the owner or person handling the horse is him/herself sensitive or allergic to Penicillin and related substances, as the owner or person handling the horse can easily come into contact with the substance during the administration. To use disposable gloves and wash the hands afterwards should be an obvious routine.

In addition, it is important to discuss where and how the substance is given in the stable, to avoid other horses coming into contact with traces of the substance and perhaps mistakenly taken for medicated at competitions.

The owner should also receive guidelines on handling surplus medication plus any needles or syringes.

ROUTINES

HORSE ID

To prevent administering the wrong substance to the wrong animal the name of the individual horse should be included in the prescription and/or on the package.

STORAGE AND EXPIRY DATES

All medication must be stored in a manner that it cannot be accessed by unauthorized persons, children or other animals.

The medication should also be stored in a manner that protects its properties. A number of factors can affect the quality negatively, for example heat and sunlight. Always observe the storage instructions from the manufacturer. Do not use substances past its sell by date.

The handling of the medicine should prevent any confusion, and all medicine should be kept in its original package. The practical handling of medicines also has a hygiene aspect. This for example includes that membranes on injection bottles are wiped with a sanitizing substance before penetrating it with a syringe, but also the importance of keeping hands clean in all handling of medicines.

DISPOSAL OF MEDICINES

Any surplus medicines should be taken to a pharmacy for disposal. This is free for private individuals, but pharmacies are not obliged to handle medical waste from a business, which includes veterinarians and also horse businesses.

Several chains of pharmacies have waste boxes for sale to businesses, including handling services. As these services differ between chains the advice is to contact your local pharmacy. Pharmaceutical companies can also give advice on disposal. Some waste disposal companies have specific services for veterinary clinics and hospitals. Your local council can also give advice on handling of medical waste from businesses.

WITHDRAWAL TIMES FOR SLAUGHTER

Horses are classified as food producing animals and any prescriptions should include withdrawal times for slaughter. Withdrawal times is the minimum time between the last treatment and slaughter and calculated in 24-hour periods. (Medication also involves withdrawal times to competition for sport and race horses, but this is not discussed in this document).

Administration of medication to food producing animals can result in residues in food from the treated animal. The so called MRL-regulation 470/09/EG has been created to protect consumers from potentially hazardous residues in food. MRL is the highest concentration of a substance allowed in different tissues in order that the food stuff can safely be consumed. For a substance to be allowed in food producing species the manufacturer must have provided an MRL-status. All substances that have been tested for MRL are listed in an annex to EU regulation 37/2010. Table 1 show substances with official MRL values or that has been evaluated as not needing MRL values. Table 2 show substances that are banned in food producing animals as they are deemed to pose a health hazard irrespective of the residue amount. The MRL value is then used to calculate withdrawal times to slaughter. The European Medicines Agency home page

(www.ema.europa.eu) lists more information about MRL and also summaries of MRL studies. The regulations 470/09/EG and 37/2010/EU can be found via EUR-Lex (http://eur-lex.europa.eu/RECH_menu.do?ihmlang=en) or through links on the Swedish Medical Products Agency (www.lakemedelsverket.se).

Once a substance is approved with an MRL value the withdrawal time is calculated by the Läkemedelsverket. The withdrawal time is listed in the summary of product characteristics (SPC), which is also the basis of the description in FASS VET. The Läkemedelsverket homepage show SPCs and a list of withdrawal times for approved substances. If a higher dosage is used than indicated in the SPC the withdrawal time should be lengthened in proportion to the increased dosage.

Withdrawal times for substances sold on license are set by the Läkemedelsverket when the license application is handled.

In cases when you use a substance that is not approved for the species in question or the particular treatment the withdrawal time is regulated by the National Food Agency (Livsmedelsverket)'s regulation (LIVSFS 2009:3; "H65"). It applies to substances approved for a different species, a human medicine or an *ex tempore*-preparation. In these cases, the withdrawal times for slaughter is a minimum of 28 days, if a longer withdrawal period than that is not stated. One main condition for using a medicine at all based on this principle is that the substance has an MRL value. The regulation in full is available on the Livsmedelsverket homepage (www.slv.se).

There are however exceptions made for horses by the EU, allowing the use of substances lacking MRL values subject to certain conditions. The EU Commission has listed substances that are deemed vital for equine use, regulation 1950/2006/EG. This regulation is sometimes called The Equine List. Substances included on this list have a withdrawal time for slaughter of six months. Any treatment of a horse expected to be included in the food chain with a substance with six months withdrawal time should be documented in the horse's EU Equine Passport. Horses without an equine passport may not be treated with these substances.

Substances that both lack MRL status and is not on the Equine List can still be used for horses, provided they are excluded from the food chain. The treating vet is obliged to check if it is declared in the passport that the horse will not be used in the food chain. Do make a note in the horse's medical record that the passport has been checked. The Swedish National Board of Agriculture (Jordbruksverket) is responsible for equine passports (www.sjv.se).

When medication is administered to horses who compete in racing or equestrian sport information about withdrawal times before competitions/races should always be given. Jordbruksverket governs regulations, but the sport organisations, for example the Swedish Equestrian Federation and the Swedish Trotting Association, might have their own and stricter rules for certain substances. These withdrawal rules are listed as part of the doping/banned medication regulations on their homepages.

5. AVAILABLE ANTIBIOTICS

BETA-LACTAM ANTIBIOTICS

Beta-Lactam antibiotics is a major group of antibiotics with bactericide effect. What the group has in common is that the structure contains a so-called beta lactam ring which is important both for antimicrobial activity and possible allergic effects. Among beta lactams are penicillins, cephalosporins and cephamycines.

Mechanism of action
Beta-Lactam antibiotics have effect through binding certain proteins in the bacteria cell wall and thereby blocking its cell wall synthesis. The bactericidal effect is due to inactivation of the inhibition of the bacteria autolysis and is correlated with how long the concentration exceeds the MIC.

Mechanism of resistance
Resistance to beta-Lactam antibiotics in beta-haemolytic streptococci is as yet unknown.

Production of beta lactamase is the most common mechanism of resistance to beta-Lactam antibiotics in both Gram-positive and Gram-negative bacteria, including *E. coli*, *Actinobacillus* sp. and probably also *Bordetella* sp. The property is often transferable. The most common type of beta lactamase, penicillinase, occurs in *S. aureus* in horses in Sweden, and in other countries. Beta lactamase inhibitors such as clavulanic acid are efficient inhibitors of many beta lactams from both Gram-positive and Gram-negative bacteria.

