Bundesministerium
für Ernährung
und Landwirtschaft

Guidelines for the prudent use of veterinary antimicrobial drugs -with notes for guidance-

Revised version (as of July 2010)

Guidelines on antibiotics

Supplement to the German Veterinary Journal 10/2010

Guidelines

General remarks

Antibiotics[1] are only to be used for bacterial infections.

Any use of antibiotics (e.g. in human and veterinary medicine) can cause the development of antimicrobial resistance. The risk increases if antibiotics are used in an untargeted manner, in sub-therapeutic doses, for prolonged periods of time, repeatedly and with emphasis on individual herds.

Antibiotics are indispensable for treating animals and livestock populations and for keeping them healthy. There are, at present, no suitable alternatives to antibiotics.

NOTES FOR GUIDANCE

Antibiotics are almost exclusively effective against bacteria and are ineffective against viruses and fungi.

These guidelines describe the preconditions for the use of antibiotics in animals. It should be borne in mind that, whenever antibiotics are used, both the bacterial pathogen to be fought and the corresponding physiological bacterial flora are exposed to selection pressure and that under this pressure, resistance can be acquired and passed on in both direct and indirect fashion. The guidelines are valid for every use of

[1] The term ″antibiotics“ that is used in the text for reasons of simplification comprises all antimicrobial substances.

antibiotics as part of "good veterinary practice".

They should therefore be observed not only when treating bacterial diseases in farm animals, but also when treating individual, small and pet animals.

The use of antibiotics is only justified in those cases where it is actually required and where the active ingredient has been carefully chosen on the merits of the particular case and the requirements to be met.

Antibiotics are not suitable for offsetting shortcomings in the implementation of "good veterinary practice", poor husbandry conditions, management errors or insufficient hygiene standards.

The guidelines set out the minimum requirements that must always be observed when administering antibiotics to animals.

They represent the rules of veterinary science for the use of antibiotics that must be heeded in any proper treatment under Section 1(a) and 12 of the Veterinary House Dispensary Ordinance (TÄHAV).

Prior to the treatment of any organ system, it has to be specifically examined whether other treatment measures would be suitable for replacing or minimising the use of antibiotics.

As long as the guidelines are complied with, it can be assumed that the use of antibiotics is suitable for achieving the therapeutic objective in each individual case, based on the latest findings in veterinary science.

Guidelines

Antibiotics may only be used if it is established or can be safely assumed that the bacterial pathogen to be controlled in the animals or herd is sensitive to the antibiotic in question.

The use is therefore only justifiable in therapeutic and metaphylactic terms.

Prophylaxis in healthy (uninfected) animals is to be avoided except in justified exceptional cases.

The use of antibiotics is only justified if, on the basis of the diagnostic approach described in point 3 of these guidelines, it is established or can be safely assumed that the disease was caused by a pathogen that is susceptible to the antibiotic in question.

If disease symptoms are only apparent in individual animals within a herd, and if antibiotics are to be used in a metaphylactic manner, it must be substantiated that the remaining symptom-free animals within the herd are expected to become infected with the infectious pathogen in question and that these animals will soon fall ill.

Prophylaxis is only acceptable in exceptional cases and with proper justification, e.g. in connection with an operation or in immunosupressed patients (as a result of the underlying illness or due to therapy with immunosuppressive drugs or cytostatics or the long-term use of glucocorticoids etc.).

The selection of and decision to administer antibiotics is the responsibility of the veterinarian in charge, after having established a proper diagnosis.

Based on his or her knowledge and the latest scientific findings, the veterinarian has to weigh up the risks and benefits for animals, humans and the environment.

Antibiotics are medicines subject to prescription.

Only the veterinarian is allowed to decide on their use.

In conformity with pharmaceutical regulations, they may only be used in specific cases in which the veterinarian, after having established the proper diagnosis, has ascertained the indication for the antibiotic and the animals in need of treatment.

In accordance with the legal provisions in force, antibiotics may be dispensed only by the attending veterinarian or on the basis of a veterinary prescription and used only in accordance with veterinary instructions and under veterinary supervision.

Administration under veterinary supervision does not mean that the veterinarian has to be present in person when the antibiotic is being administered.

However, the veterinarian has to make sure, preferably by means of written instructions, that the animal keeper administers the antibiotic correctly in accordance with the dosage regimen and the animals to be treated, and the veterinarian has to check compliance at appropriate intervals when he or she checks the therapeutic results.

