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Bovine respiratory syncytial virus infection: clinical manifestations, pathogenesis and molecular epidemiology (review)

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ABSTRACT

Introduction. Bovine respiratory syncytial infection is widespread in all countries of the world, including the Russian Federation. The etiologic agent is *Orthopneumovirus bovis*, it belongs to the family *Pneumoviridae*, genus *Orthopneumovirus*. Cattle are the main reservoir of the virus.

Objective. This literature review aims to summarize and give analysis of the published data on clinical manifestations, pathogenesis and molecular epidemiology of the causative agent of bovine respiratory syncytial infection.

Materials and methods. The study is based on publications from the most authoritative domestic (eLIBRARY.RU) and foreign (Web of Science, Scopus, PubMed) sources, as well as the results of our own studies published in the literature.

Results. Animals of all ages are susceptible to the disease, the infection is most severe in calves under 6 months of age. The incidence of the herd is on average 60–80%. The nature of the infection varies from asymptomatic and mild to severe lower respiratory tract disease, including emphysema, pulmonary edema, interstitial pneumonia and bronchopneumonia, while the mortality rate among calves can reach 20%, and in adult animals the subclinical form is more often recorded. The virus has a powerful immunomodulatory effect. Severe damage to the respiratory tract is mediated mainly by hyperactivity of the immune response, and not by the replication of the virus itself. The virus increases the susceptibility of calves to secondary infections and promotes colonization of the lower respiratory tract by bacteria. Currently, ten genetic subgroups of the virus (I–X) have been identified using phylogenetic analysis of the nucleotide sequences of the G and N genes, between which there is a geographical correlation. In regions such as the Urals, Siberia, and the Republic of Kazakhstan, isolates of the virus of genetic subgroups II and III circulate among cattle.

Conclusion. The review presents current data on the etiology, pathogenesis features and clinical manifestations of bovine respiratory syncytial infection, as well as the genetic diversity of the pathogen in the world, in the Russian Federation and the Republic of Kazakhstan.

Keywords: review, respiratory syncytial infection, BRSV, cattle, pathogenesis, molecular epidemiology

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Респираторно-синцитиальная инфекция крупного рогатого скота: особенности клинического проявления, патогенеза и молекулярной эпизоотологии (обзор)

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РЕЗЮМЕ

Введение. Респираторно-синцитиальная инфекция крупного рогатого скота широко распространена во всех странах мира, в том числе и в Российской Федерации. Этиологический агент – *Orthopneumovirus bovis*, относящийся к семейству *Pneumoviridae*, роду *Orthopneumovirus*. Крупный рогатый скот – основной резервуар вируса.

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Цель исследования. Целью данного обзора литературы являлось обобщение и анализ опубликованных данных об особенностях клинического проявления, патогенеза и молекулярной эпизоотологии возбудителя респираторно-синцитиальной инфекции крупного рогатого скота.

Материалы и методы. Информационной базой для проведения исследования служили публикации из наиболее авторитетных отечественных (eLIBRARY.RU) и иностранных (Web of Science, Scopus, PubMed) источников, а также результаты собственных исследований, опубликованных в литературе.

Результаты. Заболеванию подвержены животные всех возрастов, наиболее тяжело протекает инфекция у телят в возрасте до 6 месяцев. Заболеваемость поголовья составляет в среднем 60–80%. Характер течения инфекции варьирует от бессимптомного и легкого до тяжелого заболевания нижних дыхательных путей, включая эмфизему, отек легкого, интерстициальную пневмонию и бронхопневмонию, при этом уровень смертности среди телят может достигать 20%, а у взрослых животных чаще регистрируют субклиническую форму. Вирус оказывает мощное иммуномодулирующее действие. Тяжелые повреждения дыхательных путей опосредованы в основном гиперактивностью иммунного ответа, а не самой репликацией вируса. Вирус повышает восприимчивость телят к вторичным инфекциям и способствует колонизации нижних дыхательных путей бактериями. В настоящее время с помощью филогенетического анализа нуклеотидных последовательностей генов G и N выявлено десять генетических подгрупп вируса (I–X), между которыми существует географическая корреляция. В таких регионах, как Урал, Сибирь, а также в Республике Казахстан среди крупного рогатого скота циркулируют изоляты вируса генетических подгрупп II и III.

Заключение. В обзоре представлены актуальные данные об этиологии, особенностях патогенеза и клинического проявления респираторно-синцитиальной инфекции крупного рогатого скота, а также генетическом разнообразии возбудителя в мире, Российской Федерации и Республике Казахстан.