Resistance to cephalosporins in Gram-negative bacteria occur with the formation of beta lactams with affinity for different cephalosporins (cephalosporinases). There are several hundred different beta lactamases with effect on cephalosporins and they are usually divided into different groups based on how" broad" their spectrum is, that is if they are active only against the first and second generation cephalosporins or if they also break down substances from later generations. In *E. coli* and other *Enterobacteriaceae* there are enzymes which break down higher generation cephalosporins, for example extended spectrum beta lactamase (ESBL) including plasmid-carried AmpC. This type of resistance results in a cross resistance between for example cefotaxime, cefatzidime and related cephalosporins. In Sweden these cephalosporins are used in critical situations in human medicine. Finding ESBL including plasmid carried AmpC in bacteria from humans is notifiable, based on the Swedish Communicable Diseases Act.

Methicillin resistance in staphylococcus occur when the protein that beta lactams bind to change. This mechanism results in cross resistance against all beta-Lactam antibiotics (including cephalosporins and cephamycines). Methicillin resistant *S. aureus* (MRSA) occur in horses internationally and have also been found in equine cases in Sweden. Infections with methicillin resistant Coagulase-positive staphylococcus in animals is notifiable by law. Contact the relevant "Länsstyrelse" or County Board and the Swedish National Board of Agriculture.

BETA-LACTAM ANTIBIOTICS – PENICILLINS

Penicillin is a derivate of 6-aminopenicillin acid and differ based on one sidechain. The type of sidechain determines the molecules antibacterial activity and spectra and how sensitive the substance is to bacterial beta lactamase (enzymes that break down the beta-lactam ring).

Pharmacokinetics and dynamics
The distribution volume is small, often less than 0,3 L/kilo. The passage across biological membranes is limited due to a high degree of ionization at physiological pH, and the substances then get distributed in the extra cellular space. Half time is normally short, and most beta lactams are secreted in the active form in urine (nafcillin being the exception).

The antibacterial effect is primarily associated with how long the concentration exceeds the MIC.

BENZYLPENICILLIN

Benzylpenicillin (QJ01C E01) is a derivate of 6-aminopenicillinsyra for parenteral use. Benzylpenicillin is approved for equine use in Sweden both as an easily soluble Na-salt and as a poorly soluble benzylpenicillin-procaine (QJ01C E09).

Activity and Resistance

- **Good activity** (MIC ≤0,25 µg/mL) against Gram-positive cocci (streptococci) and rods and anaerobic bacteria

- **Lower, but still good activity against small** Gram-negative rods such as *Actinobacillus* sp. and *Taylorella equigenitalis* (MIC 0.5-1 µg/mL).

- **Insufficient activity** (MIC > 8μg/mL) against *Enterobacteriaceae* and *Bordetella* sp.

Benzylpenicillin has good activity against beta-haemolytic streptococci (*Streptococcus equi, S. zooepidemicus* and *S. equisimilis*). Resistance against these and other beta-haemolytic streptococci from humans or animals do not exist.

Pharmacokinetics and dynamics
With intravenous administration of benzyl penicillin the half time is short, usually less than one hour. The distribution volume is small (0,2-0,3 L/kg). The substance is distributed in the extracellular space and the passage across biological membranes is limited due to a high degree of ionization at physiological PH.

The secretion is mainly via the kidneys through filtration and tubular secretion, which results in much higher concentrations in urine.

The serum concentration is about 50 μg/mL 5 minutes after an IV injection of 10 mg/kilo. A serum concentration of >0,1 μg/ml will be maintained for about 4 hours. After an IV injection of 20 mg/kilo the corresponding values are about 130 μg/ml and 6 h.

Benzylpenicillin forms a poorly soluble salt with procaine. When penicillin procaine is injected i.m. there is a slow dissociation into benzylpenicillin and procaine which will be absorbed into the blood. This means that the half time and also the duration is markedly prolonged, but also that the time to maximal plasma concentration and to effective concentration will be prolonged compared to when injecting pure benzylpenicillin (in addition the maximal plasma concentration will be markedly longer). Half time will vary between 5 and 25 hours.

Comment
In cases of serious infections with reduced circulation pure benzylpenicillin (without procaine) should be administered IV. Pure benzylpenicillin should be administered at frequent intervals (maximum 6 h), due to the short half time.

Procaine can hamper the effect of s by procaine being transformed into PABA (a sulphonamide antagonist).

Penicillins are in general non-toxic for mammals. One serious exception is the risk of s- called penicillin shock when penicillin (especially penicillin procaine) is injected. One possible mechanism behind the reaction can be an allergy to either penicillin or procaine. For penicillin procaine another cause can be that by mistake the injection site is partly intravascular. This will result in a rapid dissolution of the penicillin procaine (due to it being diluted) and a toxic effect will occur from procaine. Horses are sensitive to procaine.

AMPICILLIN (AMINOPENICILLINS)

Ampicillin (QJ01C A01) and other aminopenicillins are semi-synthetic penicillins with an extended antibacterial spectrum.

Activity and Resistance

- **Good activity** (MIC ≤ 1 μg/mL) against many Gram positive and most anaerobic bacteria plus against Gram negative rods such as *Actinobacillus* sp. and *Bordetella* sp.

- **Medium activity** (MIC 2-8μg/mL) against *E. coli* and *Proteus mirabilis*.

- **Insufficient activity** (MIC > 8μg/mL) against *Klebsiella* sp, other *Proteus* spp. than *P. mirabilis* plus *Pseudomonas* spp.

  Pharmacokinetics and dynamics
  The half time is short. Half times of 0,6-0,7 h have been reported in literature. The distribution volume is small (0,2-0,3 L/kg). The substance is distributed in the extracellular space and passage across biological membranes is limited due to a high degree of ionization at physiological pH. The substance is eliminated through the kidneys through filtration and tubular secretion, which results in very high concentrations in urine compared to the concentration in plasma. With oral use the bio accessibility is very low, in adult horses reportedly circa 3-5 %. This means that oral use of ampicillin is in effect a local treatment in the gastrointestinal system.

BETA-LACTAM ANTIBIOTICS – CEPHALOSPORINS

Categories
Different cephalosporins vary significantly regarding their activity spectra. The Beta-lactam ring in different cephalosporins (from *Cephalosporium acremonium*) and cephamycins (from *Streptomyces* spp.) has a chemical configuration that protects it against certain beta lactamases, for example penicillinase. Cephalosporins are often divided into groups, so called generations, that primarily reflect differences in the activity spectra.

- First generation cephalosporins (cefalexin, cefadroxil, cephalotin) have the narrowest activity spectra. They have good activity against Gram-positive cocci, including penicillinase-forming staphylococci, but the activity against Gram negative bacteria is more limited.

