Atrophic rhinitis of pigs

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Abstract. The paper presents an overview of atrophic rhinitis, a common and widely spread infectious disease caused by Bordetella bronchiseptica. The main virulence factors of the pathogen are cell wall lipopolysaccharides, fimbriae, toxins, microcapsules, pertactin-like proteins. B. Bronchiseptica also produces tracheal cytotoxin, dermonecrotic toxin, adenylate cyclase-hemolysin, endotoxin. Clinically, the disease is manifested by progressive atrophy of the nasal bones, bronchopneumonia and / or sepsis, especially when associated with P. multocida, H. parasuis and S. suis or other bacterial and viral pathogens. The clinical manifestations of the disease include progressive atrophy of the nasal turbinate bones, bronchopneumonia and / or sepsis, especially when associated with P. multocida, H. parasuis and S. suis or other bacterial and viral pathogens. The diagnosis is established on the basis of clinical and epizootological data, the results of pathological, bacteriological and serological studies. For the treatment of the disease, antitussive antibiotic, antitussive, bronchodilators and anti-inflammatory drugs are prescribed. No domestic vaccines against atrophic rhinitis have been developed, which is why the work on the creation of new and improvement of existing means against atrophic rhinitis continues, including on the basis of Federal State Budget Scientific Institution «Federal Scientific Center VIEW» (FSC VIEV).

1. Introduction
Atrophic rhinitis is a highly common infectious respiratory disease of pigs. The clinical manifestations of the disease include a wide range of symptoms such as partial or complete atrophy of the nasal turbinate bones, twisting or shortening of the snout, nasal discharges and hemorrhage, sneezing and retarded growth rate.

German scientist, was the first to describe atrophic rhinitis 170 years ago. He called this pathological condition "Schnüffelkrankheit" i.e. sniffing disease. At the beginning of the studies, it was assumed that the disease was caused by heredity and nutritional factors. However, the theory was later refuted and the infectious nature of the disease was confirmed. Pseudomonas, Actinomyces, Sphaerophorus, Corynebacterium, or Mycoplasma, cytomegalovirus, trichomonads, etc. were seen as the main etiological agents [1 - 3]. Later, the results of numerous experiments showed that only certain defined strains of Bordetella bronchiseptica and Pasteurella multocida are able to trigger a disease with a clinical picture typical for atrophic rhinitis.

B. bronchiseptica was first isolated in association with respiratory diseases in dogs in 1910. Soon it was established that Bb also causes respiratory disease in other mammals. In the 1940s the etiological agent was isolated and associated with swine pneumonia. In the 1950s B. bronchiseptica was examined and found to be the main cause of atrophic rhinitis. Simultaneous colonization of nasal mucous
membrane by toxigenic strains of B. bronchiseptica and P. multocida brings about severe, progressive atrophic rhinitis. In piglets, B. bronchiseptica may be the cause of bronchopneumonia and the porcine respiratory disease complex in adult pigs. It also increases the severity of respiratory disease such as reproductive and respiratory syndrome virus [4, 5].

Currently, according to the veterinary service data, atrophic rhinitis is registered as sporadic cases. This is largely due to antimicrobial drugs used in modern pig husbandry as an effective preventive measure. In the case of animals raised without antibiotics as part of a strategy to combat the threat of antibiotic resistance, the disease may occur more frequently, and thus it cannot be argued that it was eliminated completely.

2. Pathogen
The causative agent (B. bronchiseptica) is of Bordetella bronchiseptica species, belonging to the genus Bordetella, family Alcaligenaceae, order Burkholderiales. It is a gram-negative coccoid motile rod the size of 0,4-0,6 1,5-2,5 microns that does not form aerobes, spores and capsules. However virulent strains form a microcapsule. The microbe can be well cultivated on conventional nutrient media (MPB, MPA, etc.) and elective media (casein-coal agar, mcconkey agar, Garthoch medium, etc.) at a temperature of 36-37°C. In 24 - 48 hours small grey-white shiny colonies 1-2 mm in diameter with smooth and clean edges may be formed. When cultivated on the mixture of agar and sheep or cattle blood, a thin zone of β-hemolysis is formed around the colonies.

As a rule, the disease is reproduced only when B. Bronchiseptica is associated with pasteurelles. The bacterium of Pasteurella genus are spherical, oval or rod-shaped cells the size of 0,3-1,0 x 1,0-2,0 microns. When taking the impression smear of animal tissues as well as cultures obtained from pathological material, pastreurelles often exhibit bipolar staining and are arranged singly, in pairs or in short chains. In further cultures pastreurelles lack bipolarity and resemble coccobacilli rods with capsules. On MPA three types of colonies may form: smooth surfaced colonies (S colonies), rough surfaced colonies (R colonies) and mucoid colonies (M colonies) [6].

