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## Antimicrobial resistance

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Most of the antibiotics currently used in human and veterinary medicine originate from substances which were produced by fungi or soil bacteria and provided the antimicrobial producer a selective advantage in the fight for resources and the colonization of ecological niches. Thus, bacteria came in contact with antimicrobial substances and consequently began to explore ways to avoid being killed or inhibited by those substances a long time before the first antimicrobial agents were introduced into clinical use. There are mainly three ways by which bacteria have gained resistance to antimicrobial agents: (a) bacteria acquired resistance genes of the antibiotic producers and modified them with regard to an optimized functionality in the new host, (b) bacteria developed resistance genes by stepwise mutation of genes whose products play a role in physiological cell metabolism, and (c) bacteria modified the target structures of the antimicrobials by either single-step or multi-step mutations and thus rendered them resistant to the inhibitory effects of the antimicrobials (Anon, 1998; Bennett, 1995; Quintilliani and Courvalin, 1995; Schwarz and Kehrenberg, 2000; Schwarz and Noble, 1999).

As a result of the exposure of bacteria to antimicrobial agents, a large number of genes and mutations associated with antimicrobial resistance has been developed. The observation that the introduction of an antimicrobial agent into clinical use has been either accompanied or followed shortly by the occurrence of resistant bacteria underlines the extraordinary capacity of bacteria to quickly and efficiently respond to the selective pressure imposed by the use of antimicrobials. In recent years, bacteria have also shown to be able to develop resistance to completely synthetic substances (Anon, 1998; Bennett, 1995).

The exchange of resistance genes between members of a mixed bacterial population has distinctly accelerated the spread of certain resistance genes to a large number of pathogenic bacteria, but also to harmless commensals. Resistance genes were usually first present in the bacteria in which they had evolved and were initially only transmitted vertically. However when integrated into mobile genetic elements, such as plasmids, transposons or integrons/gene cassettes, the resistance genes were spread horizontally among bacteria of the same, but also different species and genera by transduction, conjugation, mobilization or transformation. Thus, the driving forces of emerging antimicrobial resistance

are repeated exposure of the bacteria to antibiotics and the access of the bacteria to a large resistance gene pool in a polymicrobial environment as it is seen on the mucosal surfaces in the respiratory or alimentary tract as well as on the skin of humans and animals (Anon, 1998; Bennett, 1995; Schwarz et al., 2000).

The selective pressure imposed by the use of antimicrobial agents plays a key role in the emergence of resistant bacteria. Whenever a mixed bacterial population is exposed to antimicrobial agents, it is likely that there will be bacteria that are resistant to the respective drugs at the concentrations applied. Under selective pressure, the numbers of these will increase and some may pass their resistance genes to other members of the population (Schwarz et al., 2000). Consequently, the transfer of resistance gene(s) between harmless commensal bacteria to pathogens is likely to occur and must be considered. The application of a single antibiotic may not only incur resistance to that particular drug, but can also result in resistance to other structurally related antibiotics or even unrelated antibiotics which, however, share the same target site. In addition, co-transfer of multiple resistance genes associated with a single mobile element is often ignored when considering the population dynamics of antibiotic resistance. Numerous plasmids have been identified which carry several antimicrobial resistance genes as well as genes whose products confer resistance to disinfectants, heavy metals or nucleic acid binding substances. When such a multiresistance plasmid is transferred under the selective pressure imposed by the use of a single antimicrobial agent or disinfectant, the recipient cell will gain all resistance properties mediated by this plasmid (Neu, 1992; Schwarz et al., 2000).