- Second generation cephalosporins (cephachlor, cephoxitin[1], cephuroxim) normally have better activity against Gram-negative bacteria than first generation substances. They resist the effect of some beta lactamases that are formed by Gram negative bacteria.

- Third generation cephalosporins (ceftiofur, cefovecin, cefotaxime, ceftazidime, latamoxef[1]) has good activity against many Gram-negative bacteria through being resistant to the effect of beta lactamases that inactivate first and second generation cephalosporins.

- Fourth generation cephalosporins (cefepim, cefpirom, cefquinom) resist some of the beta lactamases that break down third generation cephalosporins.

Pharmacokinetics and dynamics
The distribution volume is small, usually under 0,3 L/kilo. The passage across biological membranes is limited due to a high degree of ionisation at physiological pH, and the substances thus are distributed in the extracellular space. The half time is usually short and most cephalosporins are secreted in active form in the urine (the exceptions are certain substances with high molecular weight and high degree of protein binding which is secreted through the bile. Some cephalosporins for oral administration are prodrugs, which means that it is metabolites that are active.

The antibacterial effect is primarily correlated to how long the concentration exceeds the MIC.

CEFTIOFUR

Ceftiofur (QJ01D A90) is an antibiotic of the cephalosporin type for parenteral use (third generation) Ceftiofur is not approved for equine use in Sweden (for exceptions see Comment).

Comment
Third generation cephalosporins may only be used in animals in case of infections where other antibiotics are not an option, for example due to bacteria resistant to other antibiotics, and life-threatening conditions when there is valid suspicion that other alternatives will not have effect. In the latter type of case the choice of antibiotics should be re-evaluated when more information is available, for example after an obvious improvement of the clinical status, confirmation of the diagnosis or results from resistance testing.

Activity och Resistance

- **Good activity** (≤ 1 µg/mL) against *Enterobacteriaceae* ,for example *E. coli,* streptococci and anaerobic bacteria. The activity against staphylococcus (also beta-lactamase producing) is also good.

- **Insufficient activity** (MIC ≥ 8 µg/mL) against *Pseudomonas* sp. and Enterococci.

Regarding resistance please note the introductions on cephalosporins and cephamycins.

Pharmacokinetics and dynamics
Ceftiofur is not absorbed after oral administration in horses and must therefore be administered parenterally. The distribution is similar to that of other beta-Lactam antibiotics. The substance is distributed in most tissues but the transport mechanism across biological membranes is poor. Ceftiofur is metabolized by plasma esterases into an active metabolite. Both the substance and the active metabolite has a high degree of plasma protein binding, which means that the half time is longer than for most other beta-Lactam antibiotics. The substance is to a large degree eliminated through the kidneys, both through filtration and secretion.

The effect of cephalosporins is correlated to how long the concentration exceeds MIC.

AMINOGLYCOSIDES

Mechanism of action

Aminoglycosides bind to the 30S-unit of the bacteria ribosomes and thereby block the protein synthesis.

Side effects

The toxic effects of aminoglycosides in kidneys and the inner ear means that systemic use should be restricted to treatment of serious infections with Gram negative bacteria. This involves situations when other, less toxic antibiotics do not have effect and if the clinical situation demands immediate treatment. If aminoglycosides are administered only once daily the risk of kidney damage will be reduced while keeping the antimicrobial effect.

Activity

Many aerobic Gram-negative and some aerobic Gram-positive bacteria are normally sensitive to aminoglycosides. Anaerobic bacteria are not sensitive to aminoglycosides as oxygen is necessary to transport aminoglycosides into the bacteria cells. The activity against other bacteria is also reduced under anaerobic conditions. It is also strongly affected by Ph and works best in a weakly alkaline environment.

Mechanism of resistance

Acquired resistance is usually due to production of plasmid mediated enzymes that inactivate amino glycosides. A great number of different such enzymes have been described and their sites of attack vary. This means that some of these enzymes can only work with a specific aminoglycoside as its substrate and cross resistance to aminoglycosides will not occur. Other enzymes are however less specific and then different patterns of cross resistance will occur.

Pharmacokinetics and dynamics

For systemic use only parenteral preparations are available as aminoglycosides are normally not absorbed from the gastrointestinal tract. The bioavailability after i.m. or s.c. administration is above 90 %. Aminoglycosides are distributed in the extracellular space but accumulate in kidney tissue and the inner ear, where it has toxic effects. The distribution volume is ca 0,15 - 0,2 L/kilogram. The binding to plasma proteins is low. The substances are excreted through filtration in the kidney.

The antimicrobial effect is bactericide and is primarily correlated with the relation between maximal plasma concentration and MIC-value.

GENTAMICIN

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

Comment

Possible side effects are kidney damage and effects on hearing and balance. If administered only once daily the risk of kidney damage is reduced while the antimicrobial effect is unaffected (See above).

Cases of impaired kidney function requires great attention and reduced dosages.

Chloramphenicol block the transport mechanism of Gentamicin into the bacteria cell and therefore has an antagonistic effect.

Aminoglycosides also have a neuro muscular blocking effect by reducing the release of acetylcholine at the motor end plate. The effect has mainly been observed in connection with anaesthesia, which means that Gentamicin should then be avoided.

Activity and Resistance

- **Good activity** (MIC ≤4 µg/mL) against aerobic Gram-negative rods and staphylococci. Also active against *Pseudomonas* sp. The activity is however much poorer in anaerobic conditions.
- **Insufficient activity** (MIC >4 µg/mL) against streptococci including *S. zooepidemicus* and many other Gram-positive bacteria plus all anaerobic bacteria.

Resistance against Gentamicin in Gram negative intestinal bacteria such as *E. coli* exist in Sweden. Resistance against Gentamicin in staphylococci including *S. aureus* do also occur. Reports from other countries describe Gentamicin resistance as a veterinary hospital problem.

Pharmacokinetics and dynamics

The distribution volume is low, about 0,2 l/kilo. Gentamicins distributed extracellularly but cannot passively pass intact biological membranes.

After an im dosage of 6,6 mg/kilo a maximal plasma concentration of about 22 µg/ml will be obtained after about 1h. With IV administration of 6 mg/kilo once daily the concentration maximum will be about 40 µg/ml.

Gentamicin is not metabolised. The excretion occur via the kidneys through filtration and the urine will have high concentrations of active Gentamicin. Very limited excretion occurs via the bile. With normal kidney function Gentamicin will have a serum half time of 1-3 hours. The half time will be extended in case of impaired kidney function.

Plasma protein binding is low (<25%).

