Review

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Multidrug resistance genes in staphylococci from animals that confer resistance to critically and highly important antimicrobial agents in human medicine

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Most antimicrobial resistance genes known so far to occur in staphylococci of animal origin confer resistance to a specific class of antimicrobial agents or to selected members within such a class. However, there are also a few examples of multidrug resistance (MDR) genes that confer resistance to antimicrobial agents of different classes by either target site methylation or active efflux via ATP-binding cassette (ABC) transporters. The present review provides an overview of these MDR genes with particular reference to those genes involved in resistance to critically or highly important antimicrobial agents used in human and veterinary medicine. Moreover, their location on mobile genetic elements and colocated resistance genes, which may play a role in coselection and persistence of the MDR genes, are addressed.

Critically important and last resort antimicrobial agents

Antimicrobial agents play a most relevant role in the therapy of bacterial infections in human and veterinary medicine. For a number of years, the development of new antimicrobial agents has considerably slowed down in human medicine [1,2] and – even more dramatically – in veterinary medicine [3]. Given this situation and understanding that antimicrobial use is one of the main driving forces in the development and spread of antimicrobial resistance, but also knowing that there is a complex interplay among human, animal, and environmental microbiota, it is the shared responsibility of human, animal, and plant sectors to prevent or at least minimize antimicrobial resistance selection pressures on both human and non-human bacteria (http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/OIE_list_antimicrobials.pdf).

To highlight the importance of the different classes of antimicrobial agents currently available, the World Health Organization (WHO) started classifying antimicrobial agents in human medicine in 2005 and the third revision of that list has been published in 2011 [4]. For this, the WHO used two criteria: (i) the antimicrobial agent is used as sole therapy or one of few alternatives to treat a serious human disease, and (ii) the antimicrobial agent is used to treat diseases caused by organisms (a) that may be transmitted via non-human sources or (b) that may acquire resistance genes from non-human sources. Substances classified as 'critically important antimicrobial agents (CIA)' must meet both criteria, whereas those classified as 'highly important antimicrobial agents (HIA)' must meet either criterion 1 or criterion 2. Antimicrobial agents that meet none of these criteria are considered as 'important antimicrobial agents (IA)'. Based on this definition, the term 'critically important' refers to a disease-specific and/or bacterium-specific situation. As an example, fluoroquinolones are classified as critically important because they represent part of a limited treatment option for *Campylobacter* spp., invasive disease due to *Salmonella* spp. and MDR *Shigella* spp. infections, and the respective diseases may result from transmission of *Campylobacter* spp. and *Enterobacteriaceae*, including *Escherichia coli* and *Salmonella* spp., from non-human sources. For staphylococci – in particular methicillin-resistant *Staphylococcus aureus* (MRSA) – the antimicrobial agents shown in Table 1 are classified as critically important or highly important by the WHO [4,5].

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Table 1. Critically and highly important antimicrobial agents in the context staphylococcal (including MRSA) infections in humans[a]

Classification	Class of antimicrobial agents	Representatives approved for therapeutic use in	
		Human medicine	Veterinary medicine
CIA	Glycopeptides	Teicoplanin, vancomycin	–[b]
	Glycylcyclines	Tigecycline	–
	Lipopeptides	Daptomycin	–
	Oxazolidinones	Linezolid	–
	Streptogramins	Quinupristin/dalfopristin, pristinamycin	–[c]
HIA	Fusidic acid	Fusidic acid	Fusidic acid
	Penicillins (Antistaphylococcal)	Cloxacillin, dicloxacillin, flucloxacillin, oxacillin, nafcillin	Cloxacillin, dicloxacillin, oxacillin, nafcillin
	Pseudomonic acids	Mupirocin	Mupirocin[d]
	Pleuromutilins	Retapamulin	Tiamulin, valnemulin

[a]Adapted from [4,5].

[b]Until the year 2000, avoparcin has been used as a growth promoter around the world except in North America.

