

THE ROLE OF BACTERIAL INFECTIONS IN THE DEVELOPMENT OF RESPIRATORY DISEASES IN SWINE

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Abstract

Respiratory disease of bacterial etiology is a serious health problem on commercial farms. Pig production on commercial farms means keeping a large number of pigs in a relatively small space with a high level of technological organization of the production process. Intensive utilization of accommodation capacities, early weaning of piglets, inadequate microclimatic conditions for most of the stabled categories and deficits in nutrition have conditioned the appearance of production or technological diseases. Production diseases of bacterial etiology are presented in this review paper. Diseases of bacterial etiology that occur at all stages of technological production are: atrophic rhinitis, enzootic swine pneumonia, pneumonia caused by pasteurellosis, bordetella, pneumonia caused by *A. pleuropneumoniae*, pneumonia caused by *Haemophilus parasuis* and pneumonia caused by *Streptococcus*. We have described the possibility of prophylaxis of these production diseases of bacterial etiology and the possibility of their control. These manufactured diseases cause economic losses (deaths, reduced daily gain, extended fattening time and treatment costs).

Key words: bacterial infections, respiratory disease swine,

INTRODUCTION

Among the most important bacterial pathogens, causative agents or synergists in the development of the most common respiratory diseases of pigs include *Mycoplasma hyopneumoniae*, *Actinobacillus pleuropneumoniae*, *Bordetella bronchiseptica*, *Pasteurella multocida*, *Haemophilus parasuis* and *Streptococcus suis*. *Mycoplasma hyopneumoniae* (Ivetić et al. 2000) is cited as the primary cause of enzootic swine pneumonia. The combined action of *Bordetella bronchiseptica* and *Pasteurella multocida* leads to the development of atrophic rhinitis. Other bacterial pathogens, alone or in interaction with others, lead to various forms of bronchopneumonia. (Lončarević A., 1997, 1998; Šamanc H., 2009; Lipej Z., 2015). Bacteria, viruses, parasites and fungi play a primary role in the development of diseased respiratory organs. Diseases of the respiratory tract can rarely be caused by a single cause (mono-infection). They are often mixed infections (polyinfections or superinfections). There is a possibility that mycoplasma,

bordetella, *paterela*, and different strains of *H. pleuropneumoniae* dominate (Šamanc H., 2009; Bojkovski J. et al., 2013, 2018).

Atrophic rhinitis

Atrophic rhinitis is a disease of the upper respiratory tract. Dystrophic changes in the upper jaw bones and frequent bleeding of the upper teeth, food intake is very difficult and reduced. Diseased animals show smaller growth and significant lag in fattening (Lončarević A., 1998). The etiopathogenesis of atrophic rhinitis is complex and includes a number of pathogens, including *Bordetella bronchiseptica*, *Pasteurella multocida*, *Haemophilus parasuis*, and porcine cytomegalovirus. Genetic factors, environmental influences and nutritional deficiencies are also predisposing. *Bordetella bronchiseptica* is thought to cause moderate turbinate atrophy and promote active colonization of the nasal mucosa by *Pasteurella multocida* bacteria. Toxogenic strains of *paste* (types A and D) produce cytotoxins that inhibit osteoblast activity and stimulate osteoclast

