ANTIBIOTIC RESISTANCE
OF *ACTINOBACILLUS PLEUROPNEUMONIAE* IN SWINE: PROBLEMS AND SOLUTIONS

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SUMMARY

Porcine pleuropneumonia is an infectious contagious disease caused by bacteria *Actinobacillus pleuropneumoniae*. Currently the disease is widespread in many countries with well-developed pig production. The disease causes significant economic damage to farms due to the large mortality and expenses for treatment of diseased pigs and implementation of veterinary and sanitary measures. Due to increased number of *Actinobacillus pleuropneumoniae* cases in pigs, and the emergence of actinobacillus-resistant forms, it is necessary to perform a more thorough study and discussion of this problem. The disease epidemic surveillance relies on continuous monitoring aimed at porcine *Actinobacillus pleuropneumoniae* identification, confirmation and registration, determination of its characteristics and trends in development of susceptibility to antimicrobial preparations. The article addresses the topic of antibiotic use and the antibiotic resistance of microorganisms, which is actual not only for veterinary medicine but also for medicine. The model of swine *Actinobacillus pleuropneumoniae* was used to study the reasons of antibiotic resistance. Possible approaches to overcoming the resistance of actinobacilli to antibiotics have been discussed. The prospects for use of antibiotics were discussed in detail to cope with this problem. Targeted surveillance, aimed at monitoring and collecting information on the prescription of antibiotics is of great importance for the solution of the problem of antibiotic resistance. The information obtained from the monitoring can be used for development of the plan and strategy for the use of antibacterial preparations (preparation selection, dose, route of administration, frequency, number of courses), development and implementation of more effective approaches to the treatment of *Actinobacillus pleuropneumoniae* in pigs, control of the antibiotic-resistant bacteria occurrence and spread.

Key words: *Actinobacillus pleuropneumoniae*, antibiotic resistance, monitoring.

Actinobacillus pleuropneumonia is an infectious contagious porcine disease. Animals of all ages can be susceptible to it. The disease agent is bacteria *Actinobacillus pleuropneumoniae*, having 15 serovars and producing four types of toxins [4, 5].

Today Actinobacillus pleuropneumonia is widely spread in many countries with well-developed pig production. Despite high susceptibility of the agent to many antimicrobials, diseased animal treatment does not always give good results. The efficacy of antibiotic therapy very often varies in different holdings.

Annual decrease in actinobacillosis cases as well as emergence and wide spread of antibiotic-resistant forms of actinobacillus [2, 6], not susceptible to many antimicrobials is accompanied with decrease in the therapy efficacy, longer treatment and higher mortality. All these factors call for the necessity of monitoring of the agent, its structure and the level of drug resistance. The significance of the problem indicates that it is necessary to perform analysis, assessment and prognosis of Actinobacillus pleuropneumonia situation on pig farms in the Russian Federation. Empiric antibiotic treatment of the disease applied today by veterinary specialists of pig farms shall take into account actual data of epidemiological monitoring of antimicrobial resistance of *Actinobacillus pleuropneumoniae* circulating on specific farms.

Today in Russia there is no Actinobacillus pleuropneumonia control system as the disease does not pose any danger to humans, does not belong to transboundary infections and is just an economically significant disease. According to many veterinary specialists, the easiest way of antimicrobial resistance control is the search for and development of new preparations. However, it should be underlined that this way is quite complicated, expensive and very often ineffective. For 30 years starting from the 70s of the last century several new classes of antibiotics were discovered and within this time resistance of some agents to some antibiotics made it impossible to use them in veterinary and human medicine. Moreover, today a great many of large pharmaceutical companies seized development of new classes of antimicrobials as they don't

produce expected results [3]. In view of this, it is necessary to preserve those drugs which are applied by veterinaries now and which still have some therapeutic effect.

To solve the problem of antimicrobial resistance you have to start with the development of the strategy for its prevention and control. It should include several areas of activities. The key activities focus on restricted use of antibiotics, targeted epidemiological surveillance, following the principles of diseased animals' isolation, training of veterinarians and implementation of the administrative control program.

