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ANTIMICROBIAL RESISTANCE ISOLATES FROM OVINE NECROTIC PODODERMATITIS: A REVIEW

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Abstract

Infectious pododermatitis is a common condition in sheep with initial lameness, with a variation in severeness over time. Independently on aetiology, the administration of antibiotics has proven to be ineffective, the disease often being exacerbated in a short time, the bacteria being refractory to antimicrobials. The use of antibiotics is common in sheep for disease treatment, health protection and as growth promoters. The main antibiotics used in farmed animals are tetracyclines, penicillin, quinolones and cephalosporins. According to the latest studies, E. coli, an ubiquitous bacterium often isolated from pododermatitis lesions, is unresponsive to all these antibiotics. Studies on the antibiotic resistance of the main pathogens of necrobacillary pododermatitis, Dichelobacter nodosus and Fusobacterium necrophorum, are not found in the literature, but the ineffectiveness of antibiotics on these bacteria directs towards a possible antibiotic resistance. Currently, multiple health organisations have identified proliferation of antimicrobial resistance as a global crisis. The decline in bacterial susceptibility to common antibiotics calls for global efforts on the rational use of antibiotics in veterinary medicine as a response to the spread of antimicrobial resistance.

Key words*: sheep, necrotic pododermatitis, Dichelobacter nodosus, Fusobacterium necrophorum, antibiotic resistance.*

INTRODUCTION

Footrot is an infectious disease caused by an interaction of two anaerobic bacteria, *Dichelobacter nodosus* and *Fusobacterium necrophorum,* and the bacterial community of the hoof (Beveridge, 1941) which in favorable environmental conditions multiply and destroy the foot tissue. This pathology develops more frequently in sheep but can also be diagnosed in other ruminants such as cattle, goats and South American camelids (Laing and Egerton, 1978; Ghimire et al., 1999).

The impact it has on animal welfare and the economic losses caused by the rapid spread within the herd, affecting a significant number of animals, gives the diseases more attention to the practices of preventing the introduction of this pathology in the flocks (Kennan et al., 2011).

Agricultural practices for fertilising the soil with manure, the content of which may be rich in antibiotic residues, are the major contributor to the emergence of antibiotic resistant bacteria, especially among sheep raised in the traditional system, which involves grazing on agricultural land (Khachatourians G.G., 1998). Unfounded administration of antimicrobial substances in various pathologies as well as their use as prophylaxis methods also participate in the emergence of antibiotic resistance; chlortetracycline, tylosin, neomycin, oxytetracycline are just some of the most commonly used antibiotics for this purpose.

This review concentrates data on the aetiology and epidemiology of footrot, the clinical evolution, the main methods of therapy as well as the resistance of bacterial strains to antimicrobial substances.

ETIOLOGY AND EPIDEMIOLOGY

Footrot is a sporadic-enzootic disease, with acute evolution that affects sheep of all ages, but the lesion picture is different depending on the age, in young animals more serious lesions can be detected. The breed also influences the evolution of the disease, in a study conducted by Beveridge in 1941, in Australia, there is a higher susceptibility of the merino breed compared to other breeds in which the disease has a milder evolution (Beveridge, 1941).

This pathology is highly contagious and can be spread by sheep that do not show clinical signs of disease and is easily transmitted from sheep to sheep via bedding, pasture or handling pens (S.C. Bishop and C.A. Morris, 2007).

Ovine footrot is caused by a Gram-negative bacillus, *Dichelobacter nodosus,* strictly anaerobic bacteria, immobile but with type IV pili, morphological aspect that gives it motility in damaged tissues (Bennett et al., 2009). This pathogen is a proteobacteria that belongs to the family *Cardiobacteriaceae*, genus *Dichelobacter*. Bacterial species belonging to this family are bacilli in the form of straight or curved stems, with round and thickened heads having a diameter between 0.5-1-7 μm and a length of 1-6 μm, usually staining gram negative.

Another anaerobic bacterium, *Fusobacterium necrophorum*, plays a secondary role in the pathogenesis of this pathology, being considered responsible for the necrosis of the tissues it populates (J.R. Egerton et al., 1969). It is a gram-negative, non-sporulated, immobile, necessarily anaerobic and fermentative spindle bacterium, belonging to the family *Fusobacteriaceae*, genus *Fusobacterium* (Roberts D.S., 1969). This bacteria is a normal inhabitant of the ruminant digestive tract and in conditions of high humidity interact with another bacteria, *Corynebacterium pyogenes,* to produce an infection of the skin between the toes. The synergistic action of the main pathogens causes lesions at the hoof which provides a portal of entry for organisms with habitat al soil, such as staphylococci and streptococci, *Escherichia coli*, *Clostridium perfringens* and *Actinomyces pyogenes* (M. A. Hurtado et al., 1998).

Under favourable environmental condition with mild air temperatures and high rainfall, the multiplication of these bacteria takes place, on the background of which the inflammation of the interdigital tissue takes place, a process that favours the invasion of the main pathogen, *Dichelobacter nodosus* (Angela Lacombe-Antoneli et al., 2007).

Compared to *Fusobacterium necrophorum,* which is ubiquitous in the soil or present in sheep faeces, *Dichelobacter nodosus* can survive in the environment for 7-10 days and for up to 6 weeks in hoof horn clippings, dry heat and cold weather significantly reducing the lifespan of this bacterium (Whittington, 1995).

