REVIEW ARTICLE

ANTIBIOTIC RESISTANCE IN ANIMALS AGAINST VARIOUS DISEASES: A REVIEW OF IMPORTANCE IN VETERINARY MICROBIOLOGY AND CLINICAL VETERINARY MEDICINE

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Abstract: The antimicrobial agents in the 1930s (sulfonamides) and 1940s (penicillin) revolutionized human medicine by substantially reducing morbidity and mortality rates from bacterial diseases. Antimicrobial use in animals originated over 50 years ago when chlortetracycline fermentation waste was found to enhance animal growth and health. Since then, major changes have taken place in food animal production as well as in companion animal medicine. However, it was soon observed that bacteria could become resistant to antimicrobials, and resistant strains emerged shortly after the introduction of every new antimicrobial drug.

Key words: Animals; Antibiotic resistance; Diseases

INTRODUCTION

Antibiotic resistance is a worldwide problem. World health leaders have described antibiotic-resistant microorganisms as "nightmare bacteria" that "pose a catastrophic threat". Resistance is a natural and unavoidable consequence of antimicrobial use. Bacteria have developed various mechanisms to neutralize the action of antimicrobial agents. The most common are enzymatic drug inactivation, modification or replacement of the drug target, active drug efflux and reduced drug uptake (Guardabassi and Courvalin, 2006).

Antibiotic resistance

Antibiotic resistance is a looming public health crisis (Landers et al., 2012). An inherent consequence of exposure to antibiotic compounds, antibiotic resistance arises as a result of natural selection (Aminov and Mackie, 2007). Due to normal genetic variation in bacterial populations, individual organisms may carry mutations that render antibiotics ineffective, conveying a survival advantage to the mutated strain. In the presence of antibiotics, advantageous mutations can also be transferred via plasmid exchange within the bacterial colony, resulting in proliferation of the resistance trait (Courvalin, 2008). There is also considerable debate in veterinary medicine regarding use of antibiotics in animals raised for human consumption (food animals). The potential threat to human health resulting from inappropriate antibiotic use in food animals is significant, as pathogenic-resistant organisms propagated in these livestock are poised to enter the food supply and could be widely disseminated in food products (Garofalo et al., 2007).

Resistance can be either intrinsic or acquired by conjugation, transformation or transduction. Since distinct resistance genes are frequently clustered together, horizontal transfer of a single genetic element can result in the acquisition by recipient bacteria of resistance to multiple unrelated antimicrobials (multi-resistance) (Ramchandani et al., 2005). Antimicrobial agents can be individually administered to animals to treat (therapy) or prevent (prophylaxis) disease. In animal production, antimicrobials can also be administered to clinically healthy animals belonging to the same flock or pen as animals with clinical signs (a form of prophylaxis called metaphylaxis), or for improving animal growth (McEwen and FedorkaCray, 2002). Metaphylaxis is typically used during disease outbreaks in aquaculture and in poultry, but is also used in swine and cattle. Infections are treated before their clinical appearance and the treatment period is usually shorter than for therapeutic treatment. For the purpose of growth promotion, antimicrobial drugs are used as a feed supplement and are continuously administered at sub-therapeutic doses. The benefits of growth promoters can be minimized, if not annulled, by improving hygiene, management conditions, and other measures aiming at disease control, such as biosecurity and vaccination. Systemic antimicrobial treatment can be administered orally, through medicated feed or water, or by injections – usually as an initiation of antimicrobial treatment typically followed by systemic or local treatment. Local antimicrobial treatment includes intra mammary infusion for mastitis treatment, intrauterine treatment and topical skin, ear and eye treatment.

Accurate diagnosis and antimicrobial susceptibility testing

Empirical use of antimicrobials should be avoided whenever possible and antimicrobials should be preferably prescribed on the basis of laboratory diagnosis and antimicrobial susceptibility testing. The use of antimicrobials should always be based upon examination of the clinical case, diagnosis of a bacterial infection and selection of a clinically efficacious antimicrobial agent. Antimicrobials should only be used when it is known or strongly suspected that the disease is caused by bacteria, since viruses are not susceptible to antibacterial therapy. The resistance patterns of certain animal pathogens such as Pasteurellaceae, *Bordetella bronchiseptica*, *Actinobacillus*, beta-haemolytic streptococci and *Erysipelothrix rhusiopathiae* can be

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predicted with relatively high certainty, and generally the use of penicillin G is sufficient to cure infections caused by these microorganisms. On the other hand, the susceptibility patterns of other bacteria, such as staphylococci, *E. coli* and *Salmonella* can hardly be predicted. For these bacteria, susceptibility testing is strongly recommended, if possible before initiation of antimicrobial treatment (Burrows *et al.,* 1993).

