RATIONALIZING ANTIMICROBIAL TREATMENT FOR RESPIRATORY INFECTIONS: STEPS TO TAKE TODAY AND TOMORROW
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Respiratory tract infections (RTIs) are the most common infections worldwide. They are a source of significant morbidity, mortality and a considerable economic burden to modern cattle farming. A particularly urgent issue is that they account for over 65% of the antimicrobial use in intensive calf rearing systems. The European Union commissions a significant reduction in antimicrobial use in food animals in the following years, as part of a more sustainable production system. With enlarging groups of animals to be managed by the same person, metaphylactic therapies (group treatments) have become increasingly popular over the last 20 years. From the perspective of human medicine or the public opinion, several aspects like treating in contact animals with mild signs and the almost standard use of antimicrobials in cases of primary viral origin are highly controversial and perceived as signs of irresponsible antimicrobial use. Additionally, the recent findings that about 40% of calves housed in herds not reporting any issues with respiratory diseases, have pneumatic lesions on lung ultrasonography (so-called subclinical pneumonia) complicate things, pointing to a possible welfare issue by not treating these animals (van Leenen et al., 2018). Looking at a recent meta-analysis of metaphylaxis for bovine respiratory disease (BRD), at first sight moderate (but highly variable) reductions in respiratory morbidity are shown. However, the number needed to treat at a common attack rate (= percentage of ill animals at the point of initiation of a group treatment) of 10%, ranges between 10 and 100. This means that many animals need to receive the treatment, before one would be saved, numbers unlikely to be accepted by consumers. Also, the highest absolute risk reductions have been shown in randomized clinical trials, with a follow-up period of less than 30 days, whereas longer trials show no effect anymore. The results of this meta-analysis clearly raise doubt whether metaphylaxis and treatment at the earliest signs are the best approach to manage respiratory infections in cattle. To tackle antimicrobial mass medication to control respiratory infections, a shift from group to individualized treatments will be essential.

In this talk, an overview of general principles to rationalize antimicrobial use based on recommendations of the world health organization directed to human medicine is provided. The example of bovine respiratory disease (BRD) is elaborated.

Rational antimicrobial therapy
Rational use of medicines requires that animals/patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community (WHO, 2019). Prudent use is defined as use which benefits the patient while at the same time minimizing the probability of adverse effects for the individual and the emergence or spread of antimicrobial resistance. In fact the terminology ‘prudent use’ is used interchangeably with judicious, rational, adequate, correct or optimal antimicrobial use. In a farm animal context rational antimicrobial therapy can be freely translated to optimum therapy for the animal (welfare aspect), farm economics (productivity aspect) and public/environmental health (resistance selection). Basic concepts for a rational use are: (1) use of effective antimicrobials in the first, empiric treatment; (2) use the narrowest spectrum possible, targeting the pathogen but with minimal collateral damage to the resident flora; (3) include microbiological testing as much as possible; (4) avoid oral therapy (order of resistance selection: oral therapy >> parenteral therapy > local therapy); (5) individual treatments (abandon group treatments) and (6) do not use combinations of antimicrobials with an unproven synergism. It is clear that the largest progress can be made with a switch from a group therapy approach towards individual therapy. Likely, a rational view point would be only to treat animals with bacterial pneumonia. Off course, veterinarians can immediately raise several practical issues for this approach, in particular how to reliably identify animals with a bacterial pneumonia.

The antimicrobial decision making process
Worldwide, thousands of veterinarians daily take numerous decisions to initiate antimicrobial therapy. Potentially not all of them realize it sufficiently, but a whole reasoning process proceeds their decision. In figure 1 an overview of steps to take...
in the antimicrobial decision making process is provided. The first step is detecting the ill animal. The initial evaluation of every case consists of clinical assessment, a diagnostic work up, therapeutic decision and ‘owner’ education. WHO recommends ‘an informed choice for an optimal antimicrobial’, which can be selected by taking 5 reasoning steps: (1) What is the severity of the infection?; (2) What is the most likely source and pathogen?; (3) How likely is it that the infection is caused by resistant bacteria?; (4) Are any patient factors to be taken into account?; (5) Do I need to sample and request culturing before initiating therapy?. Thereafter, an empiric therapy is started. An empiric therapy is defined as a therapy which is not supported by any microbiological analysis. The veterinarian basis his selection of an antimicrobial on his own experience (most likely bacteria for this presentation in this farm), own farm data and national data. When results of microbiological testing become available an evaluation should be done. This process has 4 steps: (1) review microbiological data; (2) assess spectrum of empiric therapy, (3) check for adverse effects and (4) evaluate route and duration of therapy. When antimicrobial susceptibility test results become available, the veterinarian can evaluate whether his empiric therapy can be judged as appropriate (= bacteria are susceptible to the selected drug) or inappropriate (= bacteria are resistant to the selected drug). An antimicrobial treatment which is supported by an antimicrobial susceptibility test is referred to as a definitive antimicrobial therapy. For many reasons, but especially when dealing with group treatments, veterinarians will need to base their antimicrobial regimens on susceptibility testing of representative isolates from the group. Advances in detection of animals with respiratory tract infection

