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A proposal of clinical breakpoints for amoxicillin applicable to porcine respiratory tract pathogens

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Abstract

In the present position paper, an attempt was made to establish clinical breakpoints of amoxicillin to classify porcine respiratory tract pathogens as susceptible, intermediate or resistant based on their minimum inhibitory concentrations of amoxicillin. For this, a thorough review of the published literature with regard to swine-specific pharmacological data (including dosages of amoxicillin applied and routes of administration used), clinical efficacy, and *in vitro* susceptibility of the target pathogens was performed. Based on the comparative analysis of the results, the working group ''Antibiotic Resistance'' of the German Veterinary Medical Society (DVG) proposed to classify porcine respiratory tract pathogens that show MIC

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values of amoxicillin of ≤0.5 μg/ml as ''susceptible'', those with MICs of 1 μg/ml as ''intermediate'', and those with MICs of ≥2 μg/ml as ''resistant''.

Keywords: Antibiotic therapy; Breakpoints; Swine; Respiratory diseases; Amoxicillin

1. Introduction

According to prudent use guidelines, the *in vitro* susceptibility against antimicrobial agents of bacteria, which are considered to be causative for a specific disease condition, should be determined prior to therapy. This approach shall ensure that only those substances are applied to which the causative bacterial pathogens exhibit susceptibility under *in vitro* conditions and, therefore, are likely to result in a successful treatment. The classification of the tested bacteria as either ''susceptible'', ''intermediate'', or ''resistant'' is based on breakpoints. Currently, two distinct groups of breakpoints are used: microbiological breakpoints (also referred to as epidemiological cut-off values) and clinical breakpoints (Bywater et al., 2006). Microbiological breakpoints differentiate between subpopulations which exhibit different levels of susceptibility to a specific antimicrobial agent. In bimodal distributions of MIC values, the microbiological breakpoints separate a presumably susceptible subpopulation from a presumably resistant subpopulation (Bywater et al., 2006). However, microbiological breakpoints do not consider pharmacological aspects of the antimicrobial agents administered. In contrast, the concentration of the antimicrobial agents which can be achieved by the recommended dosing at the site of infection is a key parameter for the determination of clinical breakpoints (Bywater et al., 2006). Other aspects relevant for the determination of clinical breakpoints are the minimum inhibitory concentration of the causative pathogens as well as pharmacokinetic and toxicological aspects. The complexity of parameters involved in the determination of clinical breakpoints shows that clinical breakpoints do not represent values that can be directly measured. Instead, they have to be derived from the results of extensive studies which take into account microbiological, pharmacological and clinical aspects (Böttner et al., 2000). This has previously been shown in detail for the establishment of clinical breakpoints for tilmicosin (Shryock et al., 1996) and ceftiofur (Burton et al., 1996).

Approved clinical breakpoints are an important criterion in the decision for or against a specific antimicrobial agent in therapeutic interventions (Woolcock, 1993; DIN, 2000; NCCLS, 2002b). However, it should be noted that clinical breakpoints do not guarantee in every case that the treatment will be successful, but they help to minimize the risk of therapy failures (Richter et al., 2006). While clinical breakpoints are in principle established for an antimicrobial agent, they initially apply only to the original pharmaceutical product used and are not necessarily valid for the respective generic products.

Due to the lack of veterinary-specific data, the classification of veterinary pathogens as susceptible or resistant is often based on breakpoints adopted from human medicine (NCCLS, 2002a, 2004). This applies particularly to older antibiotics that have been in veterinary use for several decades, such as tetracyclines, ampicillin, or amoxicillin. Since the spectrum of bacterial pathogens as well as the distribution and metabolism of antimicrobial agents differ distinctly in humans and animals, the non-verified adoption of breakpoints from human medicine for use in veterinary medicine is scientifically questionable.

This position paper represents an attempt to establish veterinary-specific clinical breakpoints for amoxicillin based on data available in the published literature. Amoxicillin is a member of the semi-synthetic aminopenicillin group of antibiotics which exhibit a broad spectrum of activity against Gram-positive and Gram-negative bacteria and displays a bactericidal mode of action. Amoxicillin is used extensively in the treatment of bacterial infections of animals and is approved in a variety of formulations for use in cattle, pigs, poultry, horses, dogs and cats. For pigs, aqueous and oily preparations for parenteral administration (intravenous, subcutaneous, and intramuscular) are world-wide approved. Water-soluble powders are also available for oral medication either