[c]Until the year 2000, virginamycin has been used as a growth promoter in Europe and is still used in various parts of the world.

[d]Mupirocin is not approved in the European Union for veterinary use, but may be used in non-food-producing animals under Animal Medicinal Drug Use Clarification Act (AMDUCA)-like regulations.

Based on workshops on non-human antimicrobial usage and antimicrobial resistance held in 2003 and 2004, the World Organization for Animal Health (that is, Office International des Epizooties, OIE) developed a list of antimicrobial agents of veterinary importance, in parallel with the WHO list for human medicine (http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/OIE_list_antimicrobials.pdf). For this, a questionnaire prepared by the *ad hoc* group on antimicrobial resistance was sent in August 2005 to OIE delegates of all member countries and to international organizations that had signed a cooperation agreement with the OIE. The following criteria were used: (i) the majority of the respondents (>50%) identified the importance of the antimicrobial class in their response to the questionnaire, and (ii) compounds within the class were identified as essential against specific infections and there was a lack of sufficient therapeutic alternatives. Antimicrobial agents that met both criteria were considered as 'critically important', those that met one of these criteria as 'highly important' and those that met neither criterion as 'important'. The latest update of that list is from 2012 and takes into account that – in contrast to human medicine – many different animal species have to be treated with antimicrobial agents. The wide range of applications and the nature of the diseases to be treated rendered the following classes of antimicrobial agents extremely important for veterinary medicine, and hence they were classified as 'veterinary critically important antimicrobial agents (VCIA)': aminoglycosides (including aminocyclitols), cephalosporins of the third and fourth generation, macrolides, penicillins, phenicols, second generation quinolones (fluoroquinolones), sulfonamides (including the combination with diaminopyrimidines such as trimethoprim or ormetoprim), and tetracyclines. The below-mentioned classes of antimicrobial agents were classified as 'veterinary highly important antimicrobial agents (VHIA)': ansamycins, cephalosporins of the first and second generation, ionophores, lincosamides, phosphonic acid, pleuromutilins, polypeptides, and first generation quinolones. The WHO and OIE lists show that many different antimicrobial agents are of importance in treating bacterial infections in humans and animals. Thus, development of resistance to more than one of these agents in bacteria, such as staphylococci, might result in serious problems.

Multidrug resistance

The Clinical and Laboratory Standards Institute (CLSI) has stated in the VET05-R document [6] that there is no commonly accepted definition of multidrug resistance (MDR). As a consequence, this term is used inconsistently – and sometimes even falsely – for bacteria of human and animal origin, in the published literature. One of the CLSI recommendations is that the term MDR should exclusively refer to acquired resistance properties [6]. Moreover, the definition of MDR should mainly refer to phenotypic susceptibility testing as this is the most common way to determine antimicrobial susceptibility in routine diagnostics and has the greatest impact on the choice of the antimicrobial agent for therapeutic interventions [6]. Two editorials dealing with the assessment of antimicrobial resistance in bacteria of animal origin [7,8] gave the following recommendations with respect to MDR: (i) if only phenotypic susceptibility testing is performed, resistance to three or more different classes of antimicrobial agents can be referred to as MDR; and (ii) if phenotypic susceptibility testing is supplemented with molecular analysis for the resistance genes or mutations present, bacterial isolates exhibiting the presence of three or more resistance genes or mutations, all of which are associated with a different resistance phenotype (i.e., affecting different antimicrobial classes or subgroups), may be referred to as MDR. Exceptions to this rule include cases where a single resistance gene or a gene complex is associated with resistance to structurally and/or functionally different antimicrobial agents [7,8].

Staphylococci of animal origin share a large number of antimicrobial resistance genes (Figure 1). The resistance genes so far identified in animal staphylococci also include several MDR genes, comprising *erm*, *vga*, *lsa*(E), and *cfr* genes [9–11], which are described in detail in the following sections of this review. All of them confer resistance to at least one class of antimicrobial agents that is classified as CIA/HIA or VCIA/VHIA.