Food producing animals as well as pets can act as a reservoir of resistant bacteria, as can humans (Neu, 1992; Schwarz et al., 2000). Antimicrobial resistance can develop in bacteria residing in animals and humans exposed to antimicrobial agents. Subsequent spread of the resistant bacteria between different hosts can occur directly by skin to skin contact, contact with bacteria containing material (saliva, faeces, etc.) or by the uptake of contaminated food, feed, air or water (Schwarz et al., 2000). When reaching the new host, resistant bacteria can either colonize and infect, or remain in the new environment for only a very short period of time. During this period, the resistant bacteria can spread their resistance genes to bacteria

the new host (commensals or pathogens), but can also accept resistance genes from these bacteria. Long-term residency may provide greater opportunities for transferring or receiving resistance genes than a brief co-habitation (Schwarz et al., 2000). Among the antibiotic resistant bacteria causing infections in humans, *Salmonella enterica* subsp. *enterica* (S.) serovars, *Campylobacter* spp. as well as *Enterococcus* spp. are considered the only ones which can be traced to animal sources with a high degree of certainty (Goossens, 1999; Neu, 1992; Witte, 1998). Their predominant way of reaching humans is via the food chain. However, once established in a human population (not always associated with disease), such pathogens can also be spread by various ways between humans (Molbak et al., 1999). Therefore, it is important to consider that infections with the afore mentioned zoonotic bacteria isolated from a human source may not necessarily have originated directly from animals shedding the bacteria or from contaminated animal products (Molbak et al., 1999). The transfer of (multi)resistant zoonotic bacteria from animals to humans is often difficult to prove, even by using sophisticated molecular methods. This is mainly due to (a) the clonal structure of the pathogens as proven for *S. Typhimurium* DT104 (Baggesen et al., 2000) and *S. Enteritidis* PT4 isolates (Weide-Botjes et al., 1998) from different geographical and animal sources, but also to (b) a highly diverse genomic arrangement as observed in *Campylobacter jejuni* or *Enterococcus* spp. (Van den Braak et al., 1998; Van den Boogard et al., 1997). The proof of the direction of transfer of resistance plasmids or transposons/integrations between bacteria residing in animals and humans is even more difficult to achieve. Since antibiotics of the same classes, such as tetracyclines, aminoglycosides, macrolides, and  $\beta$ -lactams, have been used for decades in both humans and animals, resistance to these antibiotics has also been selected for and transferred, probably *vice versa*, in both groups of hosts. Studies which confirmed the presence of identical resistance genes located on indistinguishable plasmids/transposons in bacteria from humans and animals (Greene and Schwarz, 1992; Schwarz et al., 1990; Schwarz and Noble, 1994) produced strong evidence for their transfer between human and animal bacteria, but in most cases it is impossible to trace back where and when the original resistance gene/plasmid/transposon had developed and which transfer events have taken place since. The spread of resistant bacteria from animals to humans is, in principle, possible and there is evidence in the literature that such transfer events have not only occurred, but occurred bilaterally (Levy et al., 1976; Seguin et al., 1999). The frequency with which

resistance properties are transferred between animals and humans is difficult to quantify. Since the efficiency of such transfer is, in part, dependant upon the type of antibiotic used, the colonisation of bacteria, the transfer of the resistance gene(s), host pharmacokinetics, immune status, or other ongoing infections, a risk assessment must be carefully performed in every single case (Schwarz et al., 2000). The excessive attention drawn by the media to the use of antimicrobials in animals as the cause of all or at least most resistance problems in human medicine is a distraction (Bywater, 1999; Phillips, 1999). Based on the present evidence, antimicrobial use in animals mainly causes resistance problems in animals while antimicrobial use in humans mainly accounts for the resistance problems encountered in human medicine. With the exception of the afore mentioned resistant zoonotic pathogens, both disciplines are mainly responsible for their own "home-made" resistance problems (Bywater and Casewell, 2000).