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activity and remodeling in the nasal bones, resulting in conch atrophy (Lončarević A. *et al.*, 1998; Shamanc H., 2009). In infected pigs, *Bordetella bronchiseptica* and *Pasteurella multocida* (serotypes A and D) produce much stronger local reactions than in individual infections caused by one of these two pathogens. The main characteristic of infection with these pathogens is very long germination (Lončarević, 1997; 1998). Sows pose a latent danger to their offspring. Infection occurs aerogenically, by vertical transmission, from suckling sows to piglets during and after farrowing or during the lactation period (Lončarević A., 1998). In the category of weaned piglets, the infection is spread by contact from infected animals to animals from uninfected litters (horizontal transmission). Piglets are considered to be the most susceptible until the age of 6 to 8 weeks. However, infection can occur after this period, but very rarely. In infected animals, characteristic morphological changes occur with atrophy of the nasal shells and deformation of the snout (Lončarević A., 1998; Šamanc H., 2009; Lipej Z., 2015). The initial symptoms of the disease are observed in piglets aged 8 to 10 days, ie at the latest at the end of the suckling period. Atrophic rhinitis occurs in subclinical or clinical form, is chronic and almost never causes direct death. In the early phase, atrophic rhinitis is clinically characterized by sneezing, coughing, nasal discharge and drying of lacrimal secretion under the medial corner of the eye (Lipej Z., 2015). With the appearance of morphological changes, in the form of deviations of different degree, we talk about atrophic rhinitis as a clinical phenomenon. The changes can be pronounced only on one side or are bilateral with a shortening of the upper jaw and a very curved line and folds on the skin of the dorsum of the snout. In severe cases, the tooth is to blame. During all phases of the disease, the animals are afebrile and do not show health disorders. In the beginning, pigs take the necessary amounts of food, but later, due to the deformity of the teeth, they find it harder to take food and slowly lag behind in growth (Lončarević A., 1998; Lipej Z., 2015). Localization of morphological changes is preventstvevno on the mucous membrane of the nasal cavity, then on the nasal shells and bones of the upper jaw. Due to the deformation or complete disappearance of the nasal septum, there is a clear asymmetry of the nasal cavities, as well as deformation of the upper jaw bones. The nasal bones are most often affected by the inflammatory process. In the initial stage of the disease, there is a partial atrophy of one or both nasal shells, while in the last phase of the disease there is often their complete atrophy (Shamanc H., 2009; Lipej Z., 2015). The key microscopic lesion

in atrophic rhinitis is a decrease in the bone density of the nasal conchas. In the later stage of the disease, the swelling of the connective tissue is also expressed, especially around the blood vessels whose lumen is narrowed, and very often obliterated (Lončarević A., 1998). The basic measure of prevention is to prevent the introduction of the pathogen into healthy areas. However, if the causative agent is "introduced" into the plant, more extensive measures should be taken so that the infection does not spread in the plant. It is necessary to correct the microclimatic conditions and reduce the population density in the facilities. Ventilation, *i.e.* appropriate ventilation, should ensure that the animals breathe clean air without dust and harmful gases. Detection of carriers among sows, and their exclusion from the herd are an important measure of prophylaxis (Lončarvić A., 1998).

Swine enzootic pneumonia

Mycoplasmas cause a mild infection, but thanks to their very pronounced immunomodulatory properties, they can greatly reduce the ability of the respiratory system to defend itself against other microorganisms. They are widely distributed in pig herds and are the primary cause of respiratory diseases. About 90% of the examined diseases are endangered by mycoplasmal infection of the respiratory tract, and in 70% to 75% of cases *Mycoplasma hyopneumoniae* is the cause of pneumonic lesions (Ivetić V., *et al.*, 2000; 2005). Enzootic pneumonia spreads as a droplet infection or directly, by contact through a discharge from the respiratory organs. In swine fever, the disease is maintained by transmitting the pathogen from sows to piglets. It is enough to infect only a few piglets, so that the disease then spreads from litter to litter, ie to affect almost all piglets at the time of regrouping and transfer to kennels. Mixing of new piglets with piglets left in the kennel contributes to the maintenance of the infection (Ivetić V., 2005). Infection occurs very early without clinical symptoms. Only in rare cases, *Mycoplasmae hyopneumoniae* can cause pneumonic changes in suckling piglets (Ivetić V., *et al.*, 2005). The disease is characterized by a long incubation period, because the causative agent multiplies slowly in epithelial cells, then high morbidity, low mortality and chronic unproductive cough (Shamanc H., 2009). By adhering to the ciliated epithelium, mycoplasmas resist phagocytic activity they are closely connected with the cell membrane, they are also protected from the body's immune defenses (Lončarević A., 1997.). By reducing the function of the mucociliary apparatus, *M. hyopneumoniae* significantly contributes to the development of

