Actual aspects of treatment and prevention of infectious bovine keratoconjunctivitis

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Abstract. Infectious bovine keratoconjunctivitis is a bacterial eye disease. The disease is characterized by inflammation of the conjunctiva, corneal ulceration and excessive lacrimation. Although this disease does not lead to the death of animals, its economic importance is enormous, since it leads to a decrease in livestock weight gain and a reduction in dairy productivity. The main etiological role in IBK belongs to Moraxella spp. (including in associations with Staphylococcus spp., Streptococcus spp., Pseudomonas aeruginosa, E. coli, Proteus). The use of traditional treatment methods, such as the use of antibacterial chemicals, for Moraxella infection may be ineffective due to the factors of resistance and immunity of these bacteria. The development of a vaccine can be expensive and time-consuming, due to the external localization of the infection; it will be difficult to achieve a protective effect. New strategies for the treatment and prevention of bacterial infection open up prospects for the use of bacteriophages. Due to the growing antibiotic resistance of circulating bacterial pathogens and to increase the effectiveness of therapeutic and preventive measures in IBK, the development of phage therapy is relevant. Fundamental studies of biological properties and exploratory studies of virulent active bacteriophages to zoopathogenic Moraxelles are an urgent problem.

1 Introduction

Young and adult cattle in the process of their development are often exposed to diseases of various origins. Eye diseases in cattle are a fairly common cause that reduces the level of livestock development and causes economic damage to the farm.

Infectious bovine keratoconjunctivitis (IBK) is commonly known as conjunctivitis, which is a bacterial disease that affects cattle worldwide. Infectious keratoconjunctivitis is the most common disease affecting meat and dairy heifers, and the second most common disease of fattening calves older than three weeks. This is a contagious disease

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characterized by lacrimation, hyperemia of conjunctival vessels, photophobia, serous-purulent discharge, opacification and ulceration of the cornea, deformation of the eyeball in the form of keratoglobus or keratoconus, partial or complete loss of vision of the affected eye of the animal. On average, 25-30% of sick animals remain blind, the same vision loss is 50%. The disease usually begins in spring, reaches its maximum intensity in early summer and decreases somewhat by autumn, and some cases may occur in winter, due to a decrease in body resistance, violation of zoohygienic conditions of animal husbandry. A number of infectious agents have been reported to cause keratoconjunctivitis in cattle, such as rickettsias, chlamydia, viruses, Mycoplasma spp., Neisseria catarrhalis and Moraxella bovis.

In our country, the first reports of epizootic outbreaks of this disease in cattle that took place on farms in the Gomel, Irkutsk regions and the North-Western zone appeared in the 70s and 80s of the last century.

Infectious keratoconjunctivitis in cattle causes significant economic damage to cattle breeding due to a decrease in milk yield of up to 50%, a decrease in body weight gain of up to 40%, as well as the cost of carrying out therapeutic and preventive measures.

Monitoring of infectious keratoconjunctivitis in the territory of the Russian Federation shows that one of the main causes of the spread of the disease is the mass import of imported breeding stock, and the movement of infected animals across the regions of the Russian Federation without appropriate diagnostic studies has led to an intensive spread of the disease and an increase in the number of dysfunctional farms.

2 Materials and methods

The analysis used an up-to-date review and analysis of articles by domestic and foreign authors from various databases of electronic libraries.