Choice of an appropriate antimicrobial product and administration route

From a strictly clinical point of view, four factors have to be considered when selecting an antimicrobial agent: clinical efficacy, toxicity to the host, risk for development of resistance and adverse effects on the commensal flora. Clinical efficacy requires not only that the pathogen is susceptible to the selected drug, but also that the drug is able to penetrate and be active at the site of infection. Attention should also be paid to the immune status of the animal and the type of infection since bacteriostatic drugs have a slower effect and rely on an active immune system to control the infection, and are therefore not appropriate for the treatment of acute life-threatening infections or for immunosuppressed animals. Other host-related factors such as pregnancy, age and allergies should also be considered in order to avoid undesirable effects on the health of the animal.

Appropriate dosage regimen

Appropriate dosage regimen (dose level, dose interval and treatment duration) is of fundamental importance to ensure rational antimicrobial use. It is essential to administer antimicrobials in accordance with the recommended dosage regimen to minimize therapy failures, exploit the efficacy potential of the drug and comply with the regulated withdrawal times. Each antimicrobial class has its own pharmacodynamic and pharmacokinetic properties that are expressed when the recommended dosage regimen is applied. Low doses, increased dose intervals and reduced treatment duration can lead to recrudescence of the infection and may increase the risk of selecting resistant organisms.

The other major factor in the growth of antibiotic resistance is spread of the resistant strains of bacteria .There are four core actions that will help fight these deadly infections:

- ✓ Preventing infections and preventing the spread of resistance
- ✓ Tracking resistant bacteria
- ✓ Improving the use of today's antibiotics
- ✓ Promoting the development of new antibiotics and developing new diagnostic tests for resistant bacteria (Peters *et al.,* 2008).

CONCLUSION

The route of administration should also be considered in order to minimize the impact of antimicrobial treatment on development of resistance. Local treatment should be preferred to systemic treatment when the infection is localized and accessible by topical products (e.g. eye, ear, udder and wound infections). When systemic

treatment is necessary in animal production, intramuscular and intravenous injection are preferable to oral administration to avoid disturbance of the normal gut flora. Furthermore, medication by feed and, to a lesser degree, water, may result in insufficient uptake by diseased animals due to loss of appetite, thus reducing the effects of medication and increasing the risks of resistance development (Belongia *et al.,* 2005).

Drug classes used to treat infections and description of important drug resistance:

Drug Class	Resistance and Other Limitations
β-lactams	Gram-negative bacteria have developed several pathways to β-lactam resistance.Perhaps the most concerning are β-lactamases, enzymes that destroy the β-lactam antibiotics. Some β-lactamases destroy narrow spectrum drugs (e.g., only active against penicillins) while newer β-lactamases (e.g.carbapenemases found in carbapenem-resistant Enterobacteriaceae or CRE) are active against all β-lactam antibiotics.
β-lactam subclass: Penicillin, aminopenicillins, and early generation cephalosporins	Resistance among gram-negative bacteria is widespread. These drugs are rarely recommended as treatment for serious gram-negative infections.
β-lactamase inhibitor combinations	These drugs are important for treatment of serious gram- negative infections but resistance is increasing. Bacteria that are resistant to extended-spectrum cephalosporins and carbapenems are usually resistant to these drugs as well. New β-lactamase inhibitor combination drugs in development have the potential to overcome some, but not all, of resistance from the most potent β-lactamases such as those found in CRE.
Extended-spectrum Cephalosporins	Resistant gram-negative infections first emerged in healthcare settings but now are also spreading in the community. When resistance occurs, a carbapenem is the only remaining β-lactam agent.
Carbapenems	Resistance found among other gram-negative bacteria including *Pseudomonas* and *Acinetobacter spp*. Once bacteria become resistant to carbapenems, they are usually resistant to all β-lactams.
Fluoroquinolones	Fluoroquinolone-resistant, hyper-virulent strains of Clostridium difficile.
Aminoglycosides	Despite growing resistance problems, these drugs continue to be an important therapeutic option.
Tetracyclines	Relatively uncommon.

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CITE THIS ARTICLE AS:
Kausar Qadri, Subha Ganguly and Praveen Kumar Praveen, Antibiotic Resistance in Animals Against Various Diseases: A Review of Importance in Veterinary Microbiology and Clinical Veterinary Medicine. *International Journal of Bioassays* 4.9 (2015): 4296-4298.