secondary bacterial infections (Zimmerman J.J. *et al*, 2012). Numerous studies have shown that mycoplasmas stimulate the division of lymphocytes, *i.e.* to have a non-specific stimulatory (mitogenic) effect on lymphocytes and to stimulate their mass accumulation peribronchially and perivascularly (Savić B. *et.al* 2009). The inflammatory reaction, accompanied by increased production of proinflammatory cytokines, plays a significant role in the development of mycoplasmal pneumonias. The inflammatory response is significant in the control of respiratory pathogens, tissue damage is more likely to be caused by the host itself than by the microorganism (Ivetić V. *et al* 2007). It has also been shown that pulmonary alveolar macrophages infected at the same time with *M. hyopneumoniae* and *A. pleuropneumoniae* have significantly reduced phagocytic abilities (Šamanc H., 2009). Based on the observed clinical symptoms, two forms of the disease can be distinguished, bronchitis and bronchopneumonia. In bronchitis, an unproductive cough occasionally occurs, body temperature is within normal physiological limits, and the frequency of breathing is somewhat accelerated. In animals with pneumonic changes in the lungs, in addition to coughing, loss of appetite and decreased physical condition, body temperature, pulse and respiration may be altered. Auscultation can hear dry and wet röhni, bronchial breathing and two-phase inspiration, as a consequence of narrowing or closing of the bronchial lumen (Šamanc H., 2009). Morphological changes are mostly found on the ventral parts of the apical and cardiac lobes of the lungs, although to a lesser extent, the anterior parts of the diaphragmatic lobes can also be affected. The altered parts of the lungs form dark red to gray-colored consolidated fields. The most prominent change in the area of the altered lung tissue is atelectasis in the form of indented parts in relation to the normal lung tissue. In cross-section, the altered parts of the lungs have a fleshy but not hard consistency. There is always a large amount of catarrhal exudate in the lumen of the tubular respiratory organs. Bronchial and mediastinal lymph nodes are often changed and enlarged (Ivetić V. *et al*, 2000, 2005). Early microscopic lesions are characterized by the accumulation of neutrophilic granulocytes in the lumen and around the airways, as well as in the alveoli. Many cases of mycoplasmal pneumonia are combined infections. The most common combinations of pathogens in the complex of respiratory diseases of pigs are precisely *M. hyopneumoniae* with the PRRS virus and the bacterium *P. multocida*. The essence of all prophylactic programs so far, includes a system of keeping and treatment in which, as much as

possible, it is impossible to maintain the causative agent in pigs, as well as its transmission to the youngest categories (Bojkovski J. *et al* 2015).