The antimicrobial effect is primarily correlated to the relation between maximal plasma concentration and MIC-value.

DIHYDROSTREPTOMYCIN

Dihydrostreptomycin (DHS) is an aminoglycoside for oral administration (QA07A A90), intended for local treatment of the gastrointestinal system, and in combination with different Penicillins (QJ01R A01, QJ51R C24, QJ51R C23) both for parenteral and local use.

Comment
In parenteral administration the risk of damage to kidneys, hearing and balance must be evaluated (see above).

Dihydrostreptomycin has been said to have a synergistic effect together with penicillin against bacteria which are sensitive or medium sensitive to the two substances. It is doubtful if this is actually applying to in vivo situations.

Activity and Resistance

- **Good activity** (MIC ≤8 µg/mL) against aerobic Gram-negative rods and staphylococcus. Please note that the activity is much reduced under anaerobic conditions.

- **Insufficient activity** (MIC >8 µg/mL) against *Pseudomonas* spp. and streptococci and many other Gram-positive bacteria. Anaerobic bacteria are not sensitive.

In Swedish horses, resistance to dihydrostreptomycin is relatively common in Gram negative bacteria (for example *E. coli*).

Pharmacokinetics and dynamics
Dihydrostreptomycin do not pass biological membranes and are normally not absorbed from the gastrointestinal canal, intact skin or mucous membranes.

In parenteral administration the halftime is short, about 2 hours, and the distribution volume small, <0,35 l/kg.

Plasma protein binding is low.

The antimicrobial effect is bactericide and primarily correlated with the relation between maximal plasma concentration and the MIC-value.

MACROLIDES

Please note
Use of macrolides and lincosamides to adult horses carry a very high risk of serious side effects in the form of colitis, with very high mortality. Subsequently the use should be restricted to foals.

Mechanism of action
Macrolides wield their effect by inhibiting the bacterial protein syntheses, by binding to ribosomes (the 50S-unit).

Activity
In general activity is good against many aerobic Gram positive and anaerobic bacteria and also against Chlamydia and Mycoplasma. Activity is insufficient against most other aerobic Gram-negative bacteria. Certain types of semi synthetic macrolides as azitromycin, claritromycin and tulatromycin can however have good activity also against Gram negative rods such as *Actinobacillus* spp.

Mechanism of resistance
Resistance is usually due to changes in the goal structure and can be due either to chromosomal mutations or uptake of transferable resistance genes. The most common is in general transferable resistance and

then in the form of so-called macrolide-lincosamide-streptogramin resistance (MLSB-type), where cross resistance occur between the three groups.

Pharmacokinetics and dynamics

Macrolides and lincosamides easily pass biological membranes, as the substances are lipophilic and mildly alkaline, and therefore to a large extent non-ionized at physiological. The distribution volume is therefore fairly large. This in turn usually means high intra cellular concentrations. For many of the substances the passage to the CNS system is very limited if the meninges are intact, as these substances are often substrates for efflux proteins.

Certain new types of semi synthetic macrolides such as azitromycin, claritromycin and tulatromycin are eliminated very slowly.

The effect of the older macrolides is bactericidal in therapeutic concentrations but in high concentrations it is regarded as bactericide and this is correlated to the duration of the concentration surpassing the MIC.

ERYTHROMYCIN

Erythromycin (J01F A01) is a macrolide antibiotic which currently is not approved for use in animals in Sweden, except with a license.

Comment

Use of erythromycin in adult horses carry a very high risk of serious side effects in the form of fatal colitis, which restricts the use to foals. Foals can also develop diarrhoea during treatment. A serious potential side effect is that the dam (mare) of a treated foal suffers colitis during the treatment. The reason is believed to be contamination, that the mare consumes traces of the substance when licking the foal or nibbling on the foal faeces.

Activity and Resistance

The lowest inhibitory concentration (MIC) for Erythromycin in isolates of *Rhodococcus equi* which have not acquired resistance is estimated at 0.25 - 1 mg/L. Erythromycin resistance occur in *R. equi* but is unlikely to be common in Sweden.

Pharmacokinetics and dynamics

In oral administration Erythromycin can be given either as a salt or as an ester. After absorption the ester is hydrolysed in the blood into the active substance. The concentration of free Erythromycin in the blood is primarily determined by the speed of hydrolysis, as it is usually slow. This means that the half time and therefore also the duration is slightly prolonged but also that the maximal concentration in plasma is lower and the time until maximal plasma concentration is longer compared to when an ester is not administered. Salts of Erythromycin are unstable in acid environments and therefore bio availability is affected.

Bio availability in foals after oral administration is low, at about 15 percent for both ester and salt. The half time of water-soluble erythromycin after i.v. injections is about 1 hour. The distribution volume is large, about 3-4 l/kilo in foals. The substance easily passes biological but the transport to CNS is believed to be small if the endothelia is intact. After oral administration of Erythromycin to foals (25 mg/kilogram) the maximal plasma concentration of 3 μg/ml with the salt and 1 μg/ml with the ester is achieved 1,5 h and 3,0 h respectively (estolate).

SEMI-SYNTHETIC MACROLIDES

Several semi synthetic macrolides are approved in Sweden for other species than horses: tulathromycin (QJ01FA94) gamitromycin (QJ01FA95) and tildipirosin (QJ01FA96).

Tulathromycin and azithromycin (J01FA10) plus clarithromycin (J01FA09) (both approved for human use) are described in literature as an alternative for treatment of infections in foals with *R. equi,* usually in combination with rifampicin.

Comment

Side effects that can be expected are gastrointestinal disturbances, and pain reactions during intramuscular injections. Regarding tulathromycin increased body temperature have also been recorded, especially in cases of high temperature in the environment. As mentioned below *R. equi* is relatively unsensitive to tulathromycin, and consequently this substance is not a suitable choice for treatment of infections with *R. equi.*

Several of semi synthetic macrolides have a long or very long half time. In general, the intra cellular concentrations are very high, probably due to complex processes involving transport proteins, and ion trapping for example in lysosomes with an acid PH.

In many antibiotics the free plasma concentration is a good surrogate for tissue concentration and can be related to MIC. Regarding antibiotics that to a large extent is distributed into tissues the pharmacokinetic parameters that relate to plasma concentrations are of limited value as they do not reflect concentrations at the infection site. Often the half time in the tissue is much longer than in plasma. This means that it is not relevant to relate plasma concentration to MIC in order to optimize the dosage.

Activity, pharmacokinetics and dynamics

Azithromycin: The MIC for *R. equi* without acquired resistance can be expected to be 0,5 - 2 μg/mL. The half time is horses shows great variation and values from 8 to 27 hours have been reported. At the dosage 10 mg/kilo orally the maximal plasma concentration will be approximately 0,8 μg/mL.

