Mannheimiosis of cattle, sheep and goats

A I Laishevtsev
Federal State Budget Scientific Institution “Federal Scientific Centre VIEV” (FSC VIEV), Ryazanskiy prospect, 24, 1, Moscow 109428, Russia

E-mail: a-laishevtsev@bk.ru

Abstract. Respiratory diseases of farm animals cause great economic losses to cattle-breeding, sheep-breeding and goat-breeding enterprises. On the territory of the Russian Federation one of the most wide-spread respiratory diseases among cattle, sheep and goats is Pasteurellosis, with Pasteurella multocida and Mannheimia haemolytica (earlier Pasteurella haemolytica) considered as its pathogens until not long ago. On the basis of the peculiarities and differences of the biological features of the mentioned microorganisms as well as on the basis of differences in aetiology, epizootiology, pathogenesis and clinicopathologic manifestations of the disease, infection caused by M. haemolytica was differentiated from Pasteurellosis and assigned to a new nosology – Mannheimiosis. In its turn Mannheimiosis is a Pasteurellosis-like disease, which needs some predisposing stress factors to appear. Unlike Pasteurellosis, Mannheimiosis does not appear independently, but can provoke secondary complications. Nowadays the peculiarities of Pasteurellosis are thoroughly studied, while there is not enough systematized data on Mannheimiosis. Due to all mentioned above we consider the relevance of the studies on Mannheimiosis of cattle, sheep and goats to be obvious. Presented work contents the information about microorganism M. haemolytica, the description of its cultural, morphological, biochemical and serological features, as well as factors of virulence of the pathogen, due to which pathogenesis of the infection develops. Moreover, there is information about the development of Mannheimiosis, the most typical signs of the infection, principles of laboratory diagnosis, treatment and specific prevention.

1. Introduction
Pasteurellosis is a contiguous infectious disease of farm, pet and wild animals, which if acute is characterized by the signs of septicaemia, croupous inflammation and pulmonary edema, pleurisy, and if chronic – purulent necrotizing pneumonia, arthritis, mastitis, keratoconjunctivitis, endometritis and sometimes enteritis [1]. For a long time P. multocida and P. haemolytica were considered as the pathogens of the disease [2, 3]. Later, due to reclassification of Mannheimia spp.to a separate group there appeared a necessity to differentiate a new nosology – Mannheimiosis [4, 5]. Mannheimiosis is a Pasteurellosis-like factorial infectious disease, mostly of ruminants, caused by pathogen M. haemolytica which is accompanied by an extensive damage to the respiratory system [5, 6].

2. Pathogen characteristics
All types of bacteria of genus Mannheimia are able of pleomorphism. Usually they look like little gram-negative motionless sticks of ovoid and coccoid shape, with possible bipolar staining due to the capsule [7]. Under the influence of the environment the form and the size of cells may change. Thus, the
cultivation of the pathogen in poor environment gives mostly elongated sticks and threads. In the tissues of pathological material or exudate, bacteria most often have the form of coccobacilli [8].

Mannheimia spp. grows on most non-selective growth media. When 5-10% defibrinated blood or serum of sheep is added to the agar, the culture grows in the form of translucent colonies of 0.5-2 mm in diameter with a small zone of β-hemolysis. The optimal cultivation time is 18-24 hours at 37-38 °C. Some isolates grow on MacConkey agar in the form of small transparent colonies. On broth media M. haemolytica causes a slight uniform turbidity of the medium after 12 hours of cultivation [9].

M. haemolytica is an oxidase- and catalase-positive, motionless microorganism, has the ability to reduce nitrate and exhibits a negative Voges-Proskauer reaction, does not thin the gelatin. It also ferments D-galactose, D-glucose, D-mannitol, D-fructose, sucrose, maltose, arabinose, D-xylene, lactose, D-sorbitol. It does not ferment adonitol and trehalose [10].

The antigenic structure of the microorganism under consideration, is based on phenotypic differences in capsular polysaccharides and implies the presence of 12 serotypes [11, 12, 13]. Data on serotyping of Mannheimia by determining somatic or other antigen is not found in the literature. Moreover, indirect hemagglutination reaction (IHA test) [11], rapid plate agglutination reaction - RPA test [14], rapid indirect hemagglutination reaction - RIHA test [15] can be used for serotyping.

3. Virulence factors
The most famous virulence factors of M. haemolytica are adhesins, fimbriae, capsule, neuraminidase, proteins of the outer membrane, proteinases, lipopolysaccharides and leukotoxins, the complex effect of which leads to the development of a pathological process in a susceptible organism [5, 16, 17, 18].

