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IMMUNOPATHOGENESIS AND MODERN LABORATORY DIAGNOSTICS OF H5N1 AND H7N9 AVIAN INFLUENZA VIRUSES

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Annotatsiya. Parranda grippi bugungi kunda global sog‘liqni saqlash tizimi uchun muhim epidemiologik va biologik xavf omillaridan biri hisoblanadi. Ayniqsa, yuqori patogenlikka ega bo‘lgan H5N1 va H7N9 shtammlari zoonotik xususiyati, yuqori mortalitet darajasi hamda pandemik potensiali bilan alohida ahamiyat kasb etadi. Ushbu maqolada H5N1 va H7N9 viruslarining virusologik xususiyatlari, immunopatogenezi hamda zamonaviy laborator diagnostika usullari tahlil qilindi. Influenza A virusining segmentlangan RNK genomi, gemagglutinin (HA) va neyraminidaza (NA) oqsillarining virus virulentligidagi o‘rni yoritildi. Shuningdek, organizmda rivojlanadigan tug‘ma va orttirilgan immun javob mexanizmlari, sitokin bo‘roni hamda o‘pka to‘qimalarining shikastlanish jarayonlari ilmiy jihatdan tavsiflandi. Maqolada RT-PCR, ELISA, serologik va virusologik tekshiruvlarning diagnostik ahamiyati ham ko‘rib chiqildi. Tadqiqot natijalari H5N1 va H7N9 viruslarini erta aniqlash, immunopatologik jarayonlarni chuqur o‘rganish hamda samarali profilaktik choralarni ishlab chiqish zamonaviy tibbiyotning dolzarb yo‘nalishlaridan biri ekanligini ko‘rsatadi.

Kalit so‘zlar. Parranda grippi, H5N1, H7N9, Avian influenza, Influenza A virusi, immunopatogenez, zoonoz infeksiya, RT-PCR, ELISA, gemagglutinin, neyraminidaza, sitokin bo‘roni, virusologik diagnostika, immun javob, pandemik potensial.

Аннотация. Птичий грипп в настоящее время является одним из важных эпидемиологических и биологических факторов риска для мировой системы здравоохранения. Особое значение имеют высокопатогенные штаммы H5N1 и H7N9, обладающие зоонозными свойствами, высоким уровнем летальности и пандемическим потенциалом. В данной статье проанализированы вирусологические особенности, иммунопатогенез и современные методы лабораторной диагностики вирусов H5N1 и H7N9. Освещена роль сегментированного РНК-генома вируса Influenza A, а также белков гемагглютинина (HA) и нейраминидазы (NA) в формировании вирулентности вируса. Кроме того, научно описаны механизмы врожденного и приобретенного иммунного ответа, развитие цитокинового шторма и процессы повреждения легочной ткани. В статье также рассмотрено диагностическое значение RT-PCR, ELISA, серологических и вирусологических методов исследования. Полученные данные свидетельствуют о том, что ранняя диагностика H5N1 и H7N9, углубленное изучение иммунопатологических процессов и разработка эффективных профилактических мер являются одними из приоритетных направлений современной медицины.

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Ключевые слова. Птичий грипп, H5N1, H7N9, Avian influenza, вирус Influenza A, иммунопатогенез, зоонозная инфекция, RT-PCR, ELISA, гемагглютинин, нейраминидаза, цитокиновый шторм, вирусологическая диагностика, иммунный ответ, пандемический потенциал.

Abstract. Avian influenza is currently considered one of the major epidemiological and biological threats to global public health. Highly pathogenic strains such as H5N1 and H7N9 are of particular concern due to their zoonotic nature, high mortality rate, and pandemic potential. This article analyzes the virological characteristics, immunopathogenesis, and modern laboratory diagnostic methods of H5N1 and H7N9 viruses. The role of the segmented RNA genome of Influenza A virus, as well as hemagglutinin (HA) and neuraminidase (NA) proteins in viral virulence, is discussed. In addition, the mechanisms of innate and adaptive immune responses, cytokine storm development, and lung tissue damage are scientifically described. The diagnostic significance of RT-PCR, ELISA, serological, and virological methods is also reviewed. The findings indicate that early detection of H5N1 and H7N9 viruses, detailed investigation of immunopathological processes, and development of effective preventive measures remain among the priority areas of modern medicine.