Gamitromycin: MIC for *R. equi* s without acquired resistance can be expected to be 0,5 - 1 μg/mL. The half time in foals is about 40 h. At a dosage of 6 mg/kilo and intramuscular injection the maximal plasma concentration will be approximately 0,3 μg/mL.

Clarithromycin: MIC for *R. equi* without acquired resistance can be expected to be 0,06 - 0,25 μg/mL. The half time in foals is about 5 hours. At the dosage 25 mg/kilo orally the maximal plasma concentration will be approximately 0,8 μg/mL. Intestinal uptake is reduced in cases of combined use of Rifampicin and this effect will be increased over time.

Tulathromycin: *R. equi* is relatively insensitive to tulathromycin (MIC 32->64 μg/mL). The half time in foals after a single injection is over 100 hours. The concentration in bronchoalveolar cells is negatively affected by combined use of Rifampicin.

FLUOROQUINOLONES

Mechanism of action
Fluoroquinolones wield their effect by inhibiting the bacteria's DNA-gyrase which result in that bacterial DNA cannot be duplicated. The effect is bactericidal.

Side effects
There are reports of joint cartilage damage in growing dogs related to enrofloxacin treatment, and tendon injuries and tendon rupture, especially of the Achilles tendon, have been reported in humans. Experimental studies of enrofloxacin indicate that equine tendon can also be negatively affected. High doses of enrofloxacin have been reported to cause mild damage in both ligaments and tendons. Ataxia and other neurological symptoms have been observed in connection to rapid iv-administration in horses. Intramuscular injections are not recommended due to unacceptable tissue reactions.

Activity
Fluoroquinolones have very good activity against aerobic Gram-negative bacteria. In addition, some mycoplasma and rickettsia are sensitive. The fluoroquinolones that are available for animal use in Sweden in general have less effect against Gram positive bacteria, but the effect is still sufficient for an effective treatment. Anaerobic bacteria are relatively resistant.

Mechanism of resistance
Resistance is usually caused by a stepwise mutation which results in a gradual increase of the MIC values. Resistance caused by mutations always result in complete cross resistance within the class of bacteria. This type of resistance is the most common today and the clinically the most important. Resistance can develop during treatment, especially in Staphylococci and *Pseudomonas* sp. In recent years several transferable plasmids carrying mechanisms that reduce sensitivity have been described. These mechanisms are believed to have the potential to interact with mutations.

Reduced sensitivity to Fluoroquinolones occurs in *E. coli* and Staphylococci in Swedish horses.

Pharmacokinetics and dynamics
Fluoroquinolones easily pass biological membranes as the substances are lipophilic and to a large extent non-ionized at physiological PH. The distribution volume is therefore relatively large. This often result in high intracellular concentrations. The passage to the CNS varies but is regarded as sufficient for therapeutic needs. The antibacterial effect is best correlated to the relationship between maximal plasma concentrations or the area under the curve and MIC for the infective bacteria.

Enrofloxacin: The distribution volume is 2,3 L/kilo and the half time around 7 h. The bio availability after oral administration is sufficient at around 60 percent but vary with the preparation. Only 3 percent of the given dosage is excreted in the urine, but the antimicrobial active main metabolite ciprofloxacin are to a large extent excreted in urine, giving a good effect also in urine tract infections if the infectious agent is sensitive to Fluoroquinolones.

Danofloxacin: The distribution volume is 2 L/kilo and half time is around 5-6 h.

Marbofloxacin: The distribution volume is 1,6 L/kilo and half time is around 7 h. Bio availability after oral administration is satisfactory at around 60 %. About 40 % of the given dosage will be excreted in urine.

TETRACYCLINES

Mechanism of action

Tetracyclines (oxytetracycline and doxycycline) wield their effect by blocking the binding of tRNA in the bacteria's ribosomes (30S-unit), which in turn blocks the bacteria's protein synthesis. The effect is bactericidal.

Comment

The use of tetracyclines in horses should be carefully evaluated in relation to the risk of serious side effects, primarily severe colitis. Oral administration of tetracycline in horses is not appropriate, for several reasons. One is it can increase the risk of colitis due to poor bio availability. The absorption of Tetracyclines is low when the substance is given in connection with feed.

In addition to antibacterial effect Tetracyclines and pridoxycycline also have an anti-inflammatory and immunosuppressive effects. Therefore, an improvement of symptoms during treatment should not automatically be interpreted as proof that the symptoms were caused by a bacterial infection.

Activity

Tetracyclines have a broad spectrum with good or medium activity against Gram negative and Gram positive aerobic and anaerobic bacteria. In addition, rickettsia and most mycoplasmas are sensitive. *Pseudomonas* spp. are resistant.

Mechanism of resistance

Resistance is usually acquired through uptake of transferable genes. The resistance is caused either by an active efflux mechanism or by the goal structure on the ribosome being protected. When resistance occurs, it is a cross resistance between all Tetracyclines.

Acquired resistance is common among bacteria such as *E. coli* and *S. aureus*.

Pharmacokinetics and dynamics

Tetracyclines are distributed well to most tissues in the body except the CNS, prostate and eyes. Doxycycline which is more fat-soluble do pass also into these tissues. There is a widespread opinion that the concentrations in the CNS are insufficient for most bacterial infections, but positive treatment results in human borrelia infection in the central nervous system have been documented. Transport into the bacterial cell is active, which means that the degree of protein binding in Tetracyclines is of limited importance when evaluating therapeutic concentrations in relation to MIC.

The effect of tetracyclines is bactericidal and is understood to be the result of a combination of both duration and concentration of MIC.

OXYTETRACYCLINE

Oxytetracycline (QJ01A A02) is a tetracycline derivate intended for parenteral use. Oxytetracycline is not approved for equine use in Sweden.

Comment

The substance should only be administered i.v, as local necrosis at the injection site can occur with intramuscular injection. Intestinal disturbances with serious colitis occur.

Please also note the introduction about Tetracyclines.

Activity and Resistance

- **Good activity (**MIC ≤ 1 μg/mL) against many Gram positive and Gram-negative bacteria, against most anaerobic bacteria and against *Borrelia* spp., *Anaplasma* spp., rickettsia, chlamydia and some mycoplasma.
- **Medium activity** against some Gram-negative intestinal bacteria such as *Klebsiella* spp and *Enterobacter* spp.
- **Insufficient activity** against *Pseudomonas* sp and *Proteus sp.*

Acquired resistance in bacterial species such as *E. coli, S. aureus* and streptococci occur.

