UDC 616.24-002.17
DOI 10.59598/ME-2305-6053-2025-117-4-8-17

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HYPERSENSITIVE PNEUMONITIS: ETIOPATHOGENETIC MECHANISMS OF DISEASE PROGRESSION

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Hypersensitivity pneumonitis is a chronic immune-mediated inflammatory lung disease that develops as a result of repeated exposure to inhaled organic or inorganic antigens. This article presents an analysis of current data on etiological factors, pathogenetic mechanisms, and regional features of disease distribution. The key elements of immunopathogenesis are discussed, including the role of T-cell-mediated immune responses, cytokine regulation, and fibrogenesis. The significance of genetic factors, such as HLA polymorphisms and telomere shortening, which determine individual susceptibility and disease severity, is highlighted. Particular attention is given to the study of potential biomarkers reflecting the activity of inflammation and fibrotic remodeling. The article emphasizes the challenges of late diagnosis and the difficulties in identifying causative antigens. Local factors, including climatic and occupational exposures, influence the risk of sensitization and disease development. A comprehensive understanding of the etiology, pathogenesis, and molecular mechanisms of hypersensitivity pneumonitis contributes to improving approaches for early detection, differential diagnosis, and prognostic assessment.

In addition, the review summarizes the results of recent studies demonstrating the overlap between fibrotic hypersensitivity pneumonitis and idiopathic pulmonary fibrosis, particularly in molecular and histopathological patterns. These findings underline the need for timely recognition of fibrotic transformation and the integration of molecular biomarkers into clinical practice. Given the lack of large-scale national studies, further research focusing on local environmental and occupational factors in Kazakhstan is crucial for clarifying regional patterns of antigen exposure and disease progression.

Key words: hypersensitivity pneumonitis; pathogenesis, etiology; pulmonary fibrosis; biomarkers; genetic predisposition; immune mechanisms

Hypersensitivity pneumonitis (HP) is an inflammatory and/or fibrotic disease affecting the lung parenchyma and small airways. It usually develops as an immune-mediated reaction triggered by an identifiable or occult inhaled antigen in susceptible individuals [1, 2, 3, 4].

HP was previously referred to as «extrinsic allergic alveolitis» and was classified as acute, subacute, or chronic. However, in clinical practice, it proved difficult to distinguish between these stages, and the subdivision was largely arbitrary. At present, the presence of fibrosis is recognized as the key prognostic factor, forming the basis for the current classification of the disease into fibrotic (mixed or predominantly fibrotic) and non-fibrotic (inflammatory) types. Naturally, some patients may exhibit overlapping features; in such cases, categorization is determined by the predominant pattern. Although the development of HP is associated with exposure to an inhaled antigen, the causative agent may remain unidentified even after thorough evaluation in patients with characteristic clinical and radiological findings. Some experts have used the term "cryptogenic" or "HP of undetermined cause" to describe such cases [4].

In recent years, conducted studies have revealed significant gaps in our understanding of the epidemiology, pathogenesis, optimal diagnostic approach, classification, treatment, and follow-up of HP. Numerous questions remain regarding the identification, duration, quantity, frequency, and intensity of exposure to the causative antigen and its source, which lead to the development of the disease, as well as the factors predisposing individuals to its occurrence. As a result, there is substantial variability in clinical practice across different countries and regions [4].

The prevalence of HP varies depending on climatic, occupational, and environmental conditions. According to population-based studies, the incidence rate ranges from 0.13 to 1.94 cases per 100,000 population, while the prevalence varies from 0.45 to 2.71 per 100,000, increasing with age up to 11.2 cases among patients older than 65

years [5]. In South Korea, the annual incidence was reported to range from 1.14 per 100,000 in 2010 to 2.16 per 100,000 in 2012 [6]. According to data from the Danish National Patient Registry, the incidence was 1.16 per 100,000, with a predominance of males (57%) [7]. An epidemiological study based on insurance claims data in the United States estimated the prevalence of HP to be 1.6-2.7 per 100,000, and the incidence to be 1.3–1.9 per 100,000 [8]. In Japan, the corresponding rates for fibrotic HP were 6.3 and 2.5 per 100,000, and for non-fibrotic HP – 3.6 and 2.0 per 100,000, respectively [9]. The proportion of HP among interstitial lung diseases (ILDs) varies markedly across regions, ranging from 1.5% to 47.3% [4, 10, 11, 12]. According to recent data, the relative frequency of HP is higher in Asia, particularly in India (14.4 – 47%) and Pakistan (12.3%), than in most North American (2%) and European countries (2-3%) [7, 13, 14, 15]. According to a meta-analysis published in 2024, the highest prevalence of HP was observed among printers (57.14%), followed by tobacco industry workers (26.32%) and water-related occupations (24.10%) [16].