Enlarging group sizes make detection of ill animals more difficult, especially when relatively the number of surveilling staff has decreased. In many countries, an increasing number of respiratory tract infection diagnoses and treatments are made by producers. A meta-analysis using Bayesian inference showed that the overall sensitivity (Se) and specificity (Sp) or producer diagnosis in feedlot systems reached 27% (12-65) and 92% (72-98)\(^2\). However, a good screening test needs a high Se, because false positive cases can still be excluded by the confirmation test after which the case will be finally diagnosed. In fact, many producers and veterinarians already apply the screening test-confirmation test principle, as they pull animals from groups based on signs like depression, and confirm disease in these animals by taking temperature. However, a danger of this selection is that Se and Sp of all tests evaluated for BRD, with much better diagnostic accuracy as interrater agreement are obtained. Also in human medicine especially use lung auscultation as a confirmation test, but both mean diagnostic accuracy as interrater agreement are poor (Pardon et al., 2016). To date lung ultrasonography has the highest Se and Sp of all tests evaluated for BRD, with much better interrater agreement\(^2\). Parallel testing looking at multiple signs at once in all animals) and the use of lung ultrasonography is the time between sampling and availability of an antibiogram. For fastidious growers like Pasteurellaceae, a disk diffusion antibiogram can be obtained as early as 48h after sample arrival in the laboratory, but on average it will take 4-5 days. For Mycoplasma bovis, standard identification procedures alone already take 6-7 days. Using the MBT-ASTRA procedure in MALDITOF mass spectrometry, susceptibility testing for oxytetracycline in Pasteurella multocida was done as fast as within 3h, starting from a purified colony. This technique had a Se of 95.7% (89.8-100) and Sp of 100% (100-100) compared to the reference test\(^1\). Also direct detection of the pathogens in broncho-alveolar lavage fluid (BALF) is likely possible, making the final target of pathogen identification and susceptibility testing within the day of sampling possible at comparable cost as standard culture and disc diffusion testing.

Precision medicine to reduce antimicrobial exposure

Not only limiting the number of animals receiving antimicrobial therapy, but within a single animal also limiting exposure of the resident flora to antimicrobial selection pressure is essential. Assuring correct dosing by weighing animals at treatment initiation will already result in better therapy, as the majority of parenterally administered antimicrobials are overdosed, whereas oral antimicrobials are often underdosed\(^5\). Especially with concentration dependent antimicrobials, like fluoroquinolones, optimal dosing strategies aiming at limiting development of antimicrobial resistance by dosing above the mutant prevention concentration have been explored\(^6\). Similarly, these studies show that the required treatment length, dosage and efficacy depend on the time of therapy initiation in the disease process\(^7\). Also, the rapid elimination of these drugs mitigated long term impacts on fecal Escherichia coli resistance\(^8\). In many situations, clinical cure is the evaluation criterion. When using antimicrobials requiring a daily dosing interval, this will typically be evaluated at a post-treatment interval of 1 day, prolonging treatment with one day when judged not cured\(^9\). Off course, evaluation of clinical cure is likely highly suggestive and prone to a higher interrater variability. When using long acting products, the likely moment to decide on prolongation or cessation of therapy would be after the registered treatment length of the specific product has passed. Based on available post treatment interval studies comparing different treatment lengths, the recommended treatment length would be 7 days\(^10\). A limitation is that these studies mainly were done by pharmaceutical companies. Also in human
In conclusion, the WHO provides clear information on steps to take in the antimicrobial decision making process, which can aid practitioners in their daily work. Clearly, many improvements in detection, diagnostics and therapy follow up are required, before veterinarians will feel safe enough to leave animals not evidenced as bacterial pneumonia untreated.

Figure 1. Overview of terminology and steps in the process of antimicrobial decision making in animals

References


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