It is inadmissible to dispense an antibiotic for an indication that has not yet been established at the time of dispensing. This is because the decision on the timing of administration and the animals to be treated must not be left to the animal keeper.

The use of antibiotics always requires a diagnosis based on an appropriate clinical examination and, if required, further diagnostic laboratory tests, taking into account the immune status of the animals, stock-specific aspects and other experiences and knowledge.

In order to justify an indication for the use of an antibiotic, an expert diagnostic investigation must be carried out in each individual case.

To this end, the guidelines leave the veterinarian with a sufficient margin to choose the required diagnostic measures in the light of the circumstances of each case.

When a bacterial infectious disease has been ascertained but the pathogen has not yet been clearly identified and immediate treatment is needed due to the disease's gravity or tendency to spread, the veterinarian can start treatment without microbiological findings being available (pathogen identification, antibiogram).

But in this case too, scientifically-verifiable clinical findings and diagnostic measures are needed.

These must be documented in accordance with the obligation to furnish evidence under point 7.

The need for the use of an antibiotic must be demonstrated through suitable verifiable diagnostic measures.

If the clinical symptoms clearly point to a specific pathogen or suggest a presumed pathogen that is known to be controllable by a narrow-spectrum antibiotic, random microbiological examination is sufficient to confirm the diagnosis and resistance situation.

If the clinical symptoms suggest a bacterial infection without the veterinarian being able to draw conclusions as to a specific pathogen and if a broad-spectrum antibiotic is used, microbiological diagnostics are generally needed in order to determine the pathogens involved and their resistance behaviour.

In the case of severe bacterial disease where conclusions cannot be drawn as to a specific pathogen, microbiological testing should (where practicable) always be conducted.

Wherever possible and appropriate, microbiological diagnostics with pathogen identification and antibiogram should, in line with good veterinary practice, be initiated on an appropriate scale when commencing antibiotic treatment.

Pathogen identification and an antibiogram are always necessary after isolation of the pathogen.

This allows targeted further treatment to be conducted in line with the guidelines after a change in medical treatment if the desired therapeutic results cannot be achieved with the initially selected antibiotic.

The isolation of the pathogen is always necessary before preparing an antibiogram because possible resistances can only be detected on this basis.

Preparing an antibiogram for mixed bacterial flora is not expedient because in this case the resistance properties cannot be precisely assigned to individual pathogens.

→ in case of a switch to another antibiotic during therapy if the treatment fails,

→ regularly if the antibiotic is used repeatedly or for a longer period of time in animal groups,

→ if a combination of antibiotics is administered for an indication,

→ in the event of deviations from the conditions for approval (off-label use)

As a rule, switching the antibiotic must be carried out on the basis of the findings of microbiological diagnostics that are initiated in good time before treatment is commenced (see also point 7 on this score, last indent).

The repeated use of antibiotics in a livestock population (e.g. at certain ages and in specific production phases or when bringing in new animals) must always be monitored by regular testing of the resistance situation.

It is not necessary to carry out microbiological diagnostics in each treatment.

The appropriate extent of these examinations depends on the particular case.

It should also be checked which alternatives to antimicrobial use might be promising (e.g. vaccination programmes).

If a combination of several antibiotics that have not been approved as a fixed combination is administered for the same underlying disease, it must be verified by diagnostics that the pathogens involved cannot be controlled with a single active ingredient.

In the case of particularly serious acute illnesses where the pathogen spectrum is not known, a combination of antibiotics may even be necessary at the beginning of treatment before microbiological test results become available.

If the first disease is followed by another infectious disease caused by a different pathogen, the administration of a further antibiotic may be warranted if the new pathogen is not sensitive to the initially used antibiotic.

As a rule, the off-label use of an antibiotic in accordance with Section 56 a (2) AMG, (i.e. administering the antibiotic to cover therapeutic indications or animal species other than those stipulated by the approval) can only be conducted on the basis of an antibiogram or other findings regarding the resistance situation that

point to a "treatment emergency" (no suitable drug has been approved for the animal species or therapeutic indication, the medical care of the animals would otherwise be seriously jeopardised).

The need for an increase in the dose must be substantiated by suitable findings on the resistance situation.

The suitable antibiotic has to be selected on the basis of the following criteria:

→ according to maximum compliance with the criteria for selection (see Annex);

→ reasons must be given for any derogation from the selection criteria;

It can be assumed in most cases that several antibiotics are effective against bacterial infections.

