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Virus-induced asthma exacerbation

Key words: *asthma, virus, exacerbation, antiviral therapy.*

Bronchial asthma (BA) continues to be a serious global health and social problem which is caused primarily by its prevalence, a fairly high rate of morbidity and mortality, as well as huge economic losses society suffers from this disease. Today there are about 300 million patients with BA worldwide and the prevalence in different populations ranges from 1 to 18 % [1, 2]. In Ukraine, according to the official statistics, a tendency towards an increase in the prevalence of asthma in the adult population has been observed over the last few years, but this figure is still about 0.5 %. This fact indicates a clear underdiagnosis of asthma in this country which is confirmed by the patient make-up: the majority of patients are people with moderate and severe disease. On the other hand, patients with milder forms of the disease prevail in the developed countries [3].

According to experts, BA causes about 250,000 deaths per year in the world with a low correlation between mortality rates and prevalence of the disease. According to the WHO BA causes a loss of 15 million so-called DALY's (Disability-Adjusted Life Year - literally «a year of life, altered or lost in connection with disability») which is 1 % of total global loss caused by all diseases [1, 2].

To date, BA is considered a chronic inflammatory disease with recurrent exacerbations which are the primary cause of seeking medical care, hospitalization and economic costs. Among major causes (triggers) of BA exacerbations the leading position is occupied by respiratory viral infections [4] leading to increased inflammation in the lower respiratory tract persisting for several weeks. In this case acute respiratory viral infections (ARVI) lead to exacerbation in 80-85 % of cases in children and approximately 75 % of cases in adults [5]. It is known that ARVI's are common pathology, especially in young children. Thus, influenza and other viral respiratory infections in Ukraine are the most common infectious diseases. According to the MoH Centre of Influenza and ARVI these viral diseases account for 91,2 % (1999) to 95,2 % (2010) of all cases of infectious disease. This prevalence of ARVI allows us to consider this pathology as a strategically important health problem which requires the implementation of effective unified anti-epidemic measures and their clear coordination to minimize the level of morbidity, social and economic losses. ARVI's remain uncontrolled infections due to antigenic variability, especially for influenza viruses, and lack of vaccination for other ARVI's [6]. These diseases are grouped together as ARVI based on a single airborne pathogen transmission mechanism and the development of basic pathological process in the respiratory tract of patients with similar clinical symptoms. The link between ARVI and BA exacerbations was established by many epidemiological studies [5, 7, 8]. In addition, there is a direct correlation between the seasonal increase of ARVI and exacerbation of BA.

Respiratory tract diseases can be caused by more than 200 characterized viruses belonging to 6 families: 1) orthomyxoviruses (*influenzavirus A, B, C*); 2) paramyxoviruses (*pneumovirus*, *metapneumovirus*, *rubulavirus, respirovirus*); 3) picornaviruses (*rhinovirus, enterovirus*); 4) coronaviruses (*coronovirus*); 5) adenoviruses (*mastadenovirus*); 6) parvoviruses (*bocavirus*) [6]. Biological properties of the viruses as well as the microorganism characteristics determine the part of the respiratory tract affected and hence clinical manifestations of the disease. Furthermore, to some extent patient's age determines susceptibility to various respiratory viruses.

According to virological studies bronchial obstruction can be caused by different viruses: respiratory syncytial virus, rhinovirus, influenza viruses A and B, adenovirus, parainfluenza viruses, coronaviruses, enteroviruses, metapneumovirus, bocavirus etc. The most common causes (80 % of all virus-induced asthma exacerbations) of bronchial obstruction in adults and older children are rhinoviruses [9–11]. In young children the primary cause of obstruction is RS-virus [12].

Respiratory viruses do not only worsen obstructive bronchopulmonary diseases but may promote allergies. A clear correlation between respiratory infection in early childhood and the first aeroallergen sensitization has been noted [13]. On the other hand, children and adolescents with allergic diseases are prone to more frequent and severe ARVI's [14]. Furthermore, the spectrum of ARVI pathogens in allergic patients is wider and virus associations are more diverse than in patients without allergies. Viral infection does not only cause asthma exacerbation, but also significantly complicates and prolongs its course [15]. BA patients with symptoms of ARVI have more severe lung ventilation function impairment and worse laboratory parameters of inflammatory reaction (eosinophil count, WBC and eosinophilic infiltration of the lungs etc.) [5]; and bronchial hypersensitivity persists after ARVI from 5 to 11 weeks [15]. A direct link between viral infection and fatal asthma exacerbations was established [16].

Mechanisms of virus-induced exacerbations of BA are extremely complex and not clearly understood. According to numerous experimental studies one of the major pathogenetic mechanisms of BA is the bronchial hyperresponsiveness which occurs on the background of «eosinophilic» inflammation [17]. Respiratory viruses, especially rhinoviruses and RS-viruses can cause or exacerbate the inflammatory process by direct alteration of bronchial epithelium and expression by damaged and effector cells (eosinophils and lymphocytes) of a number of inflammatory mediators – chemokines and cytokines (interleukins, leukotrienes, platelet activating factors, tumornekrotizing factor, histamine, neutrophil proteases etc.). This leads to further damage in the bronchial epithelium, increased inflammatory reaction and development of respiratory failure [18]. The above mentioned disorders are followed by immunological mechanisms: respiratory viruses inhibit general and local immunity and contribute to T-helper cell activation which enhances immediate and delayed hypersensitivity reactions in response to allergen stimulation which leads to increased production of specific antiviral IgE and a further enhanced allergic inflammatory process [19, 20]. Impaired neural regulatory mechanisms play a significant role in the pathogenesis of virus-induced asthma exacerbations, in particular increased activity of the parasympathetic nervous system and neuropeptide levels, decreased levels of neutral endopeptidase and NO production which play an important role in the development of bronchial constriction [19]. One of the important factors of the pathogenic effect of respiratory viruses is a worsened mucociliary clearance, as well as inhibition of alveolar macrophage phagocytosis. This leads to a joined bacterial infection and viral-bacterial association development. The most frequent infections in ARVI are *M. pneumoniae* and *C. pneumoniae* which leads to more severe course of BA exacerbation [21].

To study the role of viruses in BA exacerbations and determine the effectiveness and safety of antiviral agent Vitaglutam in this group of patients SE National Institute of Phthisiology and Pulmonology Named after F. G. Yanovsky, NAMS of Ukraine carried out an open prospective randomized comparative study in 2011-2013. The study involved 116 patients with acute exacerbation of BA: 60 (51,7 %) men and 56 (48,3 %) women aged 19–76 years (average age – (40,2 ± 2,0) years). The average asthma exacerbation rate in examined patients during the last year was (2,5 ± 0,6) times with a duration of (12,0 ± 2,1) days. 17,2 % of the patients had exacerbations which occurred for the third time during the year and 5,2 % – for the fourth time.

To clarify the role of viruses in the development of BA exacerbation and to determine the spectrum of viral pathogens SE National Institute of Phthisiology and Pulmonology Named after F. G. Yanovsky, NAMS of Ukraine developed a diagnostic algorithm (fig. 1) based on the use of modern immunochromatographic express tests (ICA) in combination with molecular biological method - polymerase chain reaction (PCR).

For express diagnosis of influenza A and B, adenovirus and RS-virus simple/express tests «CITO TEST INFLUENZA A & B» (Pharmasco, Ukraine) and «CERTEST RSV-ADENO RESP BLISER TEST» (SerTest, Spain) were used.

A real time polymerase chain reaction was performed on «RotorGene 6000» amplifier (Corbett Research, Australia) using the following test systems:

- a set of reagents for RNA and DNA isolation, «Ribosorb»;
- a set of reagents for reverse transcription «Rezerta-L»;
- a set of reagents for isolation and differentiation of influenza viruses A and B «Amply-Sens Influenza virus A/B – FL»;
- a set of reagents for isolation and identification of influenza virus A (H1N1) «Amply-Sens Influenza virus A/H1swine – FL»;
- a set of reagents for isolation of 12 viruses causing acute respiratory viral infections «RV-12 SEE GENE» (ALN, Ukraine).

Laboratory tests conducted in 80 patients with BA revealed that in 57,5 % of cases viruses participated in the process of exacerbation. Furthermore, 46 strains of viruses were identified using PCR method and 6 strains using ICA. The largest etiological parameter among viral pathogens belonged to rhinovirus (52,2 % cases). Less common were bocavirus (13,0 %), metapneumovirus (8,7 %), respiratory syncytial virus (6,5 %), coronavirus, adenovirus, parainfluenza virus and influenza A and B (4,4 % of each). In patients with infectious exacerbation of BA viral pathogens were found primarily in the winter-spring season: in December-February – in 32,5 % of cases, in March-May – in 48,8 % of cases. It should be noted that during virological examination of the subjects influenza epidemic was not officially registered in Kiev.

Depending on the amount of therapeutic measures patients were divided into 2 groups. The first group consisted of 55 patients with exacerbation of BA whose treatment was based on anti-inflammatory medications (inhaled and systemic glucocorticoids) in combination with bronchodilators (β_2-agonists and short- and long-acting anticholinergics), mucoregulators and antihistamines.

The second group consisted of 41 patients with exacerbation of BA who were administered additional antiviral agent Vitaglutam (Ingavirin, Valenta, Russia), 1 capsule (90 mg) for 5 days. Vitaglutam is a drug that shows a pronounced antiviral activity against influenza type A and B (including A/H1N1, H1N1 swl, A/H3N2 and A/H5N1), parainfluenza, adenovi-

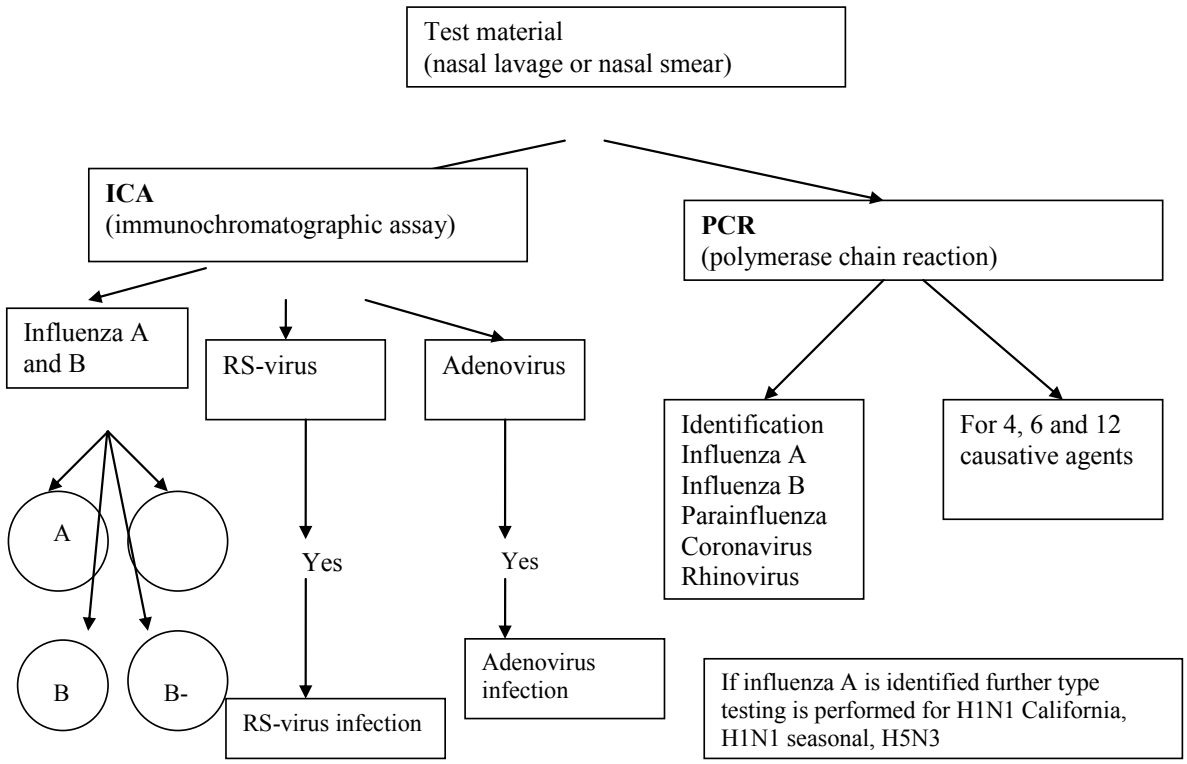

Figure 1. **Laboratory diagnostic algorithm for viral agent identification in patients with infectious BA exacerbations**