Pasteurella-induced pneumonia

Pasteurellosis occurs in peracute, acute and chronic forms. Clinical symptoms are conditioned by the intensity of morphological changes in the lungs, *ie* the activation of existing, smaller foci into acute bronchopneumonia. At the beginning of the disease, the cough is dry and unproductive, and soon, due to the exudation and accumulation of a large amount of contents, the cough becomes moist. During the disease, the body temperature is elevated, and in the peracute form of the disease it reaches a value of 42 ° C. Sick animals are apathetic and do not eat. Due to the difficult health condition and exhaustion, the animals lie down. The course of the disease lasts 5 to 10 days and ends with the death of the animals, if they are not treated. Only in a small number of cases, the disease takes a chronic course and lasts between 3 and 5 weeks. The acute septicemic form of swine pasteurellosis (hemorrhagic septicemia) is caused by *P. multocida* serotype B. After a short incubation, the disease begins suddenly, with severe clinical symptoms. In addition to high body temperature and very difficult breathing, the work of the cardiovascular system soon weakens. The first symptoms of dysfunction of this system are initially uneven redness of the skin, swelling of the pharyngeal region, and then, diffuse redness of the skin and cyanosis of the tip of the snout, ears, distal parts of the extremities and abdomen. Death occurs within hours. Very rarely, the disease can last for one or more days (Šamanc H., 2009). Pathomorphological changes caused by pasteurellosis are characterized by catarrhal-fibrinous bronchopneumonia, which is accompanied by well-limited red to gray consolidated areas of the lungs, with a predominantly cranio-ventral distribution (Ivetić V. *et al*, 2007). they are also characteristic of pig pasteurellosis. There is a smaller or larger amount of red fluid in the pleural cavity. In the peracute-septicemic form, numerous spot bleeding by serosa can be observed (Ivetić V. *et al*, 2007) The microscopic finding is characterized by lobular purulent bronchopneumonia (Ivetić V., 2007). Accumulation of fibrin masses and accumulation of neutrophilic granulocytes in the lumen of the alveoli, bronchioles and bronchi are observed. In addition to visible damage to the epithelium in the lumen of the alveoli, bronchioles and bronchi, significant amounts of fibrin can be found, which with accumulated cellular elements causes

obstruction of the respiratory tract, bronchitis obliterans, (Šamanc H., 2009).

Pneumonia caused by *Bordetella*

Bordetella bronchiseptica is a gram-negative bacterium closely related to the species *Bordetella pertussis*, but, unlike it, it does not produce pertussis toxin. In the upper parts of the respiratory tract, *B. bronchiseptica* causes inflammatory changes in the mucosa, with loss of cilia and atrophy of the turbinates. Also, this bacterium leads to primary pneumonia in newborn piglets and secondary pneumonia in older categories of pigs (Šamanc H., 2009). Virulence, as well as contagiousness are not so high and therefore do not cause acute diseases, but the disease is mainly in a chronic form. In addition to frequent coughing, sero-mucous and mucopurulent nasal discharge is also observed. The animals take smaller amounts of food and gradually lose their condition. During the disease, body temperature is in normal physiological values. Although cases of the disease have been reported in very young piglets, the disease most often occurs in nazimads at the time of fattening, when other pathogens from the complex of respiratory diseases of pigs can be found (Bojkovski J. *et al*, 2010). In dead pigs, lobular pneumonia or larger pneumonic foci that are localized in the cranial lobes of the lungs can be observed, although in rare cases they can also be localized in the caudal parts of the lungs. In primary pneumonia, changes in the lungs reach a maximum between 10 and 14 days after infection, when red areas of consolidation are observed in the lungs. After that, around the 21st day after infection, these areas become yellow-brown and contracted (Donald M. *et al*, 2008). In the lumen of the bronchi of the affected parts of the lungs, there is an abundant mucous-purulent exudate. Early pathohistological changes are characterized by the presence of blood in the lumen of the alveoli and neutrophilic granulocytes in the alveoli and bronchioles, which may be accompanied by epithelialization of the alveoli (Ivetic V. *et al*, 2007). Damaged blood vessel walls thickened due to perivascular cell infiltration. Their lumen is narrowed and sometimes obliterated. The epithelium of the small bronchi and bronchioles is hyperplastic, and the walls of the alveoli are unevenly covered with a single squamous epithelium. In some cases, pleurisy occurs with the formation of synechia, especially above the changed parts of the lungs. *B. bronchiseptica* has been shown to promote colonization and lead to exacerbation of diseases caused by *P. multocida*, *S. suis* and *H. parasuis* (Sofrenović Đ., Knežević N., 1988). In coinfection, *B. bronchiseptica* and PRRS

virus cause more severe changes in the lungs and consequently more serious clinical symptoms (Radanović O, *et al*, 2007). It has been proven that *B. bronchiseptica* and PRRS virus alone do not affect the severity of pneumonia *P. multocida*, while in co-infection they significantly contribute to the development of changes in the lungs (Radanović O. *et al*, 2007). If it is determined that *Bordetella bronchiseptica* is the main cause of pneumonia in fattening animals, the necessary preventive measures should be taken by immunizing the animals. It has been determined that the best results in endangered herds are achieved by repeated vaccination of pigs. In some countries, special programs for the production of piglets and pigs "free" from specific respiratory and other diseases are used to eradicate bordatellosis from swine. (Šamanc H., 2009; Lipej Z., 2015)