The selection criteria for antibiotics are listed in the Annex and assigned to the respective active ingredients.

Preference should be given to the active ingredient that most closely matches the selection criteria.

If several antibiotics can be used to treat a bacterial infection, preference should be given to the antibiotic with the narrowest spectrum, broad therapeutic range and, if required, bactericidal mechanism of action and good tissue penetration.

If an active ingredient is selected contrary to the criteria set out in the Annex, this must be justified with objective reasons and documented.

If, for example, a wide-spectrum antibiotic is used even though the pathogen can normally be controlled by an antibiotic with a narrower spectrum, reasons must be given for the necessity of this measure based on appropriate findings, an antibiogram or on the basis of existing data on the respective resistance situation. The necessity must also be documented.

Where primary medical care must be provided to treat severe bacterial infections with an unknown pathogen, the use of a wide-spectrum antibiotic is frequently necessary, however.

This has to be justified based on the documentation of the diagnosis including the key findings.

→ so-called "antibiotics of last resort" can only be used where there is a strict indication for this therapy in order to treat individual animals and groups of sick animals;

→ for first-line treatment, especially in the case of an acute disease, the antibiotic can be selected on the basis of clinical experience;

→ immune status of the treated animal, with bactericidal antibiotics being preferred in the case of immune-suppressed patients;

→ the pharmacokinetic properties of the antibiotic and the pharmaceutical properties of the antibiotic being used in order to achieve a sufficiently high drug level for a long enough time in the infected area;

→ if a combination of antibiotics has to be administered, the rules governing the combination of active antimicrobial ingredients must be observed.

Specific antibiotics are an important therapy of last resort against multi-resistant germs.

The availability of these antibiotics is vital for the survival of patients who suffer from life-threatening infections (e.g. MRSA infections caused by Methicillin /Oxacillin-resistant Staphylococci).

Thus a highly restrictive approach should be taken to the use of those active antibacterial ingredients whose activity spectrum and favourable resistance situation means that they are indicated for the treatment of life-threatening infections in humans or animals and where no other sufficiently effective antibiotics are available as an alternative.

These antibiotics therefore constitute "drugs of last resort".

The use of such "antibiotics of last resort" is allowed if - for example after prior sensitivity testing or based on other findings on the resistance situation of other antibiotics - the therapy is highly likely to be unsuccessful or proves inadequate after the beginning of treatment.

Given that, both in the treatment of farm animals and of small and pet animals, that are in close contact with humans, resistant strains can be selected that are of importance in human medicine, such antibiotics should be used in a restrictive manner in animals.

Some of the antibiotics authorised for use in animals include modern active ingredients that are essential for the treatment of serious infections in both humans and animals.

Compliance with strict indications and a particular duty of care applies to the use of these active ingredients, especially when groups of animals are to be treated.

The conditions for approval must be strictly adhered to especially as far as the dosing, duration of therapy and selection criteria of the antibiotic are concerned.

Their use can only be justified if it can be assumed on the basis of sensitivity testing, knowledge of the resistance situation or failure of the therapy to produce successful results that there are no alternative treatments in the case of the illness in question.

In the case of acute infectious diseases whose treatment cannot be deferred, the veterinarian can select the suitable antibiotic as first-line treatment on the basis of clinical findings or based on his experience with the farm-specific circumstances of the particular case or also other evidence (including the pharmacokinetic properties and tolerance).

Deviations from the recommendations including the selection criteria may prove necessary in such cases.

Results from the regular resistance monitoring of the herd attended by the veterinarian or, if such data do not exist, supra-regional species-specific resistance evaluations provide important guidance for decisions in these cases.

If the immune defence is impaired (for example in the case of septicaemic processes or through treatment with immunosuppressive pharmaceuticals), it must be ensured when selecting the therapy that bactericidal antibiotics are used.

Bacteriostatic antibiotics cannot, in this case, guarantee a sufficient reduction in germ load.

The level and duration of the antibacterial drug level in the infected area depend, subject to the dosing, on the pharmacokinetic properties of the antibiotic.

The tissue penetration and thus the achievable tissue level may differ significantly.

Thus, for example, active ingredients from the groups of aminoglycoside and polypeptide antibiotics have lower apparent volumes of distribution (Vd), so that they only migrate into tissues and the intracellular space to a limited degree and may not be able to achieve sufficiently high levels of active ingredients there.

Antibiotics with a high volume of distribution may produce tissue levels that exceed the blood levels (e.g. fluoroquinolones, macrolide antibiotics and phenicoles).