The severity of the illness may vary from asymptomatic carriage to lethality [7]. Using the inbred SPF mice, the 50% lethal doze (LD50) can vary by up to 100 000 times between bacterial strains. The substantial differences in virulence can be explained by strain variation. Phylogenetic lineages may have their own peculiarities in virulence factor expression [8].

Animal infection occurs primarily by aerosol droplets upon contact with infected animals. Infectious aerosols generated by sneezing or coughing contribute to the further spread of the agent, thus affecting all animals in a production unit in a short time. Most often, piglets are colonized by B. Bronchiseptica at an early age when in contact with nursing sows. The agent may persist in the nasal cavity for several months until the death of the animal. The introduction of carrier pigs into a herd exposes other animals in systems where an all-in/all-out approach is not practiced to the disease. Spread within a herd is expeditious, especially in immunologically naïve animals [9, 10].

3. Pathogen
Bordetella bronchiseptica numerous virulence factors that cause adhesion, tissue damage and immune evasion. B. bronchiseptica infection begins with attachment of the bacterium to the respiratory epithelium. The adhesion is promoted by fimbrial proteins, filamentous hemagglutinin and pertactin through multiple specific bonds. After having attached, the agent causes the extrusion of ciliated epithelial cells, which contributes to mucus accumulation within the respiratory tract. The toxins produced by agents cause inflammation that leads to epithelial metaplasia and necrosis and the infiltration of immune cells. Cytotoxicity to phagocytes allows the bacteria to evade the host immune response. The interaction of B. Bronchiseptica with basal epithelial cells contributes to the development of microcolonies or biofilms, especially within the nasal cavity. Dermonecrotic toxin is one of the main virulence factors produced by B. bronchiseptica and P. multocida. It causes turbinate atrophy.

B. bronchiseptica also produces adenylate cyclase toxin that is characterized by adenylate cyclase activity and induces cell lysis by the formation of pores. The toxin can lyse various cell types, but
phagocytic cells are a primary target. The toxin is able to regulate cytokine production and alter serum and secretory antibodies response by interacting with immune cells.

The main virulence factors of Pasteurella are capsular protein; lipopolysaccharides; fimbriae; adhesion factors (ptfA, fimA, hsf-1, hsf-2, phfA and tadD); iron-regulating proteins (exbB, exbD, tonB, hgbA, hgbB, tbpA and Fur); extracellular enzymes such as neurotransmitter (nanB and nanH) and hyaluronidase (pmHAS); superoxide dismutase (sodA and sodC); dermonecrototoxin (toxA); and many different outer membrane proteins (ompA, ompH, oma87, and plpB) playing the role of protective factors. These virulence factors are regulated by 22 genes associated with virulence. The set of virulence genes depends on the capsule type (A, B, D, E, F). For example, the hemagglutinin phylamenic gene "pfhA" is predominantly found in Pasteurella type A, B, E and F. the iron-producing Gene "tbpA" is associated with the capsule type of Pasteurella A and B. The gene "toxA" responsible for the presence of dermotoxin is characteristic of the capsule type D.

Pasteurella adhesins are a factor that provides a strong link the pathogen with the epithelial surface of the respiratory tract, so that the cells counteract physical influences in the form of cough, sputum, aimed at mechanical removal of the pathogen. For the destruction of the sputum Pasteurella produce neuraminidase, causing degradation of the mucous secretions of the epithelium [11].

Lipopolysaccharides (LPS) of bacterial cell membranes provide a high degree of adaptation to environmental factors, promote leukocyte stimulation, production of anti-inflammatory cytokines, activation of blood coagulation complements and cell cytolysis. The toxic properties of LPS can be enhanced by the formation of a complex with phospholipids, which contribute not only to pulmonary colonization, but also to the suppression of the protective action of immune cells, thereby allowing the pathogen at the stage of introduction into the body to remain on the surface of tissues and initiate inflammatory processes. Toxins of pathogens lead to atrophy of the nasal passages, liver and urogenital tract lesions, characterized by degenerative and hyperplastic changes, as well as interfere with the normal growth of bones and cartilage.