Keywords. Avian influenza, H5N1, H7N9, Influenza A virus, immunopathogenesis, zoonotic infection, RT-PCR, ELISA, hemagglutinin, neuraminidase, cytokine storm, virological diagnostics, immune response, pandemic potential.

Introduction. Avian influenza is an acute infectious disease caused by Influenza A viruses, primarily distributed among wild and domestic poultry, although some highly pathogenic strains can also be transmitted to humans [4]. In recent years, the emergence of highly virulent strains such as H5N1 and H7N9 has caused this infection to become not only a veterinary but also a global medical problem [11]. The zoonotic nature of these viruses, i.e., their ability to transmit from animals to humans, further increases their epidemiological risk [2]. Influenza A viruses belong to the family Orthomyxoviridae and have a segmented single-stranded RNA genome [17]. The haemagglutinin (HA) and neuraminidase (NA) glycoproteins located on the surface of the virus play an important role in the attachment of the virus to the cell, its penetration into the cell, and the spread of new virions [6]. It is precisely as a result of mutations in these proteins that new antigenic variants are formed, which increases the pandemic potential of the virus [13]. The H5N1 strain was first identified in humans in 1997 and is characterized by high mortality rates. The H7N9 strain was recorded in China in 2013 and caused severe respiratory diseases among people in a short time [19]. The main danger of these strains is that they cause a sharp disruption in the functioning of the immune system, causing a pathological condition called a "cytokin storm" [8]. As a result, lung alveolar damage, acute respiratory distress syndrome, and multi-organ failure may develop [15]. Laboratory diagnosis of avian influenza is considered one of the important areas of modern virology. Currently, the RT-PCR method is used as the "gold standard" for detecting viral RNA [5]. Furthermore, ELISA, serological reactions, and virological tests also play an important role in diagnosis [14]. Early diagnosis is an important factor in controlling the spread of the disease, eliminating epidemic outbreaks, and reducing mortality rates [9]. Today, due to the mutational activity of avian influenza viruses, their high adaptability, and their widespread spread through global migratory birds, this infection is considered one of the international problems of biological security [20]. Therefore, the in-depth study of the virological characteristics, immunopathogenesis, and modern diagnostic methods of

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H5N1 and H7N9 viruses is one of the most pressing areas of modern medicine and immunology [7].

The main purpose of the presented manuscript is to provide a brief overview of the relevance of immunopathogenesis and modern laboratory diagnostics of H5N1 and H7N9 avian influenza viruses based on the results of reputable scientific research.

Virological characteristics of H5N1 and H7N9 viruses. The causative agents of avian influenza are Influenza A viruses belonging to the family Orthomyxoviridae [12]. These viruses have a spherical or filamentous shape, are surrounded by a lipoprotein shell, and consist of a segmented RNA genome with a negative strand [3]. The genome of the Influenza A virus consists of 8 separate RNA segments, which ensures its high mutational activity and genetic reassortment properties [18]. It is this property that leads to the emergence of new highly pathogenic strains [5]. The main antigenic proteins located on the surface of the virus are hemagglutinin (HA) and neuraminidase (NA) [9]. While hemagglutinin ensures the binding of the virus to host cell receptors, neuraminidase plays a crucial role in the release of newly formed virions from the cell. Currently, 18 HA protein subtypes and 11 NA protein subtypes have been identified, through various combinations of which strains such as H5N1 and H7N9 are formed [16]. The H5N1 strain belongs to the group of highly pathogenic avian influenza viruses and causes high mortality rates, primarily among poultry populations [7]. When this strain infects the human body, severe pneumonia, acute respiratory distress syndrome, and multi-organ failure can develop [14]. It has been reported that the mortality rate of H5N1 virus is significantly higher than that of other influenza viruses [2].