Today two basic mechanisms of antimicrobial resistance spread are known i. e. by genetic determinants of resistance with movable genetic elements and spread of the resistant bacteria clones (mutants). The wide use of different antimicrobials in veterinary medicine and emergence of new mechanisms of antimicrobial resistance in bacteria call for more thorough studies of the problem in *Actinobacillus pleuropneumoniae*.

Monitoring of actinobacillus resistance to antimicrobials is a systemic constant process of the information collection and analysis for quantitative evaluation of antimicrobial resistance spread and its temporal dynamics.

The aim of monitoring *Actinobacillus pleuropneumoniae* resistance to antimicrobials is to obtain information necessary for development and implementation of more effective approaches to Actinobacillus pleuropneumonia treatment and to control of antibiotic-resistant *Actinobacillus* emergence and spread at the local and regional levels.

When monitoring antimicrobial resistance of *Actinobacillus pleuropneumoniae* major focus shall be given to acquisition of data on Actinobacillus pleuropneumonia associated morbidity and lethality caused by resistant actinobacillus strains.

It should be understood that monitoring performed in the present time only ascertains the fait accompli, and the future events can be predicted using different types of modelling on the basis of the monitoring data. When performing monitoring of antimicrobial resistance of the agent it is necessary to remember about epidemic monitoring of Actinobacillus pleuropneumonia as well as any other infectious disease for the purpose of controlling intensity, dynamics and level of the epidemic process.

Monitoring data on the resistance level and nature can be used for:

– assessment of temporal trends and prediction of the probability of emergence and spread of *Actinobacillus pleuropneumoniae* resistant forms, routes of spread, risk factors and possible consequences for pig production (therapy inefficacy, increase in the cost of therapy, etc);

– informing veterinary specialists and managers of pig breeding holdings on the current situation for the purpose of developing the strategy for containment of disease spread caused by antibiotic resistant actinobacilli, taking proper measures to control resistant forms of *Actinobacillus pleuropneumoniae*;

– introduction of methods for timely and reliable detection of drug-resistant actinobacilli into practice.

There are two methodical approaches to monitoring of antimicrobial resistance of bacterial pathogens in veterinary science and practice: 1) continuous monitoring of antimicrobial resistance data and 2) episodic monitoring.

As for the scope is concerned monitoring can be:

– comprehensive, i. e. investigation of the antimicrobial resistance of the Actinobacillus pleuropneumonia agent in the entire diseased pig population in a pig breeding holding which is quite problematic;

– signal, i.e. collection of data in the restricted area of the pig breeding holding or in a specific part of the diseased pig population which can serve as an indicator of antimicrobial resistance of the entire population. Herewith the population under investigation shall be representative of the entire population. This type of monitoring is more preferable in case there is a need to perform a longer and more detail data collection.

When performing routine monitoring of *Actinobacillus pleuropneumoniae* antimicrobial resistance on pig breeding farms it is necessary to test all actinobacillus isolates recovered from the pathological material for their susceptibility. This would make it possible to study the dynamics and resistance already occurred in this holding or region.

Minimum scope of relevant information shall be registered at each level (local, regional) of monitoring to make it more effective. Measures developed on the basis of the data obtained shall be science-based.

Efficacy of monitoring for Actinobacillus pleuropneumonia caused by antibiotic resistant actinobacili depends on:

– good-quality pathological material;
– successful extraction of the disease agent;
– qualified determination of susceptibility to antimicrobials;
– data analysis;
– timely use of the data obtained.

Reliability of the data obtained depends on the proper collection and delivery of the pathological material for testing, standardization of extraction methods, identification and determination actinobacillus susceptibility, interpretation of the results obtained, compliance of the laboratory with common test performance standards.

The procedure of pathological material collection from carcasses and diseased pigs and its delivery for testing is described in regulatory documents for sample collection from the pathological material for laboratory testing in veterinary laboratories.