## References

- Anon (1998) The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans. Report of the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR). Commonwealth Department of Health and Aged Care, Commonwealth Department of Agriculture, Fisheries and Forestry – Australia
- Baggesen DL, Sandvang D, Aarestrup FM (2000) Characterization of *Salmonella enterica* serovar Typhimurium DT104 isolated from Denmark and comparison with isolates from Europe and the United States. *Journal of Clinical Microbiology*, 38, 1581-1586
- Bennett PM (1995) The spread of drug resistance. In: Baumberg S, Young JPW, Wellington EMH, Saunders JR, eds. *Population genetics in bacteria*. University Press, Cambridge, 317-344
- Bywater RJ, Casewell MW (2000) An assessment of the impact of antibiotic resistance in different bacterial species and the possible contribution of animals to resistance in human infections. *Journal of Antimicrobial Chemotherapy* (in press)
- Bywater RJ (1999) Overview of antibiotic use in a veterinary setting. Lecture at the symposium 94/C "Domesticated animals and multiply-resistant enterococci: a reservoir for dissemination to humans?" during 99<sup>th</sup> General Meeting of the American Society for Microbiology, Chicago/USA
- Goossens H (1999) Suspension and ban on use of antibiotics in the European Union: the evidence. Lecture at the symposium 108.C2 "Antibiotic-resistant bacteria in humans: does it come from animals?" during 39<sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Francisco/USA
- Greene RT, Schwarz S (1992) Small antibiotic resistance plasmids in *Staphylococcus intermedius*. *Zentralblatt für Bakteriologie*, 276, 380-389
- Levy SB, Fitzgerald GB, Macone AB (1976) Spread of antibiotic resistance plasmids from chicken to chicken and from chicken to man. *Nature*, 260, 40-42
- Molbak K, Baggesen DL, Aarestrup FM, Ebbesen JM, Engberg J, Frydendahl K, Gerner-Smidt P, Petersen AM, Wegener HC (1999) An outbreak of multidrug-resistant, quinolone-resistant

- Salmonella enterica* serotype Typhimurium DT104. New England Journal of Medicine, 341,1420-1425
- Neu, HC (1992) The crisis in antibiotic resistance. Science, 257, 1064-1073
- Phillips I (1999) Scapegoats. Letter to Electronic British Medical Journal, Jan. 1999
- Quintilliani R Jr, Courvalin P (1995) Mechanisms of resistance to antimicrobial agents. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Tenover RH, eds. Manual of Clinical Microbiology, 6th edn, ASM Press, Washington D.C., 1308-1326
- Schwarz S, Cardoso M, Grölz-Krug S, Blobel H (1990) Common antibiotic resistance plasmids in *Staphylococcus aureus* and *Staphylococcus epidermidis* from human and canine infections. Zentralblatt für Bakteriologie, 273, 369-377
- Schwarz S, Kehrenberg C, Walsh TR (2000) Use of antimicrobial agents in veterinary medicine and food animal production. International Journal of Antimicrobial Agents (in press)
- Schwarz S, Kehrenberg C (2000) Antimikrobielle Resistenz: Resistenzmechanismen, Resistenzgene und Übertragungswege. Amtstierärztlicher Dienst und Lebensmittelkontrolle, 7, 55-60
- Schwarz S, Noble WC (1999) Aspects of bacterial resistance to antimicrobials used in veterinary dermatological practice. Veterinary Dermatology, 10, 163-176
- Schwarz S, Noble WC (1994) Tetracycline resistance genes in staphylococci from the skin of pigs. Journal of Applied Bacteriology, 76, 320-326
- Seguin JC, Walker RD, Caron JP, Kloos WE, George CG, Hollis RJ, Jones RN, Pfaller MA (1999) Methicillin-resistant *Staphylococcus aureus* outbreak in a veterinary teaching hospital: potential human-to-animal transmission. Journal of Clinical Microbiology, 37, 1459-1463
- Van den Boogard AE, Jensen LB, Stobberingh E.E (1997) Vancomycin-resistant enterococci in turkeys and farmers. New England Journal of Medicine, 337, 1558-1559
- Van den Braak N, van Belkum A, van Keulen M, Vliegenthart J, Verbrugh H, Endtz H (1998) Molecular characterization of vancomycin-resistant enterococci from hospitalized patients and poultry products in the Netherlands. Journal of Clinical Microbiology, 36, 1927-1932
- Weide-Botjes M, Kobe B, Schwarz S (1998) Inter- and intra-phage type differentiation of *Salmonella enterica* subsp. *enterica* serovar Enteritidis isolates using molecular typing methods. Zentralblatt für Bakteriologie, 288, 181-193
- Witte, W (1998) Medical consequences of antibiotic use in agriculture. Science, 279, 996-997