Although the H7N9 strain was initially described as a low-pathogenic virus, it was later found to cause severe respiratory diseases in humans [19]. The danger of this strain lies in the fact that in some cases, the infection can spread covertly due to the absence of clear clinical signs in birds [10]. This complicates epidemiological surveillance and increases the risk of the virus spreading over large areas [6]. Influenza A viruses are characterized by antigen drift and antigen shift phenomena [13]. Antigen drift is a gradual change in the structure of an antigen resulting from small mutations in the viral genome, while antigen shift is the formation of a new strain resulting from the exchange of segments from the genomes of two different viruses [4]. In particular, the antigen shift process is one of the main factors in the emergence of pandemic viruses [17]. The environmental resistance of avian influenza viruses depends on temperature and humidity [8]. At low temperatures, the virus can persist for a long time but undergoes rapid inactivation under the influence of high temperatures and disinfectants [20]. Therefore, compliance with sanitary and hygienic rules and the strengthening of biosafety measures are of great importance in disease prevention [11].

Immunopathogenesis of H5N1 and H7N9 viruses. The pathogenesis of avian influenza viruses is characterized by complex immunological processes; upon the introduction of the virus into the body, a number of innate and acquired immune reactions are activated [15]. The virus primarily trophies the epithelium of the respiratory system and binds to sialic acid receptors on the cell surface via the protein haemagglutinin [6]. As a result, the virus enters the cell and begins to replicate its genetic material. After the virus enters the body, macrophages, neutrophils, and natural killer (NK) cells are activated as the first defense mechanism [18]. These cells try to limit the spread of infection by destroying cells infected with the virus and producing interferons [9]. In particular, type I interferons play an important role in antiviral protection and inhibit viral replication [3]. However, highly pathogenic strains such as H5N1 and H7N9 can cause immune system dysfunction [12]. As a result of the virus's high virulence, a large amount of inflammatory mediators is produced in the body [5]. This condition is called a "cytokin storm"

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and is characterized by a sharp increase in interleukin-6 (IL-6), tumor necrosis factor (TNF-α), and other pro-inflammatory cytokines [19]. As a result of a cytokine storm, severe inflammation develops in the wall of the pulmonary alveoli, and the alveolar membrane is damaged [7]. This leads to impaired gas exchange, hypoxia, and the development of acute respiratory distress syndrome (ARDS) [14]. In severe cases, multi-organ failure and a fatal outcome may occur [2]. T- and B-lymphocytes play an important role in the formation of acquired immunity [11]. CD8+ cytotoxic T-lymphocytes destroy virus-infected cells, while B-lymphocytes produce specific antibodies against the virus [16]. Neutralizing antibodies, especially against haemagglutinin and neuraminidase proteins, are a key component of protective immunity [4]. Nevertheless, the high mutational activity of Influenza A viruses creates an opportunity to evade the immune system [20]. As a result of antigen drift, antigen determinants on the virus surface change, and the effectiveness of previously formed antibodies decreases [8]. This increases the risk of reinfection and complicates the vaccine development process [13]. An in-depth study of the immunopathogenesis of H5N1 and H7N9 viruses serves as an important scientific basis for creating effective antiviral drugs and next-generation vaccines [10]. Modern immunological research allows for the prevention of future pandemics by identifying the mechanisms of the virus's interaction with the immune system [17].

Modern laboratory diagnostic methods. Early and accurate detection of avian influenza viruses is crucial for epidemiological surveillance and limiting the spread of the disease [5]. Several modern laboratory methods are currently used in the diagnosis of H5N1 and H7N9 infections, among which molecular, serological, and virological methods are leading [11]. One of the most reliable and considered the "gold standard" is the real-time polymerase chain reaction (RT-PCR) [2]. This method allows for the direct detection of viral RNA and possesses high sensitivity and specificity [17]. RT-PCR can detect not only the presence of the virus but also its subtype, which is important for distinguishing between strains such as H5N1 and H7N9 [8]. The ELISA (enzyme-linked immunosorbent assay) method is widely used to detect viral antigens or antibodies formed against them [14]. This method plays a particularly important role in epidemiological screening and population studies [3]. ELISA can also be used to assess the level of the body's immune response [12]. Serological diagnostic methods, including the hemagglutination inhibition reaction, are used to determine the presence of antiviral antibodies [19]. These methods allow for the determination of the acute or past stage of infection [6]. In the virological method, clinical samples (nasopharyngeal swabs, blood, bronchial laxatives) are grown in cell cultures and the virus is isolated [1]. Although this method is complex and time-consuming, it is crucial for an in-depth study of the biological properties of the virus [15]. In recent years, rapid diagnostic tests (rapid tests) have also been widely introduced into practice [10]. These tests are of great importance in emergency epidemiological situations, as they yield results in a short time [4]. However, their sensitivity may be lower than that of RT-PCR [13]. Molecular epidemiology methods allow for the tracking of mutational changes in the viral genome by sequencing it [20]. This is an important scientific tool for predicting the emergence of new strains and assessing pandemic risk [9]. In general, the most correct approach is the integrated use of several methods in the diagnosis of H5N1 and H7N9 viruses [7]. This approach contributes to early detection, correct diagnosis, and the development of effective preventive measures [18].