Adhesins provide the connection of a bacterial cell with the epithelial surface of the respiratory tract, which increases its resistance to physical influences from the susceptible organism [19]. Neuraminidase is an enzyme that has a function concomitant with adhesins, since it causes degradation of the mucous components of the epithelium [20]. Fimbriae are structures on the surface of bacteria that are necessary for colonization of the epithelium of the lower respiratory tract [5, 21]. The capsule is involved in the development of the pathological process at the stage of colonization of the epithelium of the respiratory tract [21], and also contributes to the inhibition of phagocytosis by neutrophils and macrophages [22, 23, 24]. The proteins of the outer membrane participate in the process of reproduction of bacterial cells [25], and also support the viability of the microorganism in environments with a minimum content of iron which is necessary for the reproduction and production of leukotoxin [26, 27, 28]. Proteinase helps to reduce innate and adaptive immunity, facilitating the colonization process [29]. Leukotoxin is a thermostable, oxygen-resistant, water-soluble protein that provides a protective function for a bacterial cell by destroying leukocytes [30, 31]. In addition, this factor contributes to the release of neutrophilic substances, leading to damage to the lung tissue [32]. Lipopolysaccharide is a thermostable endotoxin which provides protective properties of the pathogen. Leukotoxins in combination with lipopolysaccharides form high molecular weight complexes enhancing each other's pathogenic properties, acting in synergy [33, 34, 35].

4. Species susceptibility
The disease is recorded mainly in ruminants: cattle, sheep, goats, yaks, buffaloes, bison, mules, mountain goats, pronghorns, camels, donkeys, llamas, alpacas and zebu. In isolated cases, the pathogen was taken from horses and pigs [36, 37]. In addition, cases of M. haemolytica from rabbits, dogs, cats, a jaguar and a sea turtle have been described [38, 39]. The microorganism is an opportunistic agent for ostriches, parrots, falcons, quails, peacocks, pigeons, turkeys, guinea fowls and ducks [40, 41, 42, 43].

5. Predisposing factors
The development of mannheimiosis requires the presence of predisposing conditions that reduce the natural resistance of animals.

The first factor in the occurrence of the disease is stress. The importance of the stress factor is confirmed by multiple observations, indicating a sharp outbreak of mass cases of the disease after the
change of weather or zoohygienic conditions. The weakening of the immune system can be considered as the cause of increased sensitivity under stress [44, 45, 46].

The second factor is primary viral diseases, which entail a decrease in animal resistance [47, 48, 49]. Viral infections reduce the phagocytic function of pulmonary alveolar macrophages, and this leads to a loss of the macrophages’ ability to perform phagocytic activity and the loss of the ability to produce chemotactic factors by other cells [42]. Primary mycoplasmas and bacterial infections [50, 51, 52].

Additionally, as predisposing factors can be considered: selenium deficiency, exposure to mycotoxins, airway obstruction, as well as parasitic diseases that lead to immunosuppression [53, 54, 55].

6. Pathogenesis
The pathogenesis of manheimiosis is a controversial issue because of the factorial nature of the disease. There is an opinion that this disease does not occur as monoinfection, which explains the difficulty of reproducing an experimental infection [56, 57].

The development of the pathological process is connected with the activation of a pathogen localized on the surface of the upper and lower respiratory tract [58, 59, 60]. Due to the fact that the pathogen produces neuraminidase, secreted sputum is not capable of fully fulfilling its protective function [61]. Endotoxins of M. haemolytica in the infected lobes of the lungs cause extensive intravascular thrombosis of the pulmonary veins, capillaries and lymphatic vessels. These vascular disorders ultimately lead to focal ischemic necrosis of the lung parenchyma tissue with the simultaneous manifestation of fibrinous inflammation [62]. Exposed to a predisposing factor, in a few hours the animal develops inflammatory processes in the lungs resulting in extensive necrosis. This nuance is connected with the active action of leukotoxin and lipopolysaccharides, which contribute to a decrease in the functionality of leukocytes and affect the destruction of macrophages and neutrophils. Thrombosis and bloating associated with the accumulation of fibrin and leukocytes are observed in the interlobular septa of the lungs. Necrosis spreads through interlobular septa to neighboring lobes [63]. Leukotoxin itself does not have a direct effect on epithelial cells; nevertheless, it acts as a catalyst for the pathological process [25]. The severity of the infectious process depends on the rate and degree of bacterial proliferation and the amount of the released leukotoxin [34, 61, 64].