3 Results and discussions

Bacteria of the genus Moraxella are widespread, have a wide species representation, belong to both non–pathogenic saprophytes and opportunists. Moraxella (type: proteobacteria; class: Gammaproteobacteria; order: Pseudomonas; family: Moraxellaceae) is a genus of gram-negative bacteria, currently 20 species are known – 7 isolated from humans and 13 from animals: M. canis (cats and dogs), M. ovis (sheep), M. equi (horses), M. caprae and M. boevreii (goats), M. caviae (guinea pigs) and M. cuniculi (rabbits) [1, 2]. These types of Moraxella cause various pathologies – Moraxella infections associated with chronic cholera-like lesions in birds and keratoconjunctivitis in deer and elk have been described [3, 4]. Of all the Moraxella species isolated from animals, Moraxella bovis is the most common. M. bovis and M. bovoculi are pathogenic for cattle. Among the moraxella there are also pathogenic species with pathogenicity factors, adaptability to farm animals and tropicity to organs and tissues, colonization ability, biofilm formation. The most widely known infectious disease caused by the pathogenic Moraxella bovis and Moraxella bovoculi – IBK: infectious bovine keratoconjunctivitis.

Controversy continues regarding the zoopathogenic role of different species of moraxella. Thus, there are conflicting data on the involvement of Moraxella bovis in the etiology and pathogenesis of IBK in cattle and small cattle. For example, E.A. Laak et al. (1988) indicates that Moraxella bovis can be isolated from the eyes of sheep with or without keratitis, which, according to the authors, does not play any etiological role in the development of IBK. A study conducted by Muñoz Gutiérrez, Juan F. et al. In 2018, it was possible to determine in deer that the microorganism of this species is not the main cause of eye inflammation in large ruminants, but may be involved in pathogenesis. Other researchers abroad have at various times noted the etiological significance of Moraxella bovis: Dagnall G. J. et al. (Great Britain, 1994), Pedersen K. B.(Sweden, 1972), Elad D. et al.(Israel, 1988). Theoretical analysis shows that even retrospective data on this problem are insufficient and require relevant research.

The virulence of M. bovis is influenced by both factors of the host organism and environmental factors. The pathogenesis of the disease is influenced by many factors, such as the season of the year, mechanical irritation, the immune response of the host, pigmentation of the eyelids and the simultaneous presence of pathogenic bacteria, as well as M. bovis strains. The pathogenetic and immunotropic mechanisms of the development of keratoconjunctivitis of moraxellous etiology are discussed in their work by Sotnikova L.F. et al. (2020).

The sources of infectious agents are sick animals and clinically healthy microbial carriers that secrete these microorganisms with conjunctival secretions and nasal mucus. Transmission of the pathogen is carried out by direct or indirect contact, as well as by mechanical means with the participation of flies (domestic, stable fly, field). Healthy animals become infected when they are kept together with sick people in pastures, feeding grounds, and indoors. With the airborne spread of the pathogen, the disease quickly covers large groups of animals (up to 80% of the herd can be affected within 1-4 weeks). These factors contributing to the outbreak of the disease, the effects that depress the animal's immune system, favor the rapid and intensive transfer of moraxella from animal to animal, its passage and, consequently, increased virulence.

Bacteria of the genus Moraxella safely survive the winter period on farms, and in early spring they begin to infect the animal body. Although in previous years, moraxellosis manifested itself during the mass summer of insects.

The peculiarity of the bacteria of the genus Moraxella for circulation in the body and excretion through the mucous membranes of the nose ensures the stationarity of infection and seasonal frequency associated with contact or transmissible transmission through *Stomoxys calcitrans (*stable fly*)*, as well as with immunosuppressive conditions of young cattle during the deterioration of zoohygienic parameters.

At the present stage, some authors believe that the only infectious agent of concern for its pathogenic and enormous economic impact is hemolytic M. bovis. Various research data have established that the gram-negative bacillus M. bovis is the most common microorganism causing IBK in cattle, and the most frequently isolated. he research of A.I. Laishevtsev and coauthors (2016) 87 samples of material from farms of the Russian Federation noted the primary role in infectious keratoconjunctivitis of cattle Moraxella spp. – 10.34%, Acinetobacter spp. – 8.05%, Corynebacterium spp. – 6.90%, Pseudomonas spp. – 2.3%. However, the specific role of microorganisms has not been fully disclosed. Meanwhile, the handbook "Determinant of zoopathogenic microorganisms" mentions or describes the following species as isolated from animal diseases: Moraxella bovis, M. bovoculi, M. phenylpyruvica, M. lacunata, M. cuniculi. Oxidase-positive non-fermenting non-pigmented immobile coccobacilli belonging to the Moraxellaceae family were isolated in inflammatory pathologies of the respiratory apparatus in small domestic animals [5].

