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Chronic obstructive pulmonary disease: role of infectious agents in exacerbation of the process

Key words: *chronic obstructive pulmonary disease (COPD), exacerbation, bacterial and viral pathogens, resistance.*

During recent years the incidence of respiratory diseases has increased with chronic obstructive pulmonary disease (COPD) having a particular place. This disease creates complex modern medical and social challenges due to its high prevalence and high rates of mortality and disability as well as significant economic losses incurred by society all over the world, due to this disease [1, 2].

The study Global Burden of Disease Study [3], which is held with the support of the World Health Organization and the World Bank, indicators of prevalence of COPD in the world of men and women in all age groups accounted for 9.34 and 7.33 respectively per 1000 population and in the coming years is projected to further increase these figures. At present, the prevalence of non-communicable diseases COPD ranks second only to cardiovascular disease and 4th place in the structure of causes of death.

COPD is associated with significant economic losses. Thus, in the EU, overall economic costs of respiratory diseases reach 6 % of the total health budget and the share of COPD accounts for 56 % (38.6 billion Euros) [4]. In the US, direct economic losses associated with COPD are 29.5 billion US dollars and indirect losses are 20.4 billion US dollars [5]. According to DALY (the method which determines the contribution of different medical problems to overall mortality and disability and reflects years lost due to premature death and years lived with disability, based on disease severity), in 1990 COPD took 12th place for social losses and accounted for 2.1 % of all losses and by 2030 it is expected to move to 7th position [2].

According to current views, COPD is a chronic disease that can be prevented and treated, which is characterised by persistent airflow limitations, is usually progressive and is associated with an increased response of the lungs to the action of pathogenic particles or gases [6].

A characteristic feature of COPD is the occurrence of exacerbations which according to the recommendations of the GOLD expert working group is defined as «an acute condition characterised by deterioration in patient's respiratory symptoms which is beyond normal daily fluctuations and changes the therapy used» [6].

It is established that patients with COPD usually experience from one to four or even more exacerbations during the year and their frequency increases progressively with the severity of the disease [7, 8]. COPD exacerbation is one of the most important factors contributing to the quality of life, rate of disease progression and economic costs of this disease [9, 10].

Frequent exacerbations of COPD both reduce the quality of life of patients, lead to more rapid disease progression [11, 12] and cause high mortality in these patients. Thus, hospital mortality from this disease ranges from 4.0 % to 10.0 % reaching 24.0 % in patients in intensive care units (ICU). Patients hospitalised with severe COPD exacerbations have the most unfavourable long-term prognosis and mortality in the first year is about 40.0 % in these patients [12].

Among various provoking factors (inadequate basic therapy, impact of large numbers of exogenous damaging factors, significant physical activity, aspiration, use of certain drugs, etc.) infection is considered to be the main cause of COPD exacerbations, which according to most authors accounts for 50.0-80.0 % of all exacerbations [13, 14]. The major factors of COPD infectious exacerbation (IE) are bacterial and viral pathogens.

In this context, the purpose of the study was to investigate the role of bacterial and viral microorganisms in infectious exacerbations of chronic obstructive pulmonary exacerbation.

Materