Pathogenetic aspects
of virus-induced exacerbations
of chronic bronchitis

**Keywords:** chronic bronchitis, exacerbation of the virus, antioxidant system.

Chronic bronchitis (CB) — chronic inflammatory disease of the airways, accompanied by increased mucus production, changes in its physical and chemical properties and manifested chronic cough for 8 weeks per year for the last 2 years [1]. The characteristic feature of chronic bronchitis course and one of the most common causes of the patient’s medical care is the occurrence of exacerbations of the disease [2, 3].

Was established that patients with chronic bronchitis average have from one to four or more exacerbations during the year, and their incidence with age can progressively increase [3]. It is the frequency of exacerbations of chronic bronchitis is one of the most important factors that determine the quality of life [4-6].

15–40 % of infectious exacerbation (IE) HB caused by viral or viral-bacterial pathogens [6]. Therefore, as recommended by current international consensus, the basic principle of treating patients with acute exacerbation of chronic bronchitis is mucolytic and antibacterial therapy [8-10] and, if necessary, bronchodilator and anti-inflammatory [11].

In clinical practice antibiotic therapy in patients with chronic bronchitis and chronic obstructive pulmonary disease (COPD) is an empirical. The main indications for antibiotic therapy in exacerbations of CB / COPD is the presence of purulent sputum, increased its number and dyspnea (type I and II exacerbation of CB by N. Anthonisen), and hard to aggravation of signs of acute respiratory failure [8-10]. Today there is no data about the effectiveness of the appointment of antiviral drugs in the literature [9]. The main methods of treatment and prevention of acute respiratory viral infection causal consider antiviral therapy and stimulation of non-specific resistance of the patient, vaccination [7-10].

In recent years much attention is paid to the study of the mechanism of lung diseases at one of the major mediators of the respiratory system — nitric oxide (NO) [12, 14]. An important aspect of the NO is its influence on the condition of patients with hypoxia and metabolic acidosis. Nitric oxide released by endothelial cells, prevents intra-vascular thrombosis by inhibiting adhesion, activation and aggregation of platelets [11-15]. NO metabolism depends on the content of the amino acid L-arginin which is classified as conditionally essential amino acids and is an active and versatile cellular regulator of many vital body functions. Arginine is a substrate for NO synthase — an enzyme that catalyzes the synthesis of NO in the endothelial cells. Arginine also inhibits the synthesis of asymmetric dymetylarhininu — a powerful stimulator of endogenous oxidative stress. Arginine stimulates the production of T cells, regulate blood glucose during exercise correcting acid-base balance. It is a major substrate in a cycle of urea synthesis in the liver. Reducing ammonia effect is realized by activating conversion of ammonia to urea.

Indispensable donor is arginine domestic product L-arginine aspartate. The drug has membrane stabilizing cytoprotective, antioxidant, antiradical, detoxification activity [14, 16].

It is necessary to assess the intensity of free radical oxidation processes and state enzymatic antioxidant systems in patients with acute exacerbation of chronic bronchitis, viral etiology and pathogenesis develop a reasonable approach to improve the effectiveness of their treatment.

**Material and methods**

The object of the study were patients with CB and IE biological material obtained from these patients — wipes or swabs from mucous membrane of the nasal cavity, sputum, blood. The study included patients only if their voluntary consent for the purpose and amount of planned investigations, the need for the appointment of anti-infective therapy and the possible risk of adverse effects.

Criteria for inclusion of patients in the study:
- patients older than 18 years;
- availability of informed consent signed by the patient;
availability in patients with CB;
confirmed the results of clinical and / or laboratory studies infectious cause exacerbation of CB.
Criteria did not include patients in the study:
non-infectious exacerbation of CB;
antiviral and antibiotic therapy;
tolerance to drugs;
presence in a patient of pneumonia, severe concomitant diseases: tuberculosis; cancer, HIV / AIDS in; alcohol and drug addiction; decompensated cardiac, hepatic, renal failure, etc.;
patient refusal.

Used the quick methods indication of virus and viral antigens in clinical material – «quick» tests based on immunochromatographic methods and molecular biological diagnostics (polymerase chain reaction (PCR) with fixing the result in real time (realtime-PCR) or using agarose gel and color DNA samples [18, 19].

Research intensity of free radical lipid peroxidation (LPR) and protein and antioxidant enzyme activity performed in the Laboratory of Molecular Biochemistry Department of Fundamental Research SI «NSC» Institute of Cardiology n a Strazhesko «NAMS of Ukraine». Serum samples were tested for end products of lipid peroxidation, products of free radical oxidation of proteins, the degree of modification peroxidation of LDL and very low density [20, 21]. Also evaluated the activity of the enzyme myeloperoxidase. This important biochemical marker of inflammation intensity and presence of oxidative stress, which is secreted by activated neutrophils [22].

Reference values of biochemical parameters LPR who investigated – malonic dialdehyde 7,8-9,2 mmol / ml; catalase 10,5-14,5 U / L; diene conjugates in LDL, VLDL 0,3-0,9 conditions. units; superoxide dismutase 1700-2200 IU / L; 2,4-dinitro-phenylhydrazone 4,5-7,5 conditions. U / L; 0,00126-0,00310 myeloperoxidase units / min.

Were examined and treated 20 patients with mild IE CB. Men were (42,1 ± 4,5) %, the average age of patients was (43,0 ± 1,3) years. All patients treated in control «National TB Institute and Pulmonology Institute n a FG Yanovsky AMS of Ukraine» (NIFP NAMS). IE CB patients receiving anti-infective chemotherapy (inhaled antiseptic decamethoxin – dekasan, «Yuria Pharm») and mucolytics ambroxol – lasolvan, «Boehringer Ingelheim». Some patients additional daily oral drug used amino acid L-arginine aspartate – tivortin, «Yuria Pharm». Used inhalation drug decamethoxinum at a dose of 2 ml 0,02 % solution 2 –3 times a day for 5 –7 days.

For mucolytic therapy using the drug ambroxol (at a dose of 30 mg 3 times a day orally) for 7 –10 days.

<table>
<thead>
<tr>
<th>Clinical and functional performance of patients with acute exacerbation of chronic bronchitis, viral etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indexes</strong></td>
</tr>
<tr>
<td>The duration of symptoms of intoxication (days)</td>
</tr>
<tr>
<td>Duration catarrhal changes of the nasopharynx (days)</td>
</tr>
<tr>
<td>The duration of cough (days)</td>
</tr>
<tr>
<td>Duration of sputum (days)</td>
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<tr>
<td>The duration of exacerbation (days)</td>
</tr>
</tbody>
</table>

*Notes: * p < 0,05 compared with group 1 patients; # p > 0,05 compared with group 1 patients.

<table>
<thead>
<tr>
<th>The indicators of free radical oxidation of proteins and lipids and antioxidant defense in patients with exacerbation of chronic bronchitis, viral etiology (M ± m)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indexes</strong></td>
</tr>
<tr>
<td>The products of free radical oxidation of proteins</td>
</tr>
<tr>
<td>The products of free radical oxidation of lipids (TBA-positive products, MDA)</td>
</tr>
<tr>
<td>The activity of catalase, U / l</td>
</tr>
<tr>
<td>Superoxide dismutase, U/ml</td>
</tr>
<tr>
<td>Myeloperoxidase activity</td>
</tr>
<tr>
<td>The index of atherogenic lipoproteins peroxide modification</td>
</tr>
</tbody>
</table>

*Notes:* significant difference compared with the control group, p < 0.05; # significant difference compared with the group of patients before treatment, p < 0.05.
L-arginine – an amino acid that is classified as conditionally essential amino acids and is an active and versatile cellular regulator of the many vital body functions, has important protective effects in a critical condition of the body.

To determine the feasibility and efficiency in treatment of patients with viral etiology IE CB amino acid drug L-arginine aspartate and examined 20 patients, compared with almost 10 healthy individuals (donors). Patients were divided into two groups. Group 1 received decamethoxin and lasolvan. Group 2 received an additional tivortin.

Age-sex composition of the patients, the degree of severity of exacerbation of CB in both subgroups were comparable comparison.

Clinical efficacy of therapy determined by the analysis of complex clinical and laboratory parameters and functionality of the criteria listed in the European guide clinical evaluation of antimicrobial drugs [25]. Clinically effective treatment considered if study after completely disappeared or significantly decreased symptoms and functional features exacerbation. In assessing the clinical efficacy of decamethoxinum and L-arginine into account the results of treatment of patients who have completed a course of treatment with the study and those who stopped taking drugs because of their inefficiency and/or the development of serious adverse events.