In a study by F. Morell et al., the disease was reported among bird breeders at a rate of 4.9 cases per 100,000 individuals over a 10-year period, or 54, 6 cases per 100,000 bird breeders [17].

The prevalence of HP is highest among older adults (≥65 years), with the diagnosis most commonly established in the fifth or sixth decade of life [4]. However, the disease also occurs relatively frequently in young adults and children [18]. HP is less common among current or former smokers [19]. A possible explanation is related to the immunosuppressive effects of nicotine, which reduce the activation of macrophages and T-lymphocytes. A particularly important issue at present is the high frequency of pulmonary fibrosis progression in HP [20, 21], which, according to some reports, may reach up to 86.8% [22]. An increase in mortality associated with this condition has also been observed in recent years, with a 7-year survival rate of 40.8% [23, 24]. These findings further emphasize the importance of early diagnosis and identification of antigen exposure, as they are crucial for improving clinical outcomes.

To date, more than 200 antigens capable of causing HP have been identified, and their list continues to expand [5, 25, 26]. The most extensively studied antigens are avian proteins. The disease develops upon contact with parrots, pigeons, canaries, and is also frequently associated with exposure to domestic birds such as chickens, geese, ducks, turkeys, and others. The highest risk arises from intense exposure, such as cleaning bird cages or staying in enclosed spaces where birds are kept (for example, pigeon lofts). Antigens can persist in the environment for several months after bird removal, maintaining the risk of disease. Additional sources of sensitization may include feather-containing items (such as pillows or bedding), which are capable of inducing both acute and chronic forms of HP [17, 25, 26, 27].

The role of fungi and thermophilic bacteria in both domestic and occupational environments is also significant [4, 17, 19, 28]. Fungi are ubiquitous and represent the second most common cause of HP [26]. *Trichosporon asahii* is the most frequent pathogen of summer-type HP in Japan, where it has been detected in homes with high humidity, wood decay, or straw mats (tatami). The seasonal increase in spore release during the summer months explains the term «summer-type HP» [29]. In Europe and North America, *Aspergillus* and *Fusarium* are more frequently identified, while *Penicillium*, *Cladosporium*, *Cryptococcus*, and other species are less common. These fungi are typically associated with contaminated indoor environments and household appliances such as humidifiers, air conditioners, and ventilation systems [26].

A classic example is «farmer's lung», which develops after inhalation of spores of fungi and actinomycetes from moldy hay, silage, grain, or infected crops (such as onions, potatoes, or corn).

The most common antigens are *Wallemia sebi*, *Aspergillus, Penicillium*, *Fusarium*, and *Alternaria alternata* [25, 26, 27]. Food production is also a significant risk factor for HP. In Europe, cases have been reported among workers exposed to *Aspergillus*, *Penicillium*, *Rhizopus*, *Mucor*, and *Cladosporium* during sausage manufacturing [30]. Additional sources include cork factories (suberosis), mushroom farms, and sawmills, where precipitating antigens have been associated with *Penicillium, Cladosporium, Scopulariopsis*, and *Alternaria alternata* [26].

Recent findings indicate unexpected antigen sources, including wind musical instruments. Fungi such as *Fusarium*, *Paecilomyces*, *Exophiala*, and other rare species have been isolated from bagpipes, saxophones, and bassoons [31].

Even leisure activities can serve as a source of antigens causing HP. For example, nontuberculous mycobacteria (NTM) have been detected in patients who frequently use indoor hot tubs or outdoor swimming pools. A series of cases described in the medical literature, known as «hot-tub lung», has been associated with the inhalation of *Mycobacterium avium* [2, 32, 33].

Modern industrial processes have also created new risks, including the use of isocyanates in polyurethane resins, synthetic adhesives, and paints, as well as exposure to metalworking fluids and the emergence of novel sources such as 3D printers and dental methyl acrylates [5, 17, 25, 34].

Mycobacteria isolated from metalworking fluids used in the automotive and aerospace industries are considered significant antigens capable of inducing HP. The most frequently identified species is Mycobacterium immunogenum, which is associated with a specific form of the disease known as «machine operator's lung» [26, 31].

The relationship between exposure-specific factors (such as concentration, duration, frequency of exposure, particle size, and solubility) and the clinical course of HP is frequently observed but not clearly defined [19]. According to numerous studies, continuous exposure to the offending antigen and/or failure to identify it are associated with a poor prognosis [2, 3, 5, 19, 28, 35].