7. Clinicopathologic manifestation of Mannheimiosis
The manifestation of the clinical signs of the disease of any age group of susceptible animals, first of all, should be considered as a result of a stress factor and / or primary infectious disease effect on the protective mechanisms of the organism [57]. The clinical manifestation of the infection in cattle, as a rule, has three phases. The first phase implies the appearance of acute fever with a fluctuation in body temperature of 1-2 ºC from the physiological norm. The second phase is accompanied by a manifestation of respiratory failure due to fibrinous bronchopneumonia, fibrinous pleurisy. The clinical signs of pulmonary insufficiency in an adult livestock develop within 10-14 days after activation of the pathogen, but there are cases when the period of development of clinical signs is reduced to several days. The third phase is terminal, in which septic processes cause the death of the animal. In acute outbreaks of the disease among the adult livestock, the clinical course lasts for 2-3 days, leading to death or chronic form [65]. In young cattle, a fever with an increase in body temperature up to 41 ºC, significant weight loss, cough, rapid breathing, mucous discharge from the nasal passages may be observed [34].

The high mortality among calves is explained by the low immune status in the postnatal period and / or the consequences of the primary disease. In addition, pathogen toxins are more harmful for young animals. Young animals may die even before the development of pulmonary affections [66]. During auscultation, reinforced vesicular and bronchial wet wheezes, which gradually turn into dry ones, are heard. Young animals often show signs of diarrhea. Pulmonary affections are characterized by extensive neutrophil infiltration and fibrin exudation into the alveoli and respiratory tract. The bronchi have an intact wall, with the exception of cases of necrosis and desquamation of epithelial cells. The possibility
of accumulation of leukocytes and fibrin in the bronchi is noted. The alveoli are swollen, containing fibrin and sometimes blood clots [67].

For sheep and goats, the catalyst for the disease is predominantly physical activity or poor living conditions and poor feeding. Sudden mortality among young animals is noted, usually after weaning in the autumn-winter period. In sheep and goats, the disease develops in septic form, though has similar symptoms to the previously described ones. Death in severe cases can occur after 12-24 hours [68, 69]. Sheep and goats have a mastitis form of the infection in which the pathological process most often develops in one side of the mammary gland, proceeded by necrotic processes; all that causes a number of general systemic affections - fever, anorexia, depression, loss of appetite, and immobility [40]. This form of the disease is called - blue udder [70, 71].

During mannheimiosis, petechial hemorrhages of subcutaneous connective tissue, pericarditis, and hemorrhagic damage to the heart ventricles are noted. Damage to the gastrointestinal tract consists of hyperemia of the mucous membranes, petechial or extensive hemorrhagic affections of the abomasum [72].

The septic form of the disease leads to acute hepatosplenomegalgy. The acute form of the disease involves serous, hemorrhagic and / or fibrinous pleurisy, possibly with exudate effusion. The surface of the lungs looks like marble due to the simultaneous necrotic changes and hemorrhages [54, 73]. Pulmonary affections are most often described as lobar fibrinous bronchopneumonia with the manifestation of fibrinous pleurisy. In the inflammatory process, the formation of fibrinous exudate in the alveoli of the lungs becomes the dominant phenomenon. Inflammation is accompanied by interstitial edema. The affection is always bilateral with a crane-ventral direction of development [74]. Large amount of foamy fluid can often be found in trachea and bronchi of animals [75].

Histological examination reveals diffuse capillary congestions, interstitial or alveolar edema in combination with vascular thrombosis of capillaries, small blood vessels and pulmonary lymph vessels. Alveolar necrosis can often be found throughout the affected area with a large number of fibrinous exudate and inflammatory cells inside the alveoli. The pathogen, which is in the phase of active reproduction, is found in the immediate vicinity of the necrotic sections of the lung tissue. Exudate, consisting of fibrin and dead cells, is often observed inside bronchi and bronchioles [76].

8. Laboratory diagnosis
Laboratory diagnosis in Russia is regulated by the “Methodological Instructions for Laboratory Diagnosis of Pasteurellosis of Animals and Birds” No. 22-7 / 82 of 20 August 1992. According to the instructions, the use of data on the epizootic well-being of the enterprise and the region, clinical signs and pathological changes caused by the pathogen, allows to make a presumptive diagnosis. The final diagnosis is made during laboratory research using routine microbiological methods [77].

Samples of the following tissues and organs are taken as pathological material for the post-mortem diagnosis of manheimiosis during autopsy and postmortem examination from the corpses of fallen or forcibly killed animals.

From cattle, the following material is obligatory taken: a heart with ligated blood vessels, part of the spleen, liver, kidneys, lungs on the border of the affected and non-affected tissues, exudates from the chest cavity, lymph nodes - bronchial, mediastinal and retropharyngeal.

From sheep and goats: heart with ligated blood vessels, part of the spleen, liver, kidneys, lungs on the border of affected and non-affected tissues, a mammary gland, lymph nodes - bronchial, mediastinal and retropharyngeal.