When testing antibiotic sensitivity tetracycline (oxytetracycline) is the group representative.

<u>Pharmacokinetics and dynamics</u>
Oxytetracycline pass into the placenta and also into milk. The distribution volume is 1,4 L/kilo and the plasma protein binding is between 10-40 percent. Oxytetracycline is eliminated unchanged through glomerular filtration in the kidney but is also subject to enterohepatic circulation as the substance is secreted unmetabolized in the bile. This results in high concentrations of active substance in both urine and intestines. The half time is about 10 h.

Bio availability after intramuscular administration show large variations due to Tetracyclines being a tissue irritant. Bio availability after oral administration is very low.

DOXYCYCLINE

Doxycycline (QJ01A A02) is a tetracycline derivate which is not approved for equine use in Sweden.

<u>Activity and Resistance</u>
Please note the oxytetracycline section.

When testing antibiotic sensitivity tetracycline (oxytetracycline) is the group representative.

<u>Pharmacokinetics and dynamics</u>
Doxycycline is primarily excreted to the intestines.

Bio availability after administration with feed is very low, but there is evidence of sufficient oral bio availability in foals if the substance is given by gavage tube.

<u>Comment</u>
Please note the introduction to the Tetracyclines section.

TRIMETHOPRIM AND SULPHONAMIDES

<u>Mechanism of action</u>
These two substances block the bacteria's folic acid synthesis in two steps. The effect of each substance on its own is bacteriostatic but the combination has a synergy effect and the result is in optimum situations bactericidal.

<u>Activity</u>
The combination of trimethoprim and s has good activity against gram negative bacteria such as *E. coli* and *Actinobacillus* spp, and good to medium activity against Gram positive bacteria such as staphylococcus. Trimethoprim and sulphonamides are also active against certain protozoans and coccidia.

The effect of trimethoprim on sensitive bacteria is counteracted by thymidine. In a similar way the presence of PABA will inhibit the effect of s. Both thymidine and PABA can occur in damaged tissue, especially in connection with pus. The effect of trimethoprim-sulphonamides can then be poorer than expected in certain situations, especially in anaerobic purulent processes with abscesses. PABA can also be from procaine in plasma (procaine is an ester containing PABA).

<u>Mechanism of resistance</u>
Resistance is acquired separately against trimethoprim and sulphonamide. Acquired, transferable resistance against s is widely spread and is due to either reduced uptake of the substance to the bacteria or that an enzyme in the folic acid synthesis is changed so that it becomes unsensitive to s. Resistance against trimethoprim is usually transferable and is, as for sulphonamides, usually due to the formation of an unsensitive enzyme. Resistance against the combination of trimethoprim and sulphonamide is relatively common in Sweden, for example in equine *E. coli*.

<u>Pharmacokinetics and dynamics</u>
Most are absorbed rapidly and to a high degree after oral administration. The degree of plasma protein binding, distribution volume and half time vary between different s.

The effect of the single substances is bacteriostatic, but the combinations have a synergetic effect, and will under optimum circumstances be bactericidal. The effect is dependent on the duration of when the concentration exceeds the MIC.

TRIMETHOPRIM AND SULPHADIAZINE

Trimethoprim and sulfadiazine (QJ01E W10) and trimethoprim and sulphadoxine (QJ01E W13) are combination substances approved for equine use. Trimethoprim and sulfadiazine are available for oral and

intravenous use and trimethoprim and sulphadoxine is only for intravenous use. The ratio between trimethoprim and sulphonamides is 1:5.

Comments

Anaphylactic shock has in rare cases been observed in horses. Intravenous injection should be given slowly with the solution at body temperature.

Administration of trimethoprim-sulphonamide to horses sedated with detomidine can cause fatal arrhythmias.

The dosage recommended by manufacturers is highly disputed. Manufacturers recommend a dosage interval of 12-24 hours but there are reports that the recommended dose should be administered in 12-hour intervals and that the paste is preferable to intravenous treatment, due to better kinetics. This should especially be noted when an infection is caused by bacteria with fairly high MIC values.

Activity and resistance

- **Good activity** (MIC ≤ 1+19 µg/mL, trimethoprim and sulphonamides) against many Gram-negative bacteria such as *Enterobacteriaceae* and *Actinobacillus* spp.
- **Good to medium activity** against Gram positive bacteria such as Staphylococcus and Streptococcus. Also, against other anaerobic bacteria activity can be good to medium *in vitro* but is regarded as insufficient *in vivo*.
- **Insufficient activity** (MIC >8+144 µg/mL) against *Pseudomonas* sp.

Resistance in Streptococcus is common, and relatively common in *E. coli*.

Pharmacokinetics and dynamics

With oral administration of trimethoprim and sulfadiazine both substances are absorbed to a varying degree. The greatest variation is seen with trimethoprim. The highest plasma concentration (Cmax) for trimethoprim vary between 1–4 µg/mL and for sulfadiazine between 18 - 34 µg/mL after repeated administration of trimethoprim (5 mg/kg) and sulfadiazine (25 mg/kg) twice daily in 5 days. The half time is dependent on absorption limited elimination and is ca 8 hours sulfadiazine and 5 hours for trimethoprim.

With intravenous administration the half time for sulfadiazine is ca 4-5h and for trimethoprim ca 3h.

Trimethoprim has a markedly greater distribution volume than the sulphonamide part and the concentration in tissue is higher in plasma for trimethoprim but lower for sulfadiazine. Distribution volume is 2 L/kilo for the trimethoprim part and 0,5 L/kilo for the sulphonamide part.

Trimethoprim and sulfadiazine are partly metabolized in the liver but is also excreted in active form in urine.

Protein binding in plasma is ca 20 percent for sulfadiazine and ca 35 percent for trimethoprim.

The kinetics for sulphadoxine in horses is poorly investigated. Limited information is available in literature. The half time is longer than for sulfadiazine, about 14 h, and the distribution volume is 0,4 L/kg. Protein binding is ca 60 %.

OTHER ANTIBACTERIAL SUBSTANCES

FUSIDIC ACID

Fusidic acid (J01X C01, QD06A X01, QD07C C01, QD09A A02, QS01A A13) is a lipophilic

substance based on a steroid skeleton. Fusidic acid has effect by inhibiting binding of tRNA in the bacteria ribosomes (30S-unit) which blocks the protein synthesis.

Only substances for local treatment of infections in skin, eyes and ears are available for veterinary use in Sweden, but not for horses, unless the horse is removed from the food chain. Fusidic acid should be the primary choice in superficial, uncomplicated corneal ulcers and acute conjunctivitis.