Notably, various authors have reported that the causative antigen remains unidentified in 30-50% of cases [5]. The collection of medical history requires a thorough assessment of occupational and domestic conditions, seasonal factors, and the duration of antigen exposure. When a specific antigen is identified, further testing for specific IgG antibodies may not be necessary [5]. At present, there is no standardization for measuring serum IgG antibodies to potential antigens associated with the development of HP.The methods currently used for IgG detection differ in sensitivity and specificity, which complicates the interpretation of results [36]. Undoubtedly, genetic predisposition plays an important role in the development of HP.

Most studies have focused on polymorphisms in major histocompatibility complex (MHC) class II molecules – HLA-DR and HLA-DQ – which participate in antigen presentation by antigen-presenting cells (APCs) and are recognized by the corresponding T-cell receptor (TCR) on the surface of CD4□ T lymphocytes. Recently, it has been discovered that interactions involving polymorphisms in SFTPA1 and/or SFTPA2 increase the risk of developing HP, whereas their combination with hydrophobic surfactant proteins (SFTPB and SFTPC) appears to reduce disease susceptibility [19]. In patients with fibrotic HP, a promoter polymorphism in MUC5B has been identified more frequently and is associated with reduced survival [19, 37]. Moreover, approximately 10% of patients with chronic HP carry mutations in genes regulating telomere length, which is associated with increased mortality in the absence of lung transplantation [38].

The immunopathogenetic mechanisms of HP involve several sequential stages. The first stage is sensitization to inhaled antigens, in which T and B lymphocytes play a key role. Upon repeated exposure, a pronounced T-cell response develops in susceptible individuals, characterized by the predominance of Th1 cells producing interferon-gamma (IFN-γ) and tumor necrosis factor (TNF), leading to macrophage activation and the development of granulomatous inflammation [2, 19]. Certain factors, such as continued exposure to unidentified antigens, cigarette smoking, and genetic predisposition that enhances autoantibody formation [17, 39], may contribute to chronic disease progression. In fibrotic HP (fHP), alterations in T-lymphocyte subpopulations are observed: the number of immunoregulatory and antifibrotic γδ T-cells decreases, the proportion of CD4□ cells increases, and there is a shift from the Th1 to the Th2 phenotype [19]. The latter produce interleukin-4 (IL-4) and, predominantly, interleukin-13 (IL-13), which stimulate the fibrotic response through activation of the TGF-β1 signaling pathway and enhanced fibroblast proliferation [2, 19]. Fibroblasts migrate to the site of injury and transform into myofibroblasts [40]. Macrophages and lymphocytes further release profibrotic mediators that sustain this process [37]. Thus, a direct relationship develops in which excessive extracellular matrix (ECM) deposition further activates and stimulates fibroblasts, initiating a self-perpetuating fibrotic process [2, 37, 41].

Sadeleer et al. demonstrated that in fHP, both disease-specific mechanisms and pathways determining fibrosis severity are activated [42].

At early stages, processes of extracellular matrix remodeling and T-cell activation are observed, indicating their possible leading role in fibrosis development, rather than being merely a secondary consequence of injury [40]. As the disease progresses, there is increased B-cell activity and the appearance of honeycombing, which is associated with a more severe clinical course. These findings confirm that fibrotic HP results from a combination of inflammatory and cellular immune mechanisms and demonstrates pathophysiological similarities with idiopathic pulmonary fibrosis (IPF). Furusawa et al. identified more than 400 shared genes involved in cellular pathways, ECM structure, and collagen synthesis [43]. This indicates that the molecular mechani-sms of fHP and IPF are particularly similar at advanced stages of disease progression. Thus, the presented data highlight the equally impor-tant role of immunological and genetic mechanisms in the formation of the fibrotic phenotype of HP.

An in-depth understanding of the pathogenetic mechanisms underlying HP has formed the basis for the active investigation of molecular and serum biomarkers that reflect the key processes involved in fibrosis development. In this context, the identification and clinical validation of biomarkers capable of simplifying diagnosis and optimizing patient management strategies in HP are becoming increasingly important [8, 44].

At present, intensive research is being conducted to identify biomarkers that reflect pathogenetic mechanisms, inflammatory activity, and disease prognosis.