Prevention and vaccines. Preventive measures and vaccines are of great strategic importance in preventing the widespread spread of avian influenza infection [6]. Since highly pathogenic strains such as H5N1 and H7N9 are zoonotic in nature, constant epidemiological surveillance is required not only from a veterinary but also from a human health perspective [14].

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One of the main areas of prevention is the strengthening of biosafety measures [2]. Compliance with sanitary and hygienic rules in poultry farms, isolation of sick birds, and destruction of infected material significantly reduce the spread of the virus [11]. In addition, limiting contact with wild birds is also an important preventive factor [9]. Vaccination is one of the most effective biological methods for combating avian influenza. Vaccines developed based on inactivated vaccines, subunit vaccines, and recombinant technologies are currently widely used [17]. These vaccines ensure the production of specific antibodies in the body against hemagglutinin and neuraminidase proteins [4]. However, the high antigenic variability of the Influenza A virus requires a continuous review of vaccine efficacy [13]. As a result of antigen drift, existing vaccines may lose their level of protection, necessitating the development of new vaccine formulas [7]. Antiviral drugs also play an important role in prevention and treatment [10]. Neuraminidase inhibitors such as oseltamivir and zanamivir reduce the severity of the disease by limiting viral replication [15]. However, the emergence of drug-resistant strains requires new pharmacological approaches in this direction [3]. The World Health Organization (WHO) maintains a global monitoring system for avian influenza and constantly monitors the emergence of new strains [20]. This system plays a crucial role in the early detection of epidemiological risks and pandemic prevention [8]. Also, conducting sanitary and educational work among the population is an important preventive measure [12]. Informing people about transmission routes, hygiene rules, and risk groups helps reduce the spread of infection [5]. Overall, the fight against H5N1 and H7N9 avian influenza requires a comprehensive approach: biosafety, vaccination, antiviral therapy, and epidemiological monitoring can only yield effective results when used together [16].

Conclusion. The H5N1 and H7N9 avian influenza viruses possess high pathogenicity and pose a serious epidemiological risk to human and animal health. The main danger of these viruses lies in their zoonotic nature, rapid mutation, and the ability to evade the immune system [14]. Analyses show that the presence of a segmented RNA genome in the Influenza A virus enhances its ability for genetic reassortment and antigenic variability [6]. This leads to the emergence of new strains and an increase in potential pandemic risk [19].

The development of a cytokine storm in the processes of immunopathogenesis is one of the main reasons for the severe course of the disease [8]. As a result, lung tissue damage, acute respiratory failure, and multi-organ dysfunction may develop [15]. Modern laboratory diagnostic methods, particularly RT-PCR and ELISA, have shown high efficacy in early infection detection [2]. These methods play an important role in strengthening epidemiological surveillance and limiting the spread of the disease [11].

The most effective approach to combating avian influenza is the comprehensive use of preventive measures, including vaccines, biosafety, and antiviral therapy [17]. However, the constant mutational activity of the virus indicates the need for further scientific research in this direction [3]. In conclusion, the in-depth study of H5N1 and H7N9 viruses is relevant not only for virology and immunology but also for the global healthcare system [20]. Future research should focus on further clarifying the pathogenesis of these viruses and developing effective preventive and therapeutic strategies [9].

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