rus and viruses that cause respiratory syncytial infection. The mechanism of action of Vitaglutam is based on its ability to inhibit virus reproduction on a nuclear stage, as well as inhibit migration of newly synthesized NP virus from cytoplasm to nucleus. Vitaglutam modulates the functional activity of the interferon system by increasing the plasma level of interferon and stimulation of alpha-interferon and gamma-interferon production ability of leukocytes. Vitaglutam administration increases NK-T-cell and cytotoxic leukocyte levels showing antiviral activity and killer activity against virus-transformed cells. In addition to the antiviral action Vitaglutam has an anti-inflammatory effect. The mechanism of anti-inflammatory action is based on the ability of Vitaglutam's active substance to inhibit production of proinflammatory cytokines (in particular interleukin-1β, interleukin-6 and tumour necrosis factor) and decrease myeloperoxidase activity.

Additional administration of Vitaglutam significantly reduced the duration of intoxication symptoms (from 5,9 to 4,6 days) and catarrhal symptoms (from 6,8 to 5,9 days), reduced the duration of exacerbation of BA (from 12,5 to 10,8 days) and reduced the incidence of bacterial complications (from 18,0 to 5,0 %).

Thus, this data confirms the critical role of viruses in the occurrence of BA exacerbations. Moreover, metapneumoviruses, coronaviruses and bocaviruses take a significant place in the structure of pathogens, in addition to rhinoviruses, though they have not been identified in this country before. Patients with virus-induced exacerbation of bronchial asthma will benefit from administration of Vitaglutam, 1 capsule a day for 5 days.

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ВІРУС-ІНДУКОВАНИ ЗАГОСТРЕННЯ БРОНХІАЛЬНОЇ АСТМИ

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Резюме

Мета дослідження – *підвищити ефективність лікування хворих із загостренням БА вірусної етіології шляхом використання в комплексній терапії противірусного препарату вітаглутаму.*

Об'єкт дослідження: *116 хворих із загостренням БА вірусної етіології віком від 19 до 76 років.*

Матеріали та методи дослідження: *клініко-функціональні, вірусологічні, біохімічні, статистичні.*

Результати дослідження: *однією з найважливіших причин загострення бронхіальної астми є гострі респіраторні вірусні інфекції, причиною яких можуть бути понад 200 видів вірусів. В роботі наведено сучасні уявлення про патогенез вірус-індукованих загострень БА, алгоритм лабораторної діагностики вірусних збудників та ефективність лікування хворих на БА. Відмічено, що включення в комплексну терапію у пацієнтів вірус-індукованим загостренням БА вітаглутаму дозволяє вірогідно змінити терміни симптомів інтоксикації та контрольних явищ, а також скоротити терміни загострення БА і змінити частоту розвитку бактеріальних ускладнень.*

Ключові слова: *бронхіальна астма, загострення, вірус, противірусна терапія.*

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VIRUS-INDUCED ASTHMA EXACERBATIONS

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Summary

Aim – *to improve treatment of patients with exacerbation of asthma viral etiology by using in the treatment of antiviral drug vitaglutam.*

Object of study: *116 patients with exacerbation of asthma viral etiology aged 19 to 76 years.*

Materials and Methods: *clinical, functional, virological, biochemical, statistics.*

Results: *one of the major cause of asthma exacerbation is acute respiratory viral infections can be caused by over 200 viruses. The article describes the current understanding of the pathogenesis of virus-induced asthma exacerbations, the algorithm of laboratory diagnosis of viral pathogens and the effectiveness of treatment of asthma. It is noted that the inclusion of vitaglutam in the combined therapy of patients with virus-induced asthma exacerbation can probably reduce terms of symptoms of intoxication and control events, reduce the term of asthma exacerbation and incidence of bacterial complications.*

Key words: *asthma, exacerbation, virus, anti-virus therapy.*

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