**ANTIBIOTICS IN SMALL ANIMAL PRACTICE**
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**Introduction**
Antimicrobials are among the most frequently applied medication in daily veterinary practice. In a small series of lectures, different aspects of the clinical use of antibiotics will be addressed with the aim to illustrate important decision points in the selection of the right antibiotic agent for an individual patient, taking into account therapeutic efficacy and the expected clinical outcome as well as the risk of therapy failures and the emergence of antimicrobial resistance.

**Dynamics of antimicrobials: gateway to efficacy**
The selection of a specific antibiotic for a diagnosed disease condition requires insight into the biology of the pathogen (primary and secondary infections), host factors (vulnerable tissues, innate and acquired immunity) and the mechanism of action and kinetics (absorption, tissue penetration and routes of elimination) of the applied antibiotic.

The potency of an antimicrobial agent is commonly described by the MIC value. This minimal inhibitory concentration (MIC – µg/ml broth) is determined *ex vivo* by exposing a defined bacterial population, cultured in broth, to increasing concentrations of the antibiotic under consideration. The outcome of this assay is a concentration that prevents bacterial growth during the test period (generally 24h). If this assay is conducted in a range of bacterial (field) isolates of the same bacterial species, the MIC50 or MIC90 value is recorded as the mean MIC that is effective against 50% or 90% of the isolates, respectively, of this bacterial species. The MIC determination provides, however, limited information about the mode of action of the antibiotic. Even more importantly, *ex vivo* values do not account for major kinetic parameters that determine clinical efficacy, such as free drug concentration at the target site (protein-bound drugs are not active under *in vivo* conditions) and the variable (time-dependent) concentrations of the antibiotic in the animal’s body. Taken together, this indicates that MIC values are a gold standard as a qualitative parameter, which successfully can guide the selection of an appropriate antibiotic that is likely effective against the pathogen. However, the clinical efficacy of the installed therapy depends on more parameters than just MIC values.

Antimicrobial agents are commonly classified as being either bacteriostatic (limiting bacterial growth) or bactericidal (killing bacteria). This classification is rather artificial and there are numerous reports indicating that a bacteriostatic antibiotic can become bactericidal at higher concentration, whereas a bactericidal substance may inhibit growth (comparable to a bacteriostatic antibiotic) at lower concentrations.

**Common mechanisms of antimicrobial agents comprise:**
- Interaction with cell-wall synthesis: an effect that is bactericidal for dividing bacteria but not for non-multiplying bacteria. The presence of these agents may well inhibit bacteria also at sub-bactericidal concentrations (post-antibiotic effect) and delaying the multiplication cycle. Typical examples for the group are β-lactam antibiotics i.e. penicillins and cephalosporins as well as glycopeptides.
- Alterations of the 30S and 50S ribosomal subunits of bacteria, resulting in a reversible inhibition of protein synthesis. This effect is commonly bacteriostatic. Exposure of bacteria for a longer period to high concentrations of these agents may result in an apparent bactericidal effect, reducing significantly the number of bacteria. Typical examples are the group of macrolides, ketolides, azalides, lincosamides, phenicols and tetracyclins.
- Interactions with bacterial protein synthesis and synthesis of aberrant proteins following binding of the antibiotic to the 30S ribosomal subunit, resulting in a bactericidal effect (aminoglycosides).
- Alteration of nucleic acid metabolism and/or DNA replication, resulting in a rapid bacterial killing as observed for many fluoroquinolones, which act as topoisomerase inhibitors.
- Antimetabolite activity, initially leading to bacteriostasis, which may progress into a bactericidal effect (trimethoprim, sulfonamides).
- Derangement of the electric potential of the bacterial cell membrane, leading to membrane depolarization and a bactericidal effect (cyclic lipopeptides such as daptomycin).

Proceedings of the European Veterinary Conference - Voorjaarsdagen, 2011 - Amsterdam, Netherlands
Understanding of the mechanism of action is one of the prerequisites to establish an optimal dosing regime.

**How can we develop optimal dosing regimes**

This comparison of bacteriostatic and bactericidal effects demonstrates that the therapeutic result will depend on the dose/concentration and the time of exposure of the bacterial population to an antibiotic agent. Subsequently, for a clinical interpretation of the abovementioned mechanisms the terms TDD and CDD have been coined. Time Dependent Dosing (TDD) refers to classes of antibiotics, for which the therapeutic effect is based equally upon the concentration and time of exposure. These drugs need to be given for several consecutive days to guarantee a full therapeutic response. The most critical parameter for time-dependent antibiotics is the time above MIC (T>MIC) and/or the AUC24/MIC. Pharmaceutical formulation and dosing regimes that result is constant plasma and tissue levels will exert an optimal effect.

