ANTIMICROBIAL RESISTANCE MECHANISMS: WHAT IS RELEVANT FOR MY PATIENT WITH SKIN AND EAR INFECTION

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BACKGROUND
Microbial infections of the skin and ear are common in pets and frequently involve multidrug-resistant (MDR) bacteria that are difficult to treat. In addition, the often close contact between pets and people creates opportunities for transmission of MDR bacteria between hosts and subsequently for exchange of resistance genes between bacteria from new hosts. The origins of resistance genes have been traced back millions of years (1). The ongoing selection process of resistant organisms through appropriate and inappropriate use of antimicrobials in medicine, veterinary medicine and in agriculture is still studied from many angles but reducing selection pressure is still a major challenge. In small animal practice, understanding the basic mechanisms behind antimicrobial resistance in relevant skin pathogens will support opportunities for good antimicrobial stewardship. This is particularly important for patients with skin disease which often present with recurrent infections and where pathogens are present on the body surface, ideally located for transmission between hosts.

DEFINITIONS
Bacteria that are resistant to several classes of antimicrobials are often described as multidrug-, extensively drug- or pandrug-resistant. But despite widespread use of such terminology, definitions are not internationally validated and differ in relevance between bacterial species (2, 3). In general, resistance can be intrinsic to a particular bacterial genus or species, i.e. present as an innate ability to resist a particular antimicrobial drug. Such natural insensitivity can occur if there is no bacterial target or if the bacterial cell is inaccessible to the drug, e.g. β-lactam antibiotics and glycopeptides will be ineffective in cell-wall free bacteria such as Mycoplasma. Such intrinsic resistance is usually incorporated in recommendations by drug manufacturers on indications for a particular drug. In contrast, acquired resistance is isolate-specific and can change over time in bacteria present as part of an individual’s healthy flora but also during an infection. It occurs either through mutation of genes involved in normal physiological processes or structures or from the acquisition of mobile genetic elements carrying resistance genes.

RESISTANCE MECHANISMS
All three known resistance mechanisms occur in staphylococci and Pseudomonas spp.. 1. Enzymatic modification or inactivation of drugs is frequently encountered for example through acetylation or hydrolytic cleavage of bonds within the drug molecule as for example through beta-lactamases. 2. Reduced intracellular accumulation of drug occurs either through reduced influx or increased efflux via pumps. This is of relevance for example in resistance of Pseudomonas against fluoroquinolones. 3. Alterations at target sites are involved in methicillin-resistance, sulphonamide and macrolide resistance and many others, mediated through a large number of well described resistance genes (4).

RESISTANCE GENES
Information on individual resistance genes has increased dramatically over the past few decades with the availability of molecular tools. Genetic data could be combined with information on minimum inhibitory concentrations to identify the clinically most relevant genes for bacterial pathogens. The most relevant genes will be outlined in this session. Resistance to β-lactam antibiotics in staphylococci can either be
mediated through narrow-spectrum beta-lactamases encoded on blaZ which has been identified as widespread amongst *S. pseudintermedius* and *S. aureus* (5). The gene encoding meticillin-resistance, *mecA*, is responsible for a broad resistance to all β-lactam antibiotics. It is part of a large chromosomally located cassette which, due to its size, is not very mobile and has therefore not managed to move horizontally very often in the evolution of meticillin-resistant staphylococci. Only a limited number of meticillin-resistant lineages are found compared to the genetic variation seen in *mecA*-negative lineages. Resistance to fluoroquinolones is associated with point mutations in the DNA gyrase and topoisomerase genes and the occurrence of in vitro susceptibility to one but not all members of the class is still poorly understood (6). Where fluoroquinolone therapy is initiated for an isolate showing resistance to one or more other class members, close monitoring of treatment progress is warranted.

**TRANSFER OF RESISTANCE GENES**

Chromosomal mutations that lead to resistance (such as to e.g. fluoroquinolones and sulphonamides), can only be transferred vertically. In contrast, resistance genes located on mobile genetic elements can be spread horizontally between bacteria, potentially conferring important evolutionary advantages to bacteria. Plasmids and transposons (bacteriophage) are the best known mobile genetic elements described to carry resistance genes. For those MGEs in particular, selection pressure during treatment but most importantly during recurrent infections is highly relevant and clinical scenarios will be discussed during the session.

Resistance genes and resistance mechanisms are not linked to virulence characteristics and will therefore have little direct influence on the prognosis of infections.

**REFERENCES**