Other pharmacokinetic properties, that are relevant for the dose level and interval, are taken into account in the dosage regimen in accordance with the package leaflet for the respective product.

These properties include the bioavailability, the excretory behaviour, any post-antibiotic effects that may occur, and influences exerted by the pharmaceutical formulation (e.g. prolonged or sustained-release drugs).

Combinations of antibiotics with bactericidal and bacteriostatic action should be avoided due to possible antagonistic effects.

But even within the bactericidal and bacteriostatic groups, specific combinations may be unfavourable because of a possible strengthening of side effects, a triggering of cross-resistances or a mutual neutralisation at the same site of action in the bacterium.

Sulphonamides in combination with trimethoprim are deemed appropriate, for example.

The antibiotics are to be used in accordance with the conditions for approval.

Reasons must be given for any derogation (therapeutic indication, species, dose, type and duration of application):

→ the dosage has to be sufficiently high (at least in accordance with the package leaflet),

→ treatment intervals should be sufficiently short in order to avoid sub-therapeutic active ingredient levels,

→ in the case of stock-specific oral administration, the envisaged dose level must be ensured for the animals in need of treatment, and the spread of the active ingredient must be avoided - this must be controlled at adequate intervals using suitable methods.

If an antibiotic is to be used pursuant to Section 56a (2) AMG ("off-label use"), this can only be done on the basis of a diagnosis that is substantiated, for instance, by pathogen identification, antibiogram or epidemiological evidence on the resistance situation, verifiable clinical findings or anatomicopathological tests.

Off-label use is only permissible in the event of a so-called "treatment emergency" i.e. no suitable and approved drug is available (i.e. is on the market) for the therapeutic indication or animal species and the necessary medical care would otherwise be seriously jeopardised.

In the event of any derogations from the conditions for approval, the responsibility for the efficacy and safety of the animals treated and the safeguarding of consumer safety rests with the veterinarian.

Thus, the veterinarian must ensure through sufficiently long withdrawal periods that the residues in the foodstuffs produced from the animals treated are safe.

According to Section 12a (2) TÄHAV, the veterinarian, when deviating from the conditions of approval, has to calculate the withdrawal periods on a case-by-case basis in such a way as not to exceed the specified maximum residue levels.

In the case of a redesignation of the indication, the withdrawal period indicated on the label of the drug for the species to be treated shall apply, provided there are no other derogations from the conditions for approval.

In the case of a redesignation of the species (off-label use of a drug approved for another species or for humans whose active ingredients have been included in table 1 in the Annex to Regulation (EU) No 37/2010), the withdrawal period must be at least 28 days for edible tissues, 7 days for milk, 7 days for eggs and 500 days divided by the average water temperature in degrees Celsius for fish.

A change in the route of administration or an increase in the dose can also modify the residue formation (e.g. by extending it).

Given that the indicated withdrawal periods have only been examined for the routes of administration and dosages mentioned in the package leaflet, the veterinarian has, in the event of any derogation therefrom, to specify and state a sufficiently long withdrawal period for the respective case that may in this case also be shorter than the above-mentioned minimum withdrawal periods.

When deviating from the conditions of approval, a recommendation for a withdrawal period can ultimately only be substantiated on the basis of specific residue testing.

Antibiotics must always be administered at least in the dose indicated in the package leaflet.

If, due to the resistance situation of the pathogens involved, a higher dosage is required than indicated in the package leaflet, this must be backed up by relevant findings on the respective resistance situation.

In order to enable effective germ control, the treatment interval has to be chosen so as to maintain sufficiently high antimicrobial levels in the infected areas for the entire duration of treatment.

If bacteriostatics are used, sub-therapeutic levels of the active substance should on no account arise in the target tissue.

The dosing interval depends on different substance-specific factors (e.g. on the distribution and excretory behaviour, possibly on post-antibiotic effects, mechanism of action, route of administration and on the product-specific pharmaceutical preparation - long-term formulations, for example).

In order to ensure sufficient drug levels during treatment, the preparation-specific dosing intervals that are indicated in the package leaflet must not be exceeded under any circumstances.

The administration of drugs via feed carries the risk of inaccurate dosing and dispersal.

The veterinarian must therefore ensure under Section 12a (1) TÄHAV that, when antibiotics are administered via feed, the livestock farmer has sufficient know-how and technical prerequisites in order to guarantee that the accurate dose is administered to the animals to be treated, whilst avoiding the medication of animals that do not require treatment.