CDD (Concentration Depending Dosing) describes antibiotics that are able to eradicate large parts of a bacterial population when given in an appropriate concentration/dose. The killing effect is determined by the \( C_{\text{MIC}} / \text{MIC} \). \( C_{\text{MIC}} \) should be 8-10 times higher than the \( \text{in vitro} \) MIC value. During the last decade, for such agents, including most fluoroquinolones and aminoglycosides, dose-recommendations have been amended towards higher doses given for a shorter treatment period. This dosing regimes can guarantee efficacy and prevent emergence of resistant bacteria (mutation-prevention concentrations as target in the dose estimation). In clinical practice, concentration dependent antibiotics are used in critical patients and in any other situation where an immediate result is feasible (nature of infection) or necessary (immune-compromised patients, neonates). For patients with chronic infections or with infection sites, which are difficult to reach (skin, urinary tract, bone and others) generally time-dependent antibiotics are preferred. It needs to be reiterated that an optimal dosing regime not only results in a therapeutic response but should prevent (as much as possible) the induction of antimicrobial resistance. Recent approaches aim to present animal models (\( \text{in vivo} \) and \( \text{ex vivo} \) investigations) that allow an integration of pharmacodynamic (antibacterial effect) and pharmacokinetic (absorption and organ distribution) parameters to establish optimal dosing regimes (PD/PK analyses).

Of growing interest is also the capability of bacteria to form biofilms on mucosal and internal surfaces of different tissues and organs, such as the urinary tract, the mammary gland, the endocard, the inner ear, as well as in the air sacks of birds or the skin of amphibians. Biofilms are defined as a sessile community of bacterial on a biological surface and biofilm growth confers tolerance to almost all antibiotics, and hence are prominent causes of therapy failure and recurrent infections. The formation of biofilms is promoted by diverse physico-chemical (shear forces though air flow or blood flow) and biochemical factors including changes in the local pH and oxygen supplies. In addition, antibiotics stimulate biofilm formation, particularly at suboptimal concentrations. The latter favour also emerge of bacterial resistance.

**Species differences in antimicrobial therapy**

Undesirable side effects (dysbacteriosis) are many associated with anatomical and physiological differences in the gastro-intestinal tract of the different animal species. Companion animal practices experience an ever-increasing diversity of animal species. While differences in drug susceptibility between cats and dogs are commonly reported, small pets like guinea pigs and hamsters, ornamental birds and amphibian, are certainly minor species in terms of preclinical and clinical investigations with antibiotics. While the risk of dysbacteriosis in rabbits, hamsters and other herbivorous species, following the use of antibiotics is well recognized, the differences in the sensitivity of pathogens in these species and the impact of the pharmacological formulation on the therapeutic outcome has been widely neglected. Altered absorption profiles from non-conventional application sites in birds and reptiles makes the extrapolation of common dosing regimes virtually impossible and kinetic investigations would need to be conducted in all these animal species to establish an optimal dosing regime. This became especially evident when one of the recently developed long-acting cephalosporins used in dogs, was given to different non-target animal species. A large variability in kinetic parameters are also recorded from birds, related to the common diet for individual species and categories.

**Therapeutic concepts: co-mediation and drug interactions**

The most critical question to be addressed in antibiotic therapy is the duration of treatment. Long-term antibiotic therapy is justified only under exceptionally and
for very few clinical conditions. Long-term applications bear the risk of the selection of resistant (less sensitive) bacterial population and the induction of host mechanisms (such as the expression of efflux transporters and drug-metabolizing enzymes that reduce the tissue distribution of an antimicrobial. The efficacy of antibiotics can be enhanced indirectly by a concomitant application of anti-inflammatory drugs and other supportive therapies that restore organ function and hence the innate immune response. Therefore, the application of an antibiotic alone should be confined to acute (local) infections, while systemic and chronic infection require a combined therapy and a clear therapeutic concept aiming at the prevention of tissue damage and improving and shortening the recovery period. While interactions between different classes of antibiotics may be beneficial (for examples penicillins and aminoglycosides) other combinations may be less effective (combinations of antibiotics acting on membrane synthesis with bacteriostatic agents). However, as yet, no adverse drug interactions have been reported between antimicrobials and NSAIDs and hence their combined use is increasingly promoted to alleviate discomfort for the animal and reduce tissue damage due to inflammation. Supportive therapy, particularly in broncho-pulmonary infections may have additional positive effects on the distribution of antibiotics to the alveolar surface, the residence site of many bacterial infections and hence support the efficacy of antimicrobial agents.

Conclusions
Insight in the mode of action and an optimal therapeutic use has significantly influenced the current concepts of an antimicrobial therapy. A critical review of the clinical applications of antibiotics is not only desirable in term of an increase of the number of successful treatments, but also in terms of a responsible use of antibiotics in a way that the risk of resistance is minimized. Transmission of resistant pathogens and commensal bacteria between pets and their owners has been demonstrated in various investigations. As pets often share a close relationship and many physical contacts with their owners, the correct use of antibiotics in daily practice remains a challenging tasks for the veterinary practitioner.