Activity and resistance

- **Good activity** (MIC ≤ 0,5 µg/mL) against Staphylococcus, Clostridia and Corynebacteria.
- **Medium activity** (MIC 1 – 8 µg/mL) against Streptococcus.
- **No activity** against Gram negative bacteria.

Resistance is acquired through mutations when a factor involved in the protein synthesis is changed. Such mutations can occur during ongoing treatment. The resistance mechanism is unique and does not result in

crossover resistance with other substances. Resistance do occur in *S. aureus* and can be presumed to be relatively common among Coagulase negative Staphylococcus

Pharmacokinetics and dynamics
The passage across biological membranes is good and fusidic acid is distributed well to different tissues and is also absorbed through intact skin. Fusidic acid will also pass through the cornea into the eye. The substance is lipophilic.

CHLORAMPHENICOL

Chloramphenicol is a broad spectra antibiotic, efficient against many Gram-positive and Gram-negative organisms. However, *Pseudomonas* is often resistant. The substance is fat soluble and have good penetration to the cornea. In Sweden the substance is available for use in eyes in cream and drops, for human use. In vitro studies in sheep's eyes have shown that cream gives higher concentration in the chamber fluid compared to drops. Chloramphenicol may not be used in food producing animals and if used means the animal may never go for slaughter. Considering that the substance is available for use in eyes, its spectra and good penetration to the cornea chloramphenicol is however in many cases suitable as an alternative to fusidic acid, if the horse can be removed from the food chain. The drops must be given frequently, preferably not less than every fourth hour, but the cream has longer contact time and then treatment 3 - 4 times a day is often sufficient.

METRONIDAZOLE

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

The mechanism of action for metronidazole is not fully known. In anaerobic bacteria the nitroimidazoles are reduced and metabolites cause breaks in the bacteria DNA and inhibit the nucleic acid synthesis.

Comments
Reduced appetite is reported as a side effect in horses, which also makes administration of the substance more difficult. In other species neurological symptoms are common.

Metronidazole also has effect against intestinal protozoa. Metronidazole should not be given to pregnant mares, as the substance can cause chromosomal damage.

Metronidazole is one of the few available drugs against diarrhoea caused by *C. difficile* in humans. To minimise the risk of resistance, use in animals should therefore be curtailed as much as possible.

Activity and resistance

- **Good activity** (MIC $\leq$ 8 µg/mL) against a majority of anaerobic bacteria, including *Clostridium perfringens* and *C. difficile*.
- **Insufficient activity** against aerobic bacteria, but some effect can possibly be achieved also against these in an anaerobic environment.

Resistance is unusual and is believed to be due to reduced production of active metabolites.

Pharmacokinetics and dynamics
Bio-availability is high after oral administration. Half time is 3-4 hours. Metronidazole is relatively lipophilic and is quickly distributed to tissues such as bone and CNS. The substance is metabolized in the liver and secreted via urine and faeces. The degree of protein binding in humans is less than 20 percent.

RIFAMPICIN

Rifampicin is a lipophilic molecule which to a large extent is uncharged at physiological pH.

Rifampicin inhibits the bacteria RNA-polymerase and thereby blocks the bacteria's nucleic acid synthesis.

The effect is either bacteriostatic or bactericidal, depending on the concentration and the sensitivity of the microorganism.

Comments
The substance is currently not approved for use in animals in Sweden. Rifampicin is used in human medicine for tuberculosis treatment, but also increasingly for treatment of infections with multi-resistant bacteria including MRSA. The use of Rifampicin in animals should therefore be restricted as far as possible, in order to minimize the risk of resistance in bacteria that can be transferred to humans.

The only indication for use in horses is treatment of *R equi* infection in foals. The treatment is then normally a combination of rifampicin and a macrolide. The importance of Rifampicin in this treatment is unclear, as studies comparing the effect of combined treatment versus only macrolides are lacking.

Rifampicin can cause a rust- or orange mis-coloration of urine, secretions and mucous membranes, which is completely harmless. In oral administration side effects are unusual, but when given intravenously CNS symptoms, sweating, haemolysis and anorexia have been reported.

Activity and resistance development

The lowest inhibitive concentration (MIC) in *R. equi* which has not acquired resistance is 0,06 - 0,25 µg/mL. Resistance to rifampicin develop fairly quickly through mutations and the substance should never be given as the only substance. Resistance to rifampicin in *R. equi* in Sweden has only been demonstrated on a few occasions.

Pharmacokinetics and dynamics

Bio availability vary after oral administration, between 40 - 70 percent according to literature. The half time after intravenous administration is 5 - 7 hours. After oral administration half times of 8 - 17 h have been registered. The distribution volume is approximately 1 L/kilo, which indicate that rifampicin is distributed well in tissue. The protein binding is relatively high, about 80 %. There are also reports about deviations in kinetics in foals up to six weeks old. Young foals show higher concentrations in plasma and longer half times than adult horses.

In humans it has been shown that rifampicin induces liver enzymes and therefore can affect the elimination of other medicines, and that half time is reduced after repeated administration. A reduction of the half time has also been observed in horses after repeated oral administration.

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APPENDIX 1
HANDLING AND TREATMENT OF CEM

The following instructions are based on consensus recommendations from the Swedish Veterinary Institute (SVA) and the Veterinary Faculty at the Swedish University of Agricultural Sciences.

Mares

Each treatment should be performed daily for five days.

1) The clitoris area is washed carefully with a soap solution. After careful mechanical cleaning a second cleaning is done with 4 % chlorhexidin solution, which is then rinsed off with tepid water. Sinus clitoris can be rinsed with chlorhexidin solution with the help of a syringe and needle. After the cleaning and disinfection Gentamicin cream is applied on the clitoris area.
2) Systemic treatment with antibiotics; Gentamicin or bensylpencillinprocain (secondary choice).
3) Intrauterine treatment with 3 g bensylpenicillin diluted in 100-200 ml sterile water, or gentamicin which is buffered before being put in the uterus.

Stallion

Each treatment should be performed daily for five days.

1) The penis (erect) and outer genitalia is thoroughly washed with a mild soap solution. After careful mechanical cleaning a second cleaning is done with 4 % chlorhexidin solution, which is rinsed off with tepid water. Rub it dry.
2) After cleaning and disinfection Gentamicin cream is carefully applied on the penis and outer genitalia.

APPENDIX 2
GUIDELINES – GASTROINTESTINAL DISEASES

The section on gastrointestinal disease is contained as an appendix as it was added at a late stage of the work on the document. It will be extended in later editions of antibiotic policy for equines. Foal enteritis is listed under foal diseases.