Pneumonia caused by *A. pleuropneumoniae-pleuropneumonia*

The most common cause of pleuropneumonia in piglets and pigs is *Actynobacillus pleuropneumoniae*. Changes in the lungs, *A. pleuropneumoniae* are caused by the production of APX toxins, lipopolysaccharides (LPS) and proinflammatory cytokines (Augtori B., 1990). There are large differences in the degree of virulence between individual serological types, which is most likely due to different exotoxins. There are 3 types of exotoxins: APX-I, APX-II and APX-III. APX-I is a strong hemolysin and cytotoxin, APX-II is a weak hemolysin and cytotoxin, while APX-III is not hemolytic, but is very cytotoxic, especially for neutrophilic granulocytes and macrophages (Žutić M. *et al*, 2007). Lipopolysaccharide endotoxin leads to coagulation and the development of an inflammatory reaction in the airways. The capsule protects the bacteria from phagocytosis, and they are also resistant to complement. The production of cytokines, among which the most important are IL-1 β , IL-8 and TNF, contribute to the occurrence of damage. (Žutić M. *et al*, 2007). The largest reservoirs of the causative agent are the nasal cavity and / or tonsils, and the mixing of serologically negative with infected animals, inadequate capacity and various stressful circumstances can cause the sudden appearance of clinical symptoms (Žutić M., 2007). The infection is transmitted aerogenously, with air flow being of great importance in the spread of the disease. In addition, rodents and, to some extent, birds are mentioned as possible vectors. It is possible to indirectly transmit the infection with contaminated clothes, having in mind the fact that the discharge from the nose of piglets in the acute

phase of the infection contains a large number of causes. As suckling pigs are protected from infection by colostrum antibodies, the disease is clinically manifested either in weaned piglets or in piglets in the fattening category (al 2007) .. At the site of infection, in just a few hours, neutrophilic granulocytes accumulate in large numbers. In the newly formed foci, neutrophilic granulocytes can very quickly undergo degradation processes. The process of lysing neutrophilic granulocytes is thought to be responsible for the rapid and severe destruction of lung tissue. At the same time, the presence of the capsule enables microorganisms to avoid phagocytosis, and on the other hand, the capsule can exhibit immunosuppressive action (Žutić M., 2007). The course of the disease can be peracute, acute, subacute and chronic. The peracute form of pleuropneumonia occurs suddenly in a small number of animals, with symptoms of impaired health. Body temperature is from 41.5 ° C to 42 ° C. Diseased animals are apathetic, refuse food and very often show symptoms of digestive tract dysfunction (vomiting and diarrhea). Physical weakness is soon noticed, the animals lie on the floor, without noticeable symptoms that would indicate a dysfunction of the respiratory system. In the final phase of the disease, breathing becomes rapid and difficult, the animals breathe, and a foamy content of reddish color appears from the oral cavity and nasal openings. Towards the end of the disease, symptoms appear that indicate weakness of the cardiovascular system, cyanotic color of the snout, the tips of the ears and the skin of the abdomen. Death occurs within 24 to 36 hours from the appearance of the first symptoms of the disease. Acute pleuropneumonia affects a large number of piglets or nazimads. Sick animals are apathetic and do not eat. From the very beginning of the disease, their body temperature is elevated, breathing is accelerated and difficult, cough occasionally occurs, and some animals soon develop weakness of the cardiovascular system. The subacute and chronic form of the disease occurs as a continuation of the acute form, especially in those animals that do not die during the acute phase of the disease or in those that have not been treated with drugs. The animals take less food, which makes them thin to the point of complete exhaustion. In cases of pleuropneumonia, a large number of animals are affected by the chronic form of the disease. The chronic form of the disease can be aggravated by the action of other pathogens (Žutić M., et al, 2007). Depending on the stage of the disease, the pathomorphological changes are characterized by fibrino-hemorrhagic pneumonia, with solid, dark red areas, predominantly dorsocaudal distribution, which over time necrotize and become brittle. The