Among the most extensively studied biomarkers are the mucin-like glycoprotein Krebs von den Lungen-6 (KL-6), surfactant proteins A and D (SP-A and SP-D), macrophage inflammatory proteins, Th2-type cytokines (CCL17, CCL15), matrix metalloproteinases (MMP-1, MMP-7, MMP-28), periostin, and chitinase-3-like protein 1 (YKL-40) [45, 46, 47, 48, 49].Elevated levels of KL-6 and SP-D correlate with inflammatory activity and the degree of alveolar damage, whereas increased concentrations of CCL17 and CCL15 are associated with fibrotic changes and an unfavorable prognosis [45, 48]. MMP-7 and MMP-1 are considered differential markers distinguishing idiopathic pulmonary fibrosis (IPF) from chronic HP [50], while periostin,

secreted by fibroblasts in response to IL-4 and IL-13, is associated with the severity of subepithelial fibrosis [46, 51].

The tumor markers CA 15-3 and CA 125, similar to KL-6, reflect the extent of fibrotic changes and the immune activity of the disease. At the same time, CA 15-3 and CA 125 testing offers the advantages of greater availability and lower cost, making these markers promising tools for clinical application in assessing disease activity and progression [52].

Alongside the study of serum biomarkers, considerable attention has been given to the analysis of bronchoalveolar lavage fluid (BALF), which allows for the evaluation of local immune responses within the pulmonary parenchyma. Lymphocytic infiltration in BALF is observed much more frequently in HP than in idiopathic pulmonary fibrosis (IPF) and may serve as an additional diagnostic criterion [53]. A BALF lymphocytosis exceeding 30% has been identified in 60% of patients with fHP, substantially increasing the diagnostic probability [54].

In addition to immunological and serum parameters, recent years have seen active research into genetic predictors of HP. Particularly important are the roles of MUC5B rs35705950 and telomere shortening, which contribute to tissue remodeling and progression of pulmonary fibrosis [38].

Genetic variants associated with the HLA system, as well as genes regulating immune responses – including TOLLIP, TAP1, and TNF-α – may determine individual susceptibility to the disease and the rate of its progression [55]. In the context of active research in this field, an important direction remains the investigation of correlations between biomarker levels and morphological, densitometric, and functional parameters of lung tissue.

Despite extensive international data on the prevalence and incidence of HP, information regarding this disease in Kazakhstan remains extremely limited. The lack of systematic epidemiological studies makes it difficult to objectively assess the true burden and distribution of the disease.

In rural areas, potential sources of antigens include moldy hay, organic dust, and contact with birds, whereas in urban environments, exposure is more often related to indoor mold contamination and occupational factors. Given the sharply continental climate, frequent dust storms, and seasonal agricultural activities, the likelihood of sensitization and disease development in Kazakhstan may be higher than currently recognized.

A major challenge remains the late diagnosis of HP, as most patients seek medical attention only after the development of fibrotic changes. This fact is supported by data from the Republican Multidisciplinary Expert Commission on Interstitial Lung Diseases (MEC-ILD), whose primary function is to evaluate the diagnostic accuracy of interstitial lung diseases (ILDs) and to determine indications for antifibrotic therapy. An analysis of the cases reviewed by the commission showed that patients with HP accounted for the largest proportion (35,8%), and among them, 83,3% were diagnosed with HP presenting with progressive pulmonary fibrosis. The obtained results indicate a high prevalence of the progressive form of the disease and emphasize the importance of early detection.

A low level of awareness among primary care physicians, as well as limited access to modern diagnostic modalities – such as high-resolution computed tomography (HRCT), surgical and endoscopic (transbronchial) lung biopsy, and assessment of diffusing capacity of the lungs – remain the key barriers to timely diagnosis.

These circumstances highlight the need to improve the awareness and education of specialists in the field of respiratory medicine, particularly regarding modern diagnostic approaches, interpretation of HRCT findings, and functional lung assessments.

Thus, HP is a complex, multifactorial chronic disease characterized by a high risk of development and progression of pulmonary interstitial fibrosis. Its pathogenesis results from a complex interaction between environmental factors, individual genetic predisposition, and dysregulation of immunobiological mechanisms. Despite the availability of effective diagnostic and therapeutic methods, there remains a pressing need to develop new approaches for earlier disease detection, particularly for identifying potential etiological factors and biomarkers predictive of disease progression – especially of interstitial pulmonary fibrosis.

Authors' contributions:

M. A. Yessengeldinova – concept development of the article, collection and analysis of literature data, writing and preparation of the manuscript.

R. A. Bakenova – scientific supervision, methodological consulting, and approval of the final version of the manuscript.

T. Z. Seisembekov – scientific supervision, methodological consulting, and approval of the final version of the manuscript.

K. M. Bakiyeva – technical formatting and preparation of the manuscript for publication.

Conflict of interest:

The authors declare no conflict of interest.