4. Clinical sign
Clinical signs amongst pigs infected with B. bronchiseptica vary depending on age, immune status, and coinfection with other pathogens. In uncomplicated disease, symptoms typically appear in 2–3 days after infection and are associated with sneezing, nasal and ocular discharge, and a dry, repeated cough. Neonatal pigs show more severe signs including bronchopneumonia and dyspnea. After several weeks, clinical signs may abate but carriage persists for life [12]. Coinfection with toxigenic strains of P. multocida may cause PAR, epistaxis, brachygnathia, deformation of the snout [13]. Pneumonia caused by B. bronchiseptica can also occur secondarily to infection with the following viral pathogens: porcine respiratory coronaviruses, swine influenza virus, or porcine reproductive and respiratory syndrome virus [14]. Pigs with passively acquired maternal or adaptive immunity may become carriers of infection, but remain more vulnerable to secondary infections with other bacterial pathogens. Atrophic rhinitis may be the cause of high morbidity with low mortality except in young pigs or complicated coinfections.

5. Pathological changes
One of the most typical signs of atrophic rhinitis is an atrophy of the nasal turbinate bones assessed by transverse section of the nasal cavity at the level of upper premolar teeth where the dorsal and ventral conchae are maximally developed in the healthy animal. The changes in the nasal cavity usually appear between 6 and 12 weeks of age of the piglets. The ventral scrolls of the turbinates are the most affected areas in mild and moderate cases. In more severe cases, atrophy of the dorsal scrolls of the ventral turbinate and the dorsal and ethmoidal turbinates occurs. Lateral eviation of the nasal septum may be observed as well.

Microscopic lesions of the nasal cavity are characterized by epithelial changes such as hyperplasia squamous metaplasia and loss of cilia, and submucosal infiltrates of neutrophils, lymphocytes and macrophages with occasional microabscesses in the epithelium. Replacement of the bony trabeculae of the turbinates with fibrous connective tissue is also likely to occur.
Lungs have firm red to plum or grey to yellow fibrotic lesions. Macroscopic lung lesions are characterized by bleeding, necrosis, accumulation of inflammatory infiltrates in respiratory tract and alveolar spaces. Interlobular and intra-alveolar edema is also possible. As a result, fibroplastic replacement of lung parenchyma with sequestration of necrotic areas may occur. Coinfection with other bacteria and/or viruses may change the character of the lesions, however, suppurative bronchopneumonia is present most cases.

6. Diagnosis
It may be rather difficult to isolate the causative agent and confirm its etiological significance as B. bronchiseptica is often found together with numerous respiratory disease agents. The typical lesions may be caused by SIV, PRCV, P. multocida, A. suis, A. pleuropneumoniae, M. hyopneumoniae, S. choleraesuis, S. suis, H. parasuis, etc.

In vivo bacteriological study is based on the isolation of B. bronchiseptica culture from washouts from the tonsils, nasal cavity and trachea of infected animals. It is advisable to select the material for the study from animals with an early stage of the disease, since it is difficult to isolate the pathogen in the advanced form of the disease with the deformation of the snout. When autopsies are selected and sent to the laboratory pieces of lungs, trachea, affected parts of the nasal septum.

Also, other laboratory methods are used for diagnosis: infection of laboratory animals, ELISA, molecular methods). PCR diagnosis, used for diagnosis, is a sensitive and highly specific method based on the detection of pathogen genetic material in clinical samples or microbiological crops. For the formulation of the reaction as a clinical material, smears from the nose or tonsils, nasal secretions, tracheobronchial lavage are used.

7. Treatment and prevention
For the treatment of animals prescribed antibacterial and symptomatic therapy. When selecting the drug, the sensitivity of the pathogen to antibiotics and the ability of the antimicrobial agent to accumulate in the respiratory system in therapeutic concentrations are taken into account. In easily occurring cases of infection, treatment may not be required, but it should be borne in mind that the animal will remain a long-term bacterial carrier and will pose risks to other susceptible animals.

There are various predisposing factors that increase the frequency of outbreaks of atrophic rhinitis, for example: high planting density of animals, mixing of animals from different groups, insufficient ventilation with high concentrations of ammonia and dust, insufficient consumption of colostrum.

Specific prophylaxis is based on vaccination of the breeding sows with primary vaccination with two doses (6-7 and 3-4 weeks before farrowing) and a booster dose before each subsequent farrowing (3-4 weeks before). Good colostrum intake is crucial to better protection of piglets as it ensures transmission of maternal immunity.

8. Conclusion
B. bronchiseptica is an all-pervasive pathogen. Monoinfection results in a mild disease; however the animals become chronic carriers. Measures to control the spread of atrophic rhinitis include a set of zooveterinary measures such as improving indoor air quality, application of an all-in/all-out principle, treatment of the affected animals and vaccination of pigs of parental herds. The application of these methods helps to reduce the bacterial load and in combination with the elimination of affected animals averts the risk of carrying toxigenic strains of B. bronchiseptica and P. multocida. Vaccination of animals belonging to disadvantaged herds ensures a substantial improvement and accelerates the process of recovery.

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