All research results accumulated in developed our electronic database based on the program «Excel», which made it possible to analyze the results using variational methods of analysis. Descriptive statistics (number of observations, the average error average value, frequency, percentage) are all indicators analysis based on their type (quantitative, qualitative) [98]. All statistical tests performed for bilateral level of statistical significance (p < 0.05). [26].

Research carried out by the state budget.

Results and discussion

For calculating frequencies, CB viral etiology and detection range of viral etiologic agent CB virological examination carried out screening of all patients included in the study. According to laboratory examination of 80 patients – 35 (43,7 ± 5,5) % identified viruses. Most of viral pathogens were adenovirus – at (34,3 ± 8,0) % of cases and rinovirus – at (28,6 ± 7,6) %. Much less frequently detected virus influenza A and B – of (11,4 ± 5,4) % and in (5,7 ± 3,9) % of cases respectively; respiratory syncytial virus – in (8,6 ± 4,7) %; metapneumovirus and parainfluenza virus – in (5,7 ± 3,9) % of cases each.

Of the 35 patients with viral pathogen identified exacerbation of CB 20 were selected for in-depth study of the processes of free radical oxidation and antioxidant defense system.

Comparative results of treatment effectiveness in patients with acute exacerbation of chronic bronchitis, viral etiology are shown in Table 1 and 2.

Table 1 shows the dynamics of clinical and functional performance of patients 1 and 2 with acute exacerbation of chronic bronchitis, viral etiology. The duration of exacerbation on average decreased by 2.4 days (p < 0.05), duration of intoxication syndrome on average 1.3 day (p < 0.05), duration catarrhal changes nasopharynx on average 1.3 day (p < 0.05).

The results of biochemical studies to treatment (Table 2) found that patients with CB occurs IE intensification of free radical oxidation reactions and reduce the activity of antioxidant enzymes, which may lead to the development of oxidative stress. This indicates a probable increase in blood of patients end products of lipid peroxidation average of 18,0–21,0 %, products of free radical oxidation of proteins on 80,0–86,0 % and the value of the index of peroxide modification of LDL and VLDL on average 65–67 % compared with control values donors.

It indicates the modification of the structure and functional status of blood serum proteins such as albumin, globulins, fibrinogen, plasmin, biologically active compounds of protein nature, enzymes, hormones, and others. Modification of proteins of hemostasis and fibrinolysis is a possible cause changes hemorheological properties of blood in patients with CB IE viral etiology. Data show increase in atherogenic potential of blood due to a significant increase in the index of atherogenic lipoproteins peroxidation modification. This activation of oxidative processes against the background of significant inhibition of enzyme antioxidant systems: catalase – by 20,0–24,0 %, ODS – on 31,0–34,0 % compared to the reference value in the activity of these enzymes donors.

The treatment led to normalize the value of the index compared with the values of these parameters before the start of treatment in patients with acute exacerbation of chronic bronchitis. Content of end products of lipid peroxidation and free radical oxidation of proteins under the influence of combination therapy (antiseptic and mucolytics) are respectively 9.0 and 53.0 % less compared to their values before the treatment. Also changed the value of MPO activity, which are significantly higher than the reference value respectively 129,0 %. Changed activity of antioxidant enzymes in the direction of normalization, catalase activity reaches almost control level, being lower by 11.0 %, and the activity of SOD at the end of treatment will be reduced by 14.0 % compared with the control.

These results suggest that under the influence of therapy in patients with CB IE positive changes occurring state of free radical oxidation and antioxidant protection. In patients who were administered the drug also observed amino acid normalization process of free radical processes and antioxidant enzyme systems, and reduce the severity of oxidative stress in the body of patients.

Under the influence of complex treatment with the inclusion of the drug L-Arginine aspartate is activation of antioxidant defense systems.

Application in the treatment of patients with infectious exacerbation of chronic bronchitis virus etiology of L-arginine aspartate in Pharmacopeial permissible dose and mode, can largely avoid significant impact inflammation caused by acute exacerbation of the disease and reduce the duration of exacerbation on average 2.4 day (p < 0.05); duration of intoxication syndrome on average 1.3 day (p < 0.05); duration of nasal catarrhal changes in average 1.3 day (p < 0.05) and significantly reduce the intensity of free radical oxidation and increase antioxidant enzyme systems that reduce the severity of oxidative stress.