Ключевые слова: обзор, респираторно-синцитиальная инфекция, BRSV, крупный рогатый скот, патогенез, молекулярная эпизоотология

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INTRODUCTION

Bovine respiratory syncytial infection (BRSI) is an acute, highly contagious viral disease that primarily affects the lower respiratory tract in cattle. BRSI ranks among the most significant infectious respiratory diseases in bovine populations [1, 2, 3, 4].

According to the current classification, the causative agent of the infection is *Orthopneumovirus bovis* (formerly Bovine respiratory syncytial virus, BRSV) belonging to the *Pneumoviridae* family, genus *Orthopneumovirus* [5]. To maintain consistency with the published literature the virus will be hereinafter referred to by its historical designation (BRSV).

BRSV was first isolated from calves during an outbreak of severe respiratory disease in Switzerland in 1969. Several surveys in the early 1980s and later confirmed that the virus is enzootic in calf populations worldwide. According to L. E. Larsen, the agent has the highest pathogenic potential of all viruses circulating in cattle [6].

BRSV is related to human respiratory syncytial virus (HRSV), and they exhibit similar epidemiological, clinical and pathological manifestations [7].

Cattle are the natural hosts and reservoirs of BRSV, but small ruminants may also contribute to the virus transmission [8]. The infectious virus or antibodies against it were also detected in sheep, goats, alpine chamois, bison, and camelids [9, 10, 11].

BRSI has a wide geographical distribution and is reported in many countries on all continents [12, 13, 14]. The virus spreads via airborne transmission. The seroprevalence varies greatly in different geographical regions and averages 30–70%, but may reach 100% [1, 15].

BRSV has been registered since 1975 in our country [16]. According to the Russian researchers, retrospective studies across 16 regions of the Russian Federation detected seroconversion to the virus in calves of different age groups, indicating its role in respiratory pathology: one month of age (4.0% of cases), 3–4 months of age (37.5%), 4–6 months of age (52.6%) and 7–9 months of age (50.0%) [17]. In Siberian farms, the BRSV seropositivity in animals averages 20–70% [18]. A recent study analyzing biomaterial samples collected during mass outbreaks of acute respiratory disease in 8 regions of the Ural and Siberian Federal Districts (Russia) and the Republic of Kazakhstan found the BRSV genome in 20% of cows and 14.3% of heifers. Additionally, the virus was detected in 3.05% samples from calves under one month old and 6.7% samples from calves aged 1–6 months [19].

The BRSV incidence in cattle ranges from 60 to 80%, with mortality in severe calf cases reaching up to 20% [20]. Infection rates exhibit seasonal patterns, peaking during winter months. The BRSV key characteristic is its capacity to infect hosts despite the presence of virus-neutralizing antibodies, leading to recurrent infections throughout animal lifetime [21].

BRSV affects cattle of all ages and breeds, though the most severe clinical manifestations typically occur in calves aged 1–6 months. In adult cattle, outbreaks primarily develop following either initial introduction of the pathogen into a seronegative herd or during reinfection events. The observed age-related resistance pattern, where adult animals demonstrate greater viral resistance than calves, likely reflects acquired immunity through repeated antigenic exposure. Clinical presentation patterns differ by herd im-

munity status: when BRSV is introduced to immunologically naive herds, cattle of all ages typically display clinical signs; in contrast, in herds with endemic viral circulation, clinical disease is predominantly observed in calves [22].

Risk factors affecting the prevalence of infection include animal age, herd size, animal density per unit area, introduction of new animals, seasonality, high milk production, reduced natural resistance in animals and zootechnical factors [23]. However, severe outbreaks may occur even in herds with optimal housing conditions, suggesting that BRSV can induce disease independently of predisposing environmental factors [24].

The mechanisms enabling BRSV persistence in cattle populations remain incompletely understood. Clinically affected animals are regarded as the primary infection sources, suggesting that recurrent outbreaks most commonly result from the reintroduction of the virus into herds prior to new disease events. However, BRSV can also be isolated from asymptomatic carriers, where it may persist for months, establishing latent infections that could explain outbreaks in relatively isolated calves. The virus can also circulate at minimal levels among seropositive cows, with periodic reactivation [1].

VIRAL GENOME CHARACTERISTICS

Orthopneumovirus bovis is an enveloped virus containing single-stranded negative RNA approximately 15,000 bp in length [1]. Virions may be spherical, but are usually filamentous or pleomorphic in shape, approximately 200 nm in diameter. The viral genome encodes nine structural proteins and two non-structural proteins. The structural proteins include three enveloped glycoproteins (F, G, SH), nucleocapsid proteins (N, P, L), nucleocapsid-associated proteins (M2–1 and M2–2) and matrix protein (M) [25].

The G protein mediates viral binding to host cells, while the F protein facilitates viral entry into cells, systemic spread within the host organism and formation of characteristic syncytia [21].

The F protein is involved in the immune response by stimulating the production of virus-neutralizing antibodies and facilitates the penetration of viral particles into host cells, as well as mediates the fusion of infected cells to form syncytia – multinucleated giant cells. The G protein is mainly involved in receptor binding and adsorption process [12]. The F and G genes play an important role in viral infectivity and are the main targets of the immune system [6, 20]. The F gene is highly conserved, and its nucleotide sequence variation is lower among BRSV isolates compared to the G gene [26]. Due to its high genetic variability, the G gene can be used for the evolutionary analysis of virus strains [7].

The SH protein is a short integral membrane protein. It plays an important role in inhibiting apoptosis during infection, promoting viral replication. This protein is not essential for viral replication, but is involved in evading the host immune response [27].

The nucleoprotein (N) plays an important role in viral transcription and replication, acting as a scaffold for the assembly of the viral ribonucleoprotein complex. It can be expressed on the surface of infected cells early in the viral replication cycle [28].

The phosphoprotein (P) acts as a regulatory factor for viral transcription and replication. The polymerase L is an RNA-dependent RNA polymerase responsible for viral transcription and replication [20].

The M protein is located on the inner surface of the viral envelope and plays a role in virion assembly. Unlike other viral mRNAs, M2 mRNA is translated into two distinct proteins, M2–1 and M2–2, through a ribosome termination-dependent reinitiation mechanism. The M2, M2–1, and M2–2 gene products serve as key regulatory proteins that modulate the BRSV replication cycle. M2–1 incorporates into the ribonucleoprotein complex to facilitate viral mRNA transcription, while M2–2 regulates the transition from transcription to replication [28].

The nonstructural proteins NS1 and NS2 modulate the innate immune response early in the viral replication cycle by interfering with interferon induction/signaling, dendritic cell maturation, and T-lymphocyte activation. Additionally, NS1 and NS2 inhibit apoptosis, thereby prolonging the survival of infected cells and enhancing viral production [28].

Currently, BRSV is classified into four antigenic subgroups (A, B, AB, non-typeable) [1] and ten genetic subgroups [7, 26, 29].

PATHOGENESIS

Orthopneumovirus bovis demonstrates cytopathic effects in cell cultures and induces extensive bronchial epithelial damage *in vivo*. The virus initially infects upper respiratory tract epithelial cells, then rapidly disseminates via cell-to-cell transmission to the lower respiratory tract, where it replicates in bronchioles [30]. Primary cellular targets include bronchial epithelial ciliated cells and alveolar type I pneumocytes [31]. BRSV has also been reported to infect intraepithelial dendritic cells and basal epithelial cells of the conductive airways, using *in vitro* cultures [32]. This broad cellular tropism within the respiratory tract enables efficient viral replication and systemic dissemination.

The direct pathological consequences of lytic viral replication include sloughing of necrotic epithelial cells, resulting in ciliostasis and impaired mucociliary clearance, and accumulation of exudate in the bronchioles and alveoli. The initial influx of polymorphonuclear neutrophils into the airways is rapidly replaced by a predominantly lymphomononuclear infiltration of peribronchiolar tissues and increased microvascular permeability, resulting in submucosal edema. The loss of ciliated epithelium increases the amount and viscosity of mucous secretions. Bronchiolitis, characterized by inflammation, necrosis, and obstruction of the bronchioles, leads to airway narrowing, airflow impairment, and respiratory distress. Lung consolidation occurs due to accumulation of inflammatory cells and fluid in the alveoli and bronchioles, resulting in additional respiratory distress. Interstitial pneumonia, another common pathological manifestation, develops from inflammation and thickening of the pulmonary interstitial tissue. In severe cases, the virus causes bronchiolar obstruction and alveolar damage, severely compromising the calf's respiratory function [25, 30].

The severity and duration of the disease depend primarily on the host immune response rather than on viral replication. Innate immune mechanisms provide the respiratory tract with the first barrier against establishment of productive infection. Subsequently, specific humoral and cellular immunity play a decisive role in eliminating

the infection and mitigating its course [30]. It has been established that severe BRSV disease begins at low viral load or after viral elimination and is associated with a hyperreactive immune response [33]. The detection of hyaline membranes and eosinophils in the caudal lung regions, even in areas without detectable virus, further confirms the role of immune-mediated pathological processes in BRSI pathogenesis [6].

The progression of infection and the immune response profile are primarily shaped by cytokine regulation patterns. BRSV employs multiple mechanisms to inhibit both innate and adaptive immune responses, negatively impacting immunological memory formation. During infection, dendritic cell functionality becomes compromised, resulting in dysregulated adaptive immunity: T-helper 1 (Th1) responses are delayed or suppressed, while Th2 cytokine production is upregulated [25].

The Th1-mediated immune response involves production of type I interferons (IFNs), particularly IFN-*α* and IFN-*β*, that play a critical role in inhibiting viral replication and dissemination. Various defense mechanisms are then activated, including the expression of antiviral proteins, to interfere with viral replication and dissemination. In addition to type I IFNs, innate immune cells secrete proinflammatory cytokines and mediators such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-*α* (TNF-*α*), which promote inflammation and recruitment of immune cells to the site of infection, and mediate the systemic clinical features associated with infection.

Severe infection is associated with modulation of the Th2 immune response with increased expression of Th2-promoting cytokines and elevated concentrations of BRSV-specific IgE antibodies in lymphatic fluid [34]. Pathogenesis features of severe BRSV infection in calves include rapid neutrophil infiltration, excessive mucus production, delayed T cell response, expression of IL-4, IL-5, IL-10, IL-13 and IL-17 cytokines [28, 35, 36].

NS1 and NS2 proteins play a crucial role in immunosuppression by inhibiting the type I IFN response and other immune system components [33]. This leads to reduced antiviral immunity and diminished phagocytic activity in the lungs of infected animals, contributing to the development of bronchopneumonia [4].

Despite these protective mechanisms, cattle are subject to numerous reinfections with BRSV. Subsequent infections are generally less severe but maintain circulation of the virus in the population, facilitating infection of susceptible animals [25].

BRSV induces secondary bacterial infections in the lower respiratory tract, leading to the development of severe pneumonia [37]. The virus enhances the adhesion of bacteria (*Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Trueperella pyogenes*) to the epithelial cells of the respiratory tract [18, 33, 36, 38, 39, 40, 41, 42, 43]. Studying the mechanism of bacterial superinfection caused by *Pasteurella multocida* after BRSV infection, P. E. Sudaryatma et al. found that bacterial adhesion to epithelial cells of the lower respiratory tract of cattle is enhanced by increased expression of the platelet activating factor receptor (PAFR) [42]. Infection of bronchial and lung epithelial cells with BRSV increased adhesion of *Pasteurella multocida* to these cells, but did not affect the enhancement of adhesion to tracheal epithelial cells [41]. The results of the studies confirmed the ability of the virus to preferentially replicate in the lower respiratory tract. McGill J. L. et al. found that coinfection with BRSV and *Mannheimia haemolytica* in calves results in increased expression of IL-17, IL-21 and IL-22 in the lungs and peripheral blood [36].

CLINICAL SIGNS

The incubation period for BRSI in cattle is 2 to 5 days. In experimental studies, the onset and duration of clinical disease varied significantly, but symptoms were usually present between day 2 and 8 after infection [44]. Virus replication is detected at day 2–3 after infection and continues until day 7–10 after infection. Under natural conditions, the disease can manifest in various forms – ranging from subclinical cases with minimal clinical signs to severe forms featuring pronounced respiratory lesions, dyspnea, and even animal death.

The infection may be asymptomatic, limited to the upper respiratory tract, or affect both the upper and lower respiratory tract. In mild cases involving upper respiratory tract lesions, clinical signs include cough, serous-mucous nasal discharge (rhinitis) and conjunctivitis, mildly to moderately increased respiratory rate, fever, anorexia, and lethargy. In moderate cases, affected calves exhibit a respiratory rate exceeding 80 breaths per minute, tachypnea, harsh lung sounds across most of the pulmonary fields, and a pronounced cough.

Severe infection is characterized by high fever, profound depression and marked dyspnea. Affected animals may develop acute respiratory failure accompanied by grunting expiration, open-mouth breathing with protruding tongue, neck extension, head lowering, and salivary discharge. Pulmonary emphysema and edema are consistently observed in these cases, with occasional development of subcutaneous emphysema [6, 20, 34, 45].

Pathological changes are confined to the lungs. At necropsy, characteristic findings include interstitial pneumonia with cranioventral lung consolidation. The bronchial tree contains abundant mucopurulent exudate. Caudodorsal pulmonary regions frequently exhibit overdistension due to interlobular, lobular, and subpleural emphysema. The lungs appear grossly enlarged, with notable tissue friability. Tracheobronchial and mediastinal lymph nodes often show enlargement, edema, and occasional hemorrhage. In cases of bacterial superinfection, the parenchyma demonstrates increased edema and consolidation, with potential development of fibrinous or suppurative bronchopneumonia [6, 20].