PERITONITIS

GENERAL

Bacterial peritonitis can have different aetiology: be iatrogenic (for example after a rectal examination), trauma (a difficult foaling), vascular injury (for example due to migrating parasites), contamination with intestinal fluids (for example in abdominal surgery) plus other, more uncommon causes (for example an abscess). It is often difficult to determine the aetiology of a peritonitis, which results in the diagnosis "idiopathic" bacterial peritonitis.

DIAGNOSIS

Peritonitis should be suspected in a case history of colic or fever with an abdominocentis that show (opaque, increased tubidity) and confirmed with cytological analysis of abdominal fluid. Bacterial culture should always be done on after a abdominocentis in patients with suspected or confirmed peritonitis.

The abdominocentis is taken in a sterile manner and the abdominal fluid sample is transferred to blood culture containers or immediately passed on to the laboratory for enrichment in a sterile tube (with a tight lid and filled, that is so no remaining air is available, to facilitate survival of any anaerobic bacteria).

TREATMENT

The cause of the peritonitis together with the clinical picture will determine the choice of antibiotics. When traumatic injury to the intestines are suspected (such as rectal exam tears, leakage from anastomosis etc) both gram positive and gram negative bacteria are probably involved, as are anaerobic/aerobic bacteria. In these cases, broad spectrum antibiotics should be given. In "spontaneous" peritonitis with unknown aetiology when you do not have a strong suspicion of intestinal content contamination and the horse's general condition is not affected penicillin is the primary drug of choice. Common bacteria in such cases are for example *Actinbacillus equuli* and S*treptococcus* spp. If the patient has signs of toxicity (malaise, toxic mucous membranes, tachypnoea, tachycardia) or if you suspect contamination with intestinal contents, gentamicin or trimethoprim-sulpha should be added. The antibiotic treatment should start immediately after diagnosis, awaiting test results.

If a good therapeutic response has not occurred within 24 hours after the start of penicillin treatment, medication should be broadened to gentamicin or trimethoprim sulpha. If the culture result show pure culture of bacteria which are only sensitive to one of the antibiotic substances used, those not active are discontinued. If the culture result is negative the diagnosis might have to be re-evaluated. If the horse is still showing signs of peritonitis new samples for culture can be taken.

International literature also suggests use of metronidazole in serious infections as it might involve certain anaerobes such as *Bacteroides fragilis.* It is unclear to what extent Penicillin resistant *B. fragilis* are present in Sweden. In order not to select for antibiotic resistance metronidazole can be reserved for cases when penicillin resistant anaerobic bacteria have been demonstrated in culture and resistance testing, or possibly when failure of initial therapy in combination with a negative culture result indicate that this might be warranted.

The length of treatment is decided based on clinical symptoms, inflammation markers (SAA, fibrinogen, plus with the aid of abdominal paracentesis (cytology).

LAWSONIA INFECTION

In recent years infection with *Lawsonia intracellularis* has been reported from several countries as an uncommon cause of fever, diarrea, colic, hypoproteinaemia and weight loss in older foals (normally 3-7 months). Lawsonia is a wellknown pathogen in Swedish pigs and can in rare cases be a potential diagnosis in older foals also in Sweden. Diagnosis is made based on clinical findings and PCR analysis (faecal sample) or postmortal analysis of tissue samples in connection with autopsy.

Infection in foals with *L. intracellularis* can be fatal if untreated, but the prognosis is good with adequate treatment, that include antibiotics and supportive treatment. As the bacteria is intracellular antibiotics that give sufficient concentrations inside the cells be used. Macrolides (for example erythromycin) or tetracyclines are recommended in literature, with 3-6 weeks duration of treatment.

Rectal abcess

The cause of rectal abscesses is often unknown. Common symptoms are problems to pass faeces plus fever and mild malaise. The diagnosis is made with the help of rectal examination, possibly combined with a rectal ultrasound. One common localisation is the dorsal part of the rectal lumen. With palpation and ultrasound it can be difficult to differ between an abscess, hematoma and reactive lymph node. Aspiration for bacterial culture confirms the diagnosis. In cases where a hematoma is suspected a rectal aspiration is not suitable. Then instead the medical history (for example foaling trauma), blood tests (inflammation markers) and ultrasound imaging can be used to guide the diagnosis.

Bacteria associated with rectal abscesses in horses are *Streptococcus zooepidemicus* and *E. coli.* This means that penicillin or trimetroprim sulpha is the primary choice, in combination with supportive treatment (laxatives/feed causing loose faeces). Empirically a relatively long treatment period is needed. The response to treatment can be monitored palpation and rectal ultrasound. Chirurgical drainage can be indicated. The prognosis for rectal abscesses that do not involve the abdominal cavity is good.

Salmonellosis

Please note that cases of salmonellosis are a reportable disease and handled based on Sweden's Zoonosis legislation (SFS 1999:658). If Salmonellosis is suspected the horse owner must always be informed about the risk of spread to humans and other animals, and how this risk can be minimized.

General/Aetiology

Salmonella infection in horses is relatively unusual in Sweden. Clinical signs of enterocolitis caused by Salmonella can be colic, reduced appetite and general condition plus diarrhoea often acute and watery. Abdominal pain can vary from mild to severe and can precede the loose faeces by a few hours or days. Faeces often smell badly and is green or black in colour. The diarrhoea can develop gradually during a few days or be acute. As the faeces can be watery careful observation of the progress of symptoms are needed, if the diarrhoea is absorbed by thick, absorbent stable bedding. There is a risk of septicaemia, especially in newborn foals, and other organs can then also be affected.

Diagnosis

Bacterial culture from faeces or an organ is necessary to confirm the diagnosis. The earlier in the diarrhoea phase the test is taken, the greater the likelihood is to find the bacteria. Faecal samples (at least 25 grammes) should be taken rectally. As the bacteria are secreted intermittently testing is recommended daily for 3-5 days, to increase the sensitivity of the testing. If infection is suspected in a group of horses the whole group should be tested. Then a single test is usually sufficient to get acceptable sensitivity. The result should then be handled at group level.

Treatment

Treatment of Enterocolitis caused by Salmonella in adult horses is mainly supportive. Antibiotics treatment may even aggravate the condition.

Antibiotics may however be relevant in cases at risk of septicaemia, for example in new born foals, or complications with a spread to the lungs or joints. The choice of antibiotics should be based on resistance testing. In view of the risk of human infection antibiotics such as third generation cephalosporines and fluorochinolones be avoided.

REFERENCES

The text is to a large extent based on reference literature and scientific articles.
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