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DEVELOPMENT AND CHARACTERIZATION OF BACTERIAL ANTIMICROBIAL RESISTANCE MECHANISMS

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Since the introduction of antimicrobials into veterinary medicine some 45 years ago, animal health and productivity has improved appreciably (1,5,12,17). Despite considerable use, and some misuse, many antimicrobials continue to remain effective today. However, loss of effectiveness through emergence of bacterial antibiotic resistance is always an ever-present threat (1,3,4,8,20,21,25). The sometimes-excessive use of antimicrobials has consequently resulted in the rapid emergence and dissemination of antimicrobial resistance in both human and veterinary bacterial pathogens. Antimicrobial resistant bacterial pathogens in animals not only pose a risk with respect to animal health, but are a growing concern regarding possible transmission to humans as foodborne pathogens (9,11,15,21,24). Currently, there is increased public and scientific interest regarding the administration of therapeutic and subtherapeutic antimicrobials to animals, due primarily to the possible emergence and dissemination of multiply-drug resistant zoonotic bacterial pathogens. However, there is still no consensus on the significance of antimicrobial use in animals and/or resistance in bacterial isolates from animals on the development and dissemination of antibiotic resistance among human bacterial pathogens. In fact, this debate regarding antimicrobial use in animals and potential human health implications has been going on for over 30 years, initiated by the release of the Swann report (21). The recent isolation and detection of vancomycin-resistant enterococci, fluoroquinolone-resistant campylobacters and multi-drug resistant *Salmonella typhimurium* DT104 from animal sources or their immediate environment has resurrected this controversy. While much of the antimicrobial resistance in human medicine may be attributed to overuse in human patients, it is being adamantly argued that antimicrobial use in veterinary medicine and food animal agriculture contributes to the problem for several bacterial pathogens (2,21,25). Regardless, it is clear that the use of antimicrobials in both animals and humans select for resistant bacterial populations. The question then becomes "are the populations of resistant bacteria in people and animals independent or do they form a common pool with resistant bacteria in animals posing a threat to human health and vice versa?" (2).

The emergence of antimicrobial resistance in microorganisms is a serious crisis and several strategies have been proposed to try to deal with it. Prevention should be the ultimate solution, and vaccines have been suggested as a strategy that can be used to decrease the therapeutic use of antimicrobials (19). Another strategy is to increase our understanding of the complex ecological and biochemical origins of antimicrobial resistance mechanisms which would then shed insight into new preventive and therapeutic strategies for overcoming resistance development and transfer (Figure 1).

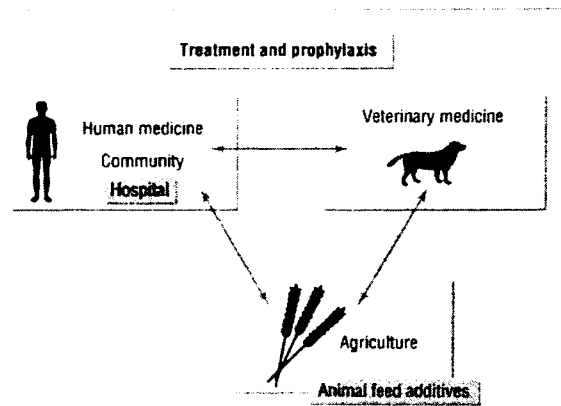


Figure 1. Antibiotic ecosystems (Johnston, 1998)

The dilemma of antibiotic resistance is worsened by the certainty that many of the more virulent bacterial strains have acquired resistance to multiple, structurally unrelated antimicrobials, and to the fact that few new veterinary antimicrobials are likely to be available before the end of the decade (5,10,17). Diseases requiring the most extensive use of antimicrobial drugs for treatment or prophylaxis are respiratory and enteric diseases in pigs and cattle, mastitis in dairy cattle, and airsacculitis in poultry. The most commonly used antimicrobial drugs in animals reared for food are from five major classes: • -lactams, tetracyclines, aminoglycosides, macrolides, and sulphonamides. In addition, quinolones have been available in some European countries for more than 20 years with large animal approval occurring in the United States last year. This recent approval of fluoroquinolones for bovine respiratory disease by FDA-CVM attracted tremendous attention in the scientific community.

Several epidemiological studies have demonstrated an association between use of antimicrobials in animals and the subsequent isolation of resistant bacterial from the same animals. For example, *Salmonella* sp. isolated from healthy animals possessed an antibiotic resistance profile that matched the antibiotics used in the animal feed (7). Another study profiled the emergence of both gentamicin and apramycin resistant *E. coli* and *Salmonella* sp. following the use of these antibiotics in food animals. The same plasmid carrying the resistance gene (aminoglycoside-3-N-acetyltransferase) was isolated from both the animals and the workers caring for them (6).

Once antibiotic pressure has been introduced into an environment, antimicrobial resistance quickly develops and spreads (22). With time, the antimicrobial resistance can move from one microbial species to the next. This movement is often orchestrated by plasmids (22). On the farm, multidrug-resistant bacteria quickly become a normal component of the gut flora, persisting in numerous hosts (18). Drug-resistant bacteria can, over time, displace the antibiotic-susceptible population (13,17,22).

The majority of antimicrobial resistant phenotypes are obtained by the acquisition of foreign genes that may provide resistance to a class of antimicrobials (22,23). There are several different mechanisms by which bacteria can acquire resistance to antimicrobials (17,22). Bacterial resistance to antimicrobials most likely results from either the mutation of normal cellular genes, over-expression of genes coding for various efflux pumps, or by the acquisition of foreign DNA

coding for antimicrobial resistance. In recent years, a number of these resistance genes have been associated with large, transferable, extrachromosomal DNA elements, called plasmids, on which may be other DNA mobile elements, termed transposons and integrons (16,23). These DNA mobile elements have been shown to possess genetic determinants for several different antimicrobial resistance mechanisms and may be responsible for the rapid dissemination of resistance genes among different bacterial genera and species (3,16,22,23). In fact, some of these determinants have been found to contain genes encoding resistance to disinfectants and heavy metals in addition to antimicrobial resistance genes (22,23). This raises an unsettling question, what is the actual selection pressure that maintains these combined resistant phenotypes? The existence of mobile plasmids in the Enterobacteriaceae predates the use of antibiotics (14). The ability of the mobile DNA elements to establish genetic associations between widely different bacterial species makes them likely to be principal components in the dissemination of a wide variety of antimicrobial resistance determinants.

In conclusion, as is the case for particular bacterial related human infections, therapeutic options for treatment of bacterial diseases in animals is diminishing. It is possible that some day veterinarians may confront bacterial infections that no longer respond to antimicrobial therapy. It is therefore imperative that new prevention and infection control strategies be created, evaluated, and implemented to lessen the occurrence of this possible scenario. Furthermore, we must continue our efforts at deciphering the molecular basis of how antimicrobial resistance genes are acquired and disseminated among bacterial pathogens. This will inevitably lead to the evolution of novel antimicrobial strategies and perhaps influence current management practices that will reduce the incidence of multi-drug resistant bacterial pathogens in the animal production environment.

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