CLINIC PICTURE

The benign and virulent are the two forms of the disease that are well-studied and described. In the benign footrot the strains of *D. nodosus* do not have virulence factors and from a lesional point of view only the interdigital skin is inflamed, comparative with virulent strains, underrunning of the hoof horn occurs (J.R. Egerton et al., 1969). The virulence of *Dichelobacter nodosus* is due to the number of members that are responsible for the secretion of thermostable proteins that allow this bacterium to digest the connective tissue between the horn and the flesh of the hoof (K.J. Smith et al., 2021).

Infectious pododermatitis suddenly begins with a lameness caused by pain in the foot, the animal avoiding using his affected limb accompanied with decrease appetite (John F. Currin et al., 2005). The skin and soft tissues of the interdigital space become erythematous and congested, pathological changes that in the absence of therapy will progress to erosion. The cracks created at the level of the hoof constitute a path of penetration of pathogens that will colonise the affected tissue and the activity of bacterial enzymes causes their destruction, the infection spreading to the sole of the hoof, undermining and causing the separation of the horny tissues (Whittier W.D. & Umberger S.H., 2010). Moderate to severe fever with significant increase of heart and respiratory rates are general changes in health (Wessam Monther Mohammed Saleh et al., 2019).

ANTIBIOTIC THERAPY

Antibiotics, substances capable of inhibiting the growth or destruction of microorganisms are widely used as bacteriostatic or bactericidal drugs used in the infection (Pomorska-Mól & Z., 2012). The rational use of antibiotics against pathogens is conditioned by the accurate diagnosis and knowledge of bacterial strains involved in the pathogenesis of the disease by sampling lesions, culture of bacterial species and their identification by specific

methods. It is most important that antibiograms be performed after the bacteria have been identified to test for bacterial susceptibility to the antibiotics tested. It is also important to know the pharmacological properties of the antibiotic and evaluating host factors (Gürdal Y. et al., 2018).

In the therapy of footrot there are two important limitations in the use of antibiotics. First of all it has a high efficacy only if the animals under treatment are held in dry conditions for 24 h following treatment. Second, the rapid elimination of the antibiotic from the body does not provide protection against reinfection (Abbott & Lewis, 2005). Despite these limitations, the administration of antibiotics in the case of this pathology remains the main form of therapy used in current practice.

ANTIBIOTIC RESISTANCE

Antibiotics are certainly the most widely used form of chemotherapy of all time. The beneficial effect of bread on which filamentous mushrooms were grown has been known since ancient Egypt and has been used to treat wounds and burns (Pecanac M. et al., 2013).

Penicillin was accidentally discovered in 1928 by Alexander Fleming, who forgot about hys staphylococcal culture and later found it in the laboratory and noticed how their growth was inhibited by a bluish-green mould of the genus *Penicillium,* which he later called penicillin.

Starting with penicillin, between the years 1940-1970, up to 23 classes of antibiotics were identified and obtained by the pharmaceutical industry, which were and are successfully used by clinicians. After this time, the rate of emergence of new classes of antibiotics is slowed down in contrast to the increasing rate of emergence of antibiotic resistance.

Many bacterial strains have become resistant to antibiotics, a large percentage of which are resistant to several classes of antibiotics, a process that has led to the phenomenon of multidrug resistance (Martinez J.L., 2014).

Antimicrobial resistance is old and is the expected result of the interaction of several microorganisms with the environment. Most antimicrobial compounds are naturally occurring molecules and such co-occurring bacteria have developed antibiotic defence mechanisms to survive these organisms being often considered intrinsically resistant to one or more antimicrobials (Khachatourians, G.G., 1998).

Although some species show a natural resistance to different classes of antibiotics, most species acquire this resistance through mutations in cell genes that lead to cross-resistance and the transfer of genes from one microorganism to another through plasmids, transposons, integrons and bacteriophages. Once bacteria gain resistance genes that help protect them from microbial agents, they can use various biochemical resistance mechanisms, the most common of which are enzymatic inactivation, altering target receptors and actively expelling the antibiotic through efflux cell pumps (Georgina Cox & Gerard D. Wright, 2013).

Repeated use of antibiotics increases bacterial adaptability to used antibiotics, some microbes exhibit cross selection and co-selection to different antibiotics along with direct selection (O'Brien, 2002).

Cross-resistance is in the situation in which resistance to one drug is associated with resistance to another drug and due to a single mechanism. Cross resistance can be limited to some antimicrobial class, can occur between all members or involve antimicrobials belonging to different classes. Co-resistance is due to the coexistence of genes or mutations in the same strain, each conferring resistance to a different class of drugs (Luca Guardabassi & Patrice Courvalin, 2006).

In a study of 97 strains of *Dichelobacter nodosus* bacteria isolated from small ruminants with lesions in which antibiotic treatment was attempted, 50% of the tested strains were resistant to penicillin and 70% were found to be resistant to the tested aminoglycosides (kanamycin, streptomycin, gentamicin and neomycin) (Angela Lacombe-Antoneli et al., 2007). In the same study, *Fusobacterium necrophorum*, the other bacterial strain isolated from pododermatitis lesions, is sensitive to penicillin and aminoglycosides.

CONCLUSIONS

Lameness is a common cause of well-being and economic concerns in most sheep-keeping

countries. Making a correct diagnosis is essential in setting up treatment and controlling lameness (A.C. Winter, 2008).

Footrot remains a difficult to treat infectious disease and the use of antibiotics as the first line of treatment in various diseases increases antibiotic resistance among bacterial strains (Georgina Cox & Gerard D. Wright, 2013).

Continuing the misuse of antibiotics will hamper our ability to effectively treat infectious diseases in the future.

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