With regard to the BMELV manual of 19 June 2009 on the oral administration of veterinary drugs in the livestock sector, oral treatment shall be administered via feed or drinking water.

When antibiotics are administered via drinking water, it has to be ensured that a sufficient therapeutic concentration is achieved without delay in all areas of the watering device.

It is necessary to ensure that the recommended dose per kilogramme of body weight is fully absorbed by the individual animal for the recommended treatment period.

Attention must be paid to sufficient water intake, especially in the case of sick animals.

After the end of treatment, the watering device and the equipment that has come into contact with the drug or the medicated feed must be properly cleaned in order to prevent a spread of the active substance that may lead to an intake of sub-therapeutic, resistance-promoting residues of the antibiotic used.

When drugs are dispensed for food-producing animals, the dosage instructions must be specified in the written or electronic documentation of dispensing in accordance with Section 13 (1) TÄHAV that the veterinarian hands over or transmits to the animal keeper without delay.

→ animal keepers shall be instructed about dosing in writing.

Likewise in the case of small and pet animals, animal keepers must be provided with written dosage instructions that contain the length of therapy, type of application, level of individual dose and the treatment intervals in order to ensure the proper use of the antibiotic and compliance.

The duration of therapy has to be as short as possible but sufficiently long to fight the infection in individual cases.

It is based on the organ-specific and pathogen-specific need in each case.

Each therapy with antibiotics must be consistently implemented.

Only in very exceptional cases is a single dose of antibiotic sufficient, e.g. in the case of uncomplicated infections of the lower urinary tract or if a long-acting formulation is used.

A treatment lasting several days is usually required.

In the case of bacterial infections with fever, for example, treatment should be continued at least until the second day after the fever has subsided.

In order to minimise the selection pressure on the bacteria and thus the risk of resistance development, the duration of treatment must be kept to the minimum required for the therapy.

Any unnecessary exposure of the animals to antibiotics has to be avoided.

This applies in particular to the treatment of livestock populations.

In the treatment or post-treatment of bacterial infections, it is usually sufficient to administer antibiotics for three to seven days .

However, in the case of some indications, a longer antimicrobial treatment may be required for individual animals, e.g. in the case of osteomyelitis, deep pyodermas, infections of the upper urinary tracts or infections with high recidivism.

Records must be kept on

→ diagnostic measures,

→ reasons for deviations from the recommendations,

→ controls of the therapeutic results,

→ findings on the pathogen and resistance situation in the herd,

→ in the case of loss of efficacy due to decreasing sensitivity and/or the resistance development of target pathogens, notification of the competent bodies within the scope of the reporting system for adverse drug effects.

When carrying out checks, the supervising authority must be able to understand the justification for each use of antibiotics.

In line with the obligation to retain information laid down in Section 13 (2), first sentence, no. 4 TÄHAV for records in the veterinary house dispensary, the following records shall be drawn up and kept in a clear format (e.g. ordered according to animal keepers) for a period of five years when applying or dispensing antibiotics.

All findings upon which the diagnosis for the use of antibiotics is based under point 3 of these guidelines (e.g. the results of clinical testing, anatomicopathological tests, microbiological diagnostics or epidemiological surveys);

Findings (especially the results of microbiological diagnostics) that can demonstrate the need for off-label use, deviation from the dosage regimen specified in the package leaflet or from the selection criteria for antibiotics;

Date and result of the follow-up examination of the animals treated or the livestock population.

In line with the rules of veterinary science, a control of the therapeutic result is required for every proper treatment at appropriate intervals for the respective individual case and prescribed under Section 12 (2) no.2 TÄHAV.

Regularly collected findings from microbiological diagnostics in livestock populations where antibiotics are repeatedly administered (e.g. at specific ages or in specific production phases, when new animals enter the herd or in the case of adverse drug reactions) are important indicators of stock-specific problems.

According to the professional code of conduct, every veterinarian is required to report adverse drug effects (or a suspicion thereof) to the National Veterinary Association (Bundestierärztekammer) or the Federal Office of Consumer Protection and Food Safety.

This also includes the loss of efficacy of an antibiotic, e.g. caused by decreasing sensitivity and/or the resistance development of target pathogens.

Report sheets are available for notification. These can be downloaded online at (www.vet-uaw.de) and are also published at regular intervals in the German Veterinary Journal (Deutsches Tierärzteblatt).

http://www.vet-uaw.de