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Received 11.11.2024
Sent for revision 23.01.2025
Accepted 04.03.2025
Published online 30.12.2025

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ГИПЕРСЕНСИТИВНЫЙ ПНЕВМОНИТ: ЭТИОПАТОГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ ПРОГРЕССИРОВАНИЯ

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Гиперсенситивный пневмонит – это хроническое иммуновоспалительное заболевание легких, развивающееся в результате повторного воздействия вдыхаемых антигенов органического или неорганического происхождения. В статье представлен анализ современных данных об этиологических факторах, патогенетических механизмах и региональных особенностях распространения заболевания. Рассмотрены ключевые звенья иммунопатогенеза, включая роль Т-клеточного иммунного ответа, регуляцию цитокинов и процессы фиброгенеза. Отмечено значение генетических факторов, таких как полиморфизмы HLA и укорочение теломер, определяющих индивидуальную восприимчивость и тяжесть течения болезни. Особое внимание уделено изучению потенциальных биомаркеров, отражающих активность воспаления и фиброзного ремоделирования легочной ткани. Подчеркнуты трудности ранней диагностики и идентификации причинно-значимых антигенов. Местные факторы, включая климатические и профессиональные воздействия, влияют на риск сенсибилизации и развития заболевания. Комплексное понимание этиологии, патогенеза и молекулярных механизмов гиперсенситивного пневмонита способствует совершенствованию подходов к раннему выявлению, дифференциальной диагностике и прогнозированию.

Кроме того, приведены результаты последних исследований, демонстрирующих сходство фиброзного гиперсенситивного пневмонита с идиопатическим легочным фиброзом на молекулярном и морфологическом уровне. Эти данные подчеркивают необходимость своевременного выявления признаков фиброзной трансформации и интеграции молекулярных биомаркеров в клиническую практику. Учитывая отсутствие масштабных отечественных исследований, дальнейшее изучение влияния местных экологических и профессиональных факторов в Казахстане представляется крайне актуальным для уточнения региональных особенностей антигенного воздействия и течения болезни.

Ключевые слова: гиперсенситивный пневмонит; патогенез; этиология; биомаркеры; генетическая предрасположенность; легочный фиброз; экологические факторы

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ГИПЕРСЕНЗИТИВТІ ПНЕВМОНИТ: АУРУДЫҢ ПРОГРЕССИЯСЫНЫҢ ЭТИОПАТОГЕНЕТИКАЛЫҚ МЕХАНИЗМДЕРІ

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Гиперсензитивті пневмонит (ГСП) — өкпенің созылмалы иммундық-қабыну ауруы, органикалық немесе бейорганикалық шығу текті ингаляциялық антигендердің қайталама әсерінен дамиды. Мақалада аурудың этиологиялық факторлары, патогенетикалық механизмдері және аймақтық таралу ерекшеліктері туралы қазіргі заманғы деректердің талдауы келтірілген.

Иммунопатогенездің негізгі буындары қарастырылған, оның ішінде Т-жасушалық иммундық жауаптың рөлі, цитокиндік реттеу және фиброгенез процестері сипатталған. Аурудың дамуында адамның генетикалық факторларының, мысалы, HLA полиморфизмдері мен теломерлердің қысқаруының маңыздылығы атап өтіледі.

Қабыну белсенділігі мен өкпе тініндегі фиброздық қайта құрылу процестерін көрсететін әлеуетті биомаркерлерді зерттеуге ерекше назар аударылған. Диагностиканың ерте кезеңінде

қиындықтар мен себепті маңызды антигендерді анықтаудағы күрделілік мәселелері айқындалған. Жергілікті факторлар, соның ішінде климаттық және кәсіби әсерлер, сенсибилизациялану мен ауырудың даму қаупіне ықпал етеді.

Сонымен қатар, соңғы зерттеулер нәтижелері гиперсензитивті пневмониттің фиброздық түрінің идиопатиялық өкпе фиброзымен молекулалық және морфологиялық деңгейде ұқсастығын көрсетеді. Бұл деректер фиброздық трансформация белгілерін уақтылы анықтау мен молекулалық биомаркерлерді клиникалық тәжірибеге енгізудің қажеттілігін айқындайды.

Қазақстанда ауқымды отандық зерттеулердің жеткіліксіздігін ескере отырып, жергілікті экологиялық және кәсіби факторлардың әсерін одан әрі зерттеу аймақтық антигендік әсер ету мен ауру ағымының ерекшеліктерін нақтылау үшін өзекті болып табылады.

Кілт сөздер: гиперсензитивті пневмонит; патогенез; этиология; өкпе фиброзы; биомаркерлер; генетикалық бейімділік; иммундық механизмдер.