The success of measures aimed at the prevention and elimination of the disease largely depends on timely diagnosis, which is based on the analysis of epizootic data, clinical examination of animals with mandatory laboratory (bacteriological) studies.

In most cases, even in farms unfavorable for infectious keratoconjunctivitis, the frequency of isolation of Moraxella bovis from pathological material does not exceed 20%, which significantly complicates the diagnosis of the disease, and, consequently, the development and implementation of necessary therapeutic and preventive measures.

When diagnosing bovine moraxellosis, it is necessary to differentiate it from telaziosis, chlamydia, mycoplasmosis, rickettsiosis, and also exclude viral diseases infectious rhinotracheitis. For example, in some cases, the infectious rhinotracheitis virus can cause acute conjunctivitis, but the inflammatory process does not progress to ulceration and severe turbidity, as is often the case with moraxellosis. Animals that have been ill with acute and chronic forms of ICC have resistance to reinfection at an older age – immunity is formed, which reduces the level of reinfection.

Good moraxella infection control practices are of paramount importance to reduce or prevent the spread of infectious keratoconjunctivitis in cattle, sheep and goats. Temporary isolation and preventive treatment of animals recently introduced into the herd may be beneficial, as some of these animals may be asymptomatic carriers. Ultraviolet radiation can exacerbate the disease (especially in cattle), so shade should be provided to affected animals.

To reduce the number of insects, important vectors of Moraxella bovis, it is proposed to use insecticide-impregnated ear tags. The addition of vitamin A to food can help prevent the occurrence of insects, since vitamin A is involved in maintaining the integrity of the surface of the eye, mucous membranes and skin, which are effective barriers to bacteria and viruses, reducing the risk of eye infections, respiratory problems and other infectious diseases [6]. One of the methods of prevention and treatment of this disease is vaccination against infectious keratoconjunctivitis in cattle using monovalent and polyvalent vaccines. But despite years of research on vaccines against infectious keratoconjunctivitis, no vaccine has been widely used. Researchers have gained an understanding of the immunology of IBK and the antigenic nature of M. bovis and other pathogens, but the factors contributing to the epizootic efficacy of the vaccine remain unattainable [7, 8].

Currently, antibiotics remain one of the most widely used classes of medicines for the treatment of infectious keratoconjunctivitis. However, there are problems in modern antibacterial therapy, among which one of the main ones is the irrational use of antibiotics, which, in turn, is the main reason for the appearance and spread of resistant strains of bacterial pathogens.

M. bovis has been reported to be sensitive to beta-lactam antibiotics – penicillin G, bicillin, ampicillin, amoxicillin/clavulanic acid, and cephalosporins; fluoroquinolones – moxifloxacin, ofloxacin, norfloxacin, levofloxacin and enrofloxacin; chloramphenicol and florfenicol, trimethoprim/sulfomethaxosol, tetracycline and bacitracin. This type of moraxella may show resistance to the beta-lactam antibiotic cloxacillin, aminoglycosides (spectinomycin and kanamycin), sulfonamide preparations (sulfadimesine and sulfadimethoxine), tylosin, phthalazole, nystatin, resorcinol, nitrofurazone. The sensitivity of M. bovis strains to macrolides (erythromycin, clarithromycin), aminoglycosides (streptomycin, gentamicin) and lincomycin is variable [9-10].

As a rule, funds in farms are used empirically, without conducting a study of the antibiotic sensitivity of field strains of the pathogen, and, therefore, they receive contradictory effects. Often, the initial positive clinical dynamics is replaced by relapses, keratopathies, leads to clouding of the cornea, a decrease in breeding qualities and productivity of cattle. Thomas K. Shryocka and coauthors reported that other major losses from infectious keratoconjunctivitis include the direct cost of repeated drug treatment of infected animals.