altered parts of the lungs are compact and sharply demarcated from the surrounding healthy tissue. Fibrinous pleurisy is a regular occurrence in pleuropneumonia, and over time, adhesions can occur. In the pleural cavity, there are larger amounts of bloody fluid. In cases of peracute disease, in the lumen of the trachea and bronchi, there is a reddish-colored serous mucosa in the form of foam. In chronic cases, nodules of various sizes are regular, which are mostly located in the parenchyma of the diaphragmatic lobes. They are similar in appearance to abscesses and are bordered by a thin capsule from the surrounding healthy tissue. The pathohistological appearance of the altered parts of the lungs indicates that pleuropneumonia is a necrotic.

Pneumonia caused by *Haemophilus parasuis*

Infections aided by nonspecific stress factors in piglets occur sporadically and are characterized by systemic bacteremia, after which polyserositis syndrome may develop (serofibrinous to fibrinopurulent peritonitis, pleuritis, pericarditis, meningitis, and arthritis) (Šamanc H., 2009). Clinical symptoms include fever, anorexia, swollen joints and lameness, dyspnea, and symptoms of central nervous system disorders. Sudden deaths often occur, with no noticeable macroscopic lesions (Šamanc H., 2009). In the pneumonic form of the disease, hemophilus may have a primary or secondary role.). They raise piglets in rearing, aged from 4 to 6 weeks. Fifteen serovars of *Haemophilus parasuis* were identified. Cross-protection is provided only by a natural infection. Maternal immunity disappears at 6 weeks, Active immunity begins at 8 weeks. Vaccination of sows provides immunity that lasts for about 6 months. Due to the weak resistance of the pathogen in the external environment, diagnosing the disease is in many cases very difficult (Gagrčin M., et al, 2002). Examinations have shown that *Haemophilus parasuis* colonizes the tonsils more often than the nasal cavities. After the initial colonization and penetration of the microorganism, bacteremia and systemic spread in the susceptible organism develop, and the factors responsible for the occurrence of bacteremia are not known (Šamanc H., 2009).

Pneumonia caused by *Streptococcus spp.*

Streptococcus suis is a gram-positive bacterium that often inhabits the tonsils and nasal cavity of pigs, sporadically causing respiratory disorders. Transmission from sows to offspring occurs early, so that early weaning of piglets does

not play a role in interrupting the transmission cycle of this microorganism (Šamanc H., 2009; Lipej Z., 2015; Simeunović P., 2016). 35 capsular serotypes of *S. suis* were identified. Serotype 2 is most often isolated from material derived from diseased pigs. The earliest symptom is fever that accompanies bacteremia, which in severe cases can lead to meningitis with symptoms of central nervous system disorders, arthritis and lameness, polyserositis, endocarditis and pneumonia. *S. suis* invades the tonsils and reaches the lymph nodes through the lymph vessels. Infected monocytes spread the bacterium throughout the body. Several key virulence factors of this causative agent have been identified. Fimbriae and hemagglutinins play a role in adhesion, while the capsule inhibits phagocytosis (Jakić D., Ranisavljević M., 1989). There are several other potential virulence factors, but none of them is capable of causing infection on its own, so virulence is multifactorially conditioned. Pathomorphological changes induced by *S. suis* are characterized by fibrinopurulent meningitis, polyserositis, and purulent bronchopneumonia. A number of pathogens interact with *S. suis* and cause nonspecific changes to the lung (Šamanc H., 2009).

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