BRSV MOLECULAR EPIZOOTOLOGY

Orthopneumovirus bovis, as most RNA viruses, exhibits significant genomic heterogeneity and low replication fidelity, facilitating the development of diverse viral subpopulations within a single host [1, 46].

Molecular genetic studies of BRSI outbreaks have demonstrated the circulation of identical viral strains among animals within single herds. During recurrent outbreaks, genomic divergence between viral strains can reach 11%, with emerging genetic variants becoming dominant [47].

Molecular epizootiological studies of BRSV have revealed significant geographic correlation between viral variants and emergence of new genetic lineages [46].

Currently, ten genetic subgroups of BRSV have been identified through phylogenetic analysis of G and N gene nucleotide sequences [14]. Subgroup I comprises strains isolated in Europe prior to 1980 [48]. This group strains were last recorded in cattle in Belgium in 1997.

Subgroup II strains circulate predominantly in Denmark, Sweden, Norway, and Japan [7, 14, 49]. Subgroup III incorporates strains originating from the USA, Italy, China, and Turkey [14, 46, 50]. Chang Y. et al. confirm the dominance of these strains in China [12]. Subgroup IV contains two distinct subclasses: IA and IB. Subgroup IV IA includes strains isolated in England in 1971 and 1976, and IB includes those isolated in the Netherlands in the 1980s [7]. Subgroups V and VI were identified in France and Belgium [7, 49], while subgroups VII and VIII were detected in Croatia (2018) and Italy [29, 46]. Recent surveillance has revealed two additional subgroups: IX (identified in Brazil [51] and Japan) and X (found in Japan) [26].

Until recently, there was no information on the genotypes of virus strains circulating in Russia. Glotov A. G. et al. were the first in our country to sequence the complete nucleotide sequence of the glycoprotein G gene of five virus isolates circulating among high-yield dairy cattle in Siberia and two vaccine strains. Based on phylogenetic analysis, it was established that the population of Siberian BRSV isolates is represented by two subgroups and one independent clade. Thus, NSO1 and NSO2 isolates recovered from calves in the Novosibirsk Oblast, were assigned to subgroup II of BRSV strains. The nucleotide similarity of these isolates with the Croatian strain was 99.09%, with the Swedish strain – 98.44%, with the Italian strain – 98.31%, and nucleotide mutations were found in the G gene sequence relative to other strains of subgroup II, leading to a number of unique amino acid substitutions. Alt3 and Alt4 isolates recovered from animals in the Altai Krai, were assigned to subgroup III. The nucleotide similarity of the Altai isolates with the Chinese strains was 98.73–97.34%. Unique amino acid substitutions were found in the sequences of isolate Alt3. A separate clade was formed by isolate K18, recovered from diseased heifers imported from Canada during an outbreak of mass respiratory disease after mixing them with local cattle, as well as the attenuated strain 375, included in the composition of two vaccines. The complete nucleotide sequences of the G glycoprotein gene obtained from BRSV isolates were deposited in the GenBank database under accession numbers OR426499–OR426505 [19].

CONCLUSION

The analysis of the presented data allows us to conclude that BRSI is widespread in many countries worldwide, including the Russian Federation. The infection causes significant economic losses in dairy and beef cattle production due to morbidity, mortality, and treatment and prevention costs. Cattle serve as the main reservoir of BRSI. BRSV replication is restricted exclusively to the respiratory tract. The virus increases susceptibility of calves to secondary infections and facilitates bacterial colonization of the lower respiratory tract, resulting in severe pathological manifestations that progress to bronchopneumonia or fibrinous pneumonia. A characteristic feature of BRSV is its capacity to induce immunopathology. The pathogenic effect of the virus stems from an imbalanced immune response skewed toward Th2-dependent processes. The pathogen exerts potent immunosuppressive effects, which contribute to disease complications and recurrent infections.

The relatively rapid evolutionary rate leads to significant genetic and antigenic heterogeneity among field virus strains. The identification and characterization of genetically distinct BRSV subgroups circulating within regional farms, along with comprehensive studies of their antigenic properties, are crucial for implementing effective infection control measures. This includes developing precise diagnostic methods and effective vaccines to reduce economic impacts.

Given BRSV's pronounced genetic variability, investigations into its molecular epizootology are of particular importance. Continued research on the genetic diversity of circulating BRSV strains and their pathogenic potential within our country remains essential for formulating effective immunoprophylaxis strategies against this infection.

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