Bacteriological examination of pathological and clinical material includes:

- Receiving and sending samples for bacteriological research;
- Production and microscopy of imprint smears;
- Obtaining a suspension of pathological material for carrying out broth accumulation;
- Sowing on nutrient media;
- Isolation of a pure culture of the microorganism;
• Identification and differentiation of selected cultures.

There are kits for ELISA diagnosis, in particular, M. haemolytica ELISA KIT BioX of Belgian production. In addition, there are domestic innovations [78].

Among commercial PCR diagnostic tools, there is a kit for the detection of P. multocida and M. haemolytica by PCR method - LSI VetMAX ™ Triplex P. multocida & M. haemolytica.

9. Mannheimiosis treatment
According to the data by the European Committee on Antimicrobial Susceptibility Testing (Eucast), therapeutic tactics for the disease are based on the use of non-specific etiotropic treatment - antibacterial drugs, as well as preventing the influence of the primary stress factor. Before starting a treatment course, it is necessary to select the most effective antibacterial drugs. According to the scientific data, the most effective antibiotics for the treatment of this disease are drugs of various groups. Thus, antibiotics that have high therapeutic efficacy are: among penicillins is amoxiclav; among fluoroquinolones are danofloxacin, marbofloxacin; among the group of lincosamides is lincomycin; among tetracyclines is oxytetracycline; among aminoglycosides is spectinomycin; among macrofidos are tilmicosin, tylosin; among cephalosporins are cefazolin, cepahelix; among phenicols is florfenicol. As complex medication, it is more advisable to use medicines: intramicine, quinocol, cobactan, neopen, penbex, spectam, enroxil. In a number of countries, the use of antibacterial drugs on animals newly introduced into the herd is used as a preventive measure that allows to lower the sickness and mortality rate [79, 80, 81, 82].

Other researchers have found that there are strains of M. haemolytica circulating in the Russian Federation that are resistant to cefepime and vancomycin. In addition, the studied cultures had intermediate sensitivity to gentamicin, neomycin, clindamycin, clarithromycin, erythromycin, tetracycline, ceftazidine. About 60% of cultures were resistant to meropenem and polymyxin B; 40% of cultures were resistant to amikacin, rifampicin, amoxiclav, lincomycin, pefloxacin and ceftriaxone; 20% of isolates to streptomycin, trimethoprim, ampicillin, carbenicillin, cefoperazone and cefotaxime. Medications such as kanamycin, fosfomycin, imipenem, co-trimoxazole, doxycycline, norfloxacin, ciprofloxacin, enrofloxacin, cefazolin and cefalexin showed high activity against the studied strains. The best antibacterial activity against strains of Mannheimia was shown by moxifloxacin, which inhibits the growth of 100% of cultures [83].

10. Specific prevention
For the development of means for the specific prevention from Mannheimia infection, it is possible to use various components of the bacterial pathogen cell, in particular in the form of: a bacterin-toxoid vaccine, a vaccine made from leukotoxin, a live vaccine and a vaccine made from an extract of the outer membrane proteins. It is proved that the best immune response is achieved by using bacterin-toxoid [84]. At the same time, the mechanisms of immunity formation from vaccination differ in different animal species, for example, sheep have higher antibody titers at injection of M. haemolytica antigen than titers in cattle [85].

11. Conclusion
Mannheimiosis is pasteurellosis-like disease in cattle, sheep and goats which manifests itself in respiratory and septic forms. Mannheimiosis is mainly found in ruminants, while pasteurellosis is found in all species of animals and birds. Moreover, according to published data, Mannheimia infection in other animal species is recorded in sporadic cases. The infection mechanism is initiated by the influence of predisposing factors. These factors include stress (technological, transport, etc.), primary viral or bacterial infections, as well as mycotoxins in fodder, parasitic diseases, etc. which cause a decrease in the immune status of animals. Among the clinical signs that are most typical for mannheimiosis are: fever, dry cough, that gradually turns into moist one, profuse mucous and serous-mucous discharge from the nasal passages, sometimes - signs of catarrhal enteritis, keratoconjunctivitis in lambs. A decrease in
milk production is often found in lactating animals. The pathological autopsy of animals shows: lobular fibrinous bronchopneumonia or croupous pneumonia; interstitial pulmonary edema; serous-fibrinous pleurisy, serous-fibrinous pericarditis, bronchial lymphadenitis, passive hyperemia of the tracheal vessels with multiple hemorrhages. Among adult animals’ diarrhea is not observed, while inflammation of the bronchial lymph nodes and lymph nodes above udder is noted. The final diagnosis can be made by isolation and identification of the culture of M. haemolytica by routine bacteriological methods. The main methods of treating the infections are the treatment with the help of antibacterial drugs according to sensitivity and the use of specific prevention agents - vaccines.

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