Antimicrobial resistance (AMR) can make IBK treatment very difficult, and these problems are serious challenges and have begun to appear all over the world. This thesis was reflected in the first Global Report on Antibiotic Resistance, expressed through the World Health Organization on antimicrobial resistance, which she highlighted as the main struggle of human and animal medicine of the 21st century. Infections caused by resistant pathogens impose a financial burden on health systems, agriculture and society as a result of exacerbation or prolongation of the disease and subsequent inpatient treatment with potentially critical consequences for the health of both humans and animals. There are several works in the literature on AMP strains isolated from infectious conjunctival diseases.

Proper selection of antimicrobials requires knowledge of sensitivity to them and their distribution in the tissues of the eye and lacrimal fluid. To date, it has been established that all tested M. bovis strains were resistant to cloxacillin, since growth was not inhibited by discs containing 1 mcg of the drug; 68% of hemolytic isolates were resistant to streptomycin, whereas all non-hemolytic isolates were sensitive to streptomycin. One hemolytic isolate was resistant to sulfonamides.

Simultaneously with the increase in the number and expansion of the field of application of antibacterial agents, the downside of their active use has manifested itself – the growth of antibiotic resistance of pathogens. In these circumstances, the question arises: how to overcome such stability? Secondary (acquired) resistance of microorganisms to antibiotics is a key problem of infection therapy in the 21st century. It is mainly she who prevents the effective treatment of animals with bacterial infections, contributes to the formation of chronic, recurrent infections.

The spread of strains resistant to the main classes of antibiotics is observed on a global scale. The main reasons contributing to the development of antibiotic resistance of microorganisms include the following: irrational use of antimicrobials, their incorrect choice and incorrect combination, unjustified appointment for the treatment of viral and mild bacterial infections; unjustified use of broad-spectrum antimicrobials in situations where antimicrobials with a narrow spectrum of action can be effectively used; inadequate dosing regimen (insufficient doses, violation of the frequency of administration and duration of administration); low level of infection control; widespread use of antimicrobials as feed additives in agriculture and veterinary medicine; free over-the-counter sale of antimicrobials in the pharmacy network [11, 13-14].

4 Conclusion

In connection with the above, the development of phage therapy, the development of an experimental drug and the evaluation of its therapeutic effectiveness on target models are relevant for the implementation of a strategy to combat antibiotic resistance and increase the effectiveness of therapeutic and preventive measures in IBK.

Separate attempts to use various bacteriophages in infectious animal diseases were made back in the 20-30s of the previous century.

Bacteriophages have great potential to solve this problem, they are species-specific and do not have a harmful effect on healthy cells, in addition, they multiply only at the site of infection [12-13]. A bacteriophage, or phage, is a virus that specifically infects bacteria. Sharma S. et al. (2017) noted that phage particles are becoming popular as a biotechnological tool and treatment of pathogenic bacteria in a number of applied fields. The prospects of bacteriophagy as a basis for solving the global problem of antibiotic resistance of pathogenic bacteria have been repeatedly noted in numerous works of researchers. However, to date, there are not enough studies on this topic and they are very limited, which requires further study [13, 15-16].

Therefore, the development and manufacture of therapeutic and prophylactic phage preparations for the needs of veterinary medicine is currently becoming more relevant for practice. The advantage of these products is their environmental safety, harmlessness, even in large doses and the absence of side effects on the animal body. At the same time, phage therapy and phage prophylaxis do not exclude the use of symptomatic treatment, serotherapy and seroprephylaxis, probiotics, antibiotic therapy, vaccine prophylaxis, as well as the entire complex of veterinary, sanitary and zoohygienic measures.

Acknowledgement

The research was carried out at the expense of a grant from the Russian Science Foundation No. 24-26-00168, https://rscf.ru/project/24-26-00168/.

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