When testing samples of pathological material you should consider the epidemic situation, tasks and objectives of the testing and laboratory's potential.

In order to obtain comparative data on the frequency of extraction of antibiotic resistant *Actinobacillus pleuropneumoniae* forms the agent extraction and identification shall be performed according to the current regulatory documents. The ultimate goal of the tests performed is detection of the agent, determination of the agent's susceptibility to antimicrobials and assessment of antibiotic-resistant actinobacilli in the herd.

In the regions with high and average spread of Actinbacillus pleuropneumonia agent isolation shall be performed for periodical screening of the disease changes, assessment of control intervals between the tests to determine the efficacy of measures performed and inclusion of necessary changes into the testing schedule as well as for detection of Actinobacillus carriers in normal pigs.

When performing monitoring tests it is preferably to perform initial trial control of Actinobacillus serovars associated with the pig disease. It is known that in most cases the severe forms of Actinbacillus pleuropneumonia caused by antibiotic-resistant bacteria strains are characterized by a higher frequency of deaths than the same

infection caused by susceptible strains. Nevertheless, further studies of high lethality cause should be conducted.

Contemporary standardized methods of detecting susceptibility of bacterial pathogens to antimicrobials are a serial dilution method and diffusion method [1].

A serial dilution method is based on the direct determination of the quantitative value, characterizing microbial activity of antibiotics – minimum inhibitory concentration (MIC).

MIC – minimum concentration inhibiting *Actinobacillus pleuropneumoniae* growth in broth culture or in solid nutrient medium.

For MIC determination preset concentrations of antimicrobials are added into the nutrient medium which is subsequently inoculated with actinobacillus culture and after incubation the presence or absence of growth is assessed.

Depending on the used medium the serial dilution method can be performed using agar or broth.

Diffusion method for susceptibility detection implies antibiotic diffusion in the solid medium and inhibition of actinobacillus culture in the zone where antibiotic concentration exceeds MIC.

Several varieties of the diffusion method are known today the most popular of which is disc diffusion method [7].

In the disk diffusion method a paper disc is used as an antibiotic carrier. Growth inhibition zone is formed as a result of antibiotic diffusion in the nutrient medium. The zone diameter is in inverse proportion to MIC. However, the disk diffusion method is only indirectly indicative of the MIC value. The outcome of the test is verification of the microorganism susceptibility profile (susceptible, intermediate and resistant).

When performing the test preference should be given to the quantitative susceptibility determination method, which allows determining antibiotic MIC values for the tested actinobacillus strain. When using the disk diffusion method it is necessary to record not only qualitative values of actinobacillus susceptibility category but also qualitative values – inhibition zone diameter.

In most cases standard Russian antimicrobial susceptibility test-kits can be used for routine monitoring of actinobacillus antimicrobial resistance. For scientific and research purposes or if there is a specific necessity the antibiotic test kit used for antimicrobial resistance monitoring can be extended.

Ultimately, the choice of antimicrobials and tests depends on the objectives of the monitoring.

CONCLUSION

Actinbacillus pleuropneumonia treatment is still one of the complicated issues of veterinary science. The reason for insufficient efficacy of the antimicrobial therapy is growth of actinobacillus resistance to traditional antimicrobials used in veterinary medicine.

Basing on national and international publications as well as own research it can be concluded that antimicrobial resistance of different bacteria species including actinobacilli is the result of widespread irrational use of antimicrobials.

Monitoring studies of actinobacillus resistance to antimicrobials is a long-pending problem the solution of which will allow the veterinary service developing proper measures for control and containment of actinobacillus antimicrobial resistance development and spread, optimization of Actinbacillus pleuropneumonia antimicrobial treatment and publication of data on *Actinobacillus pleuropneumoniae* antimicrobial resistance in Russia.

Comprehensive studies of antimicrobial resistance problem will make it possible to develop a system allowing performing monitoring of antibiotic use (selection of the preparation, dose, administration route, frequency, number of courses), assessment of its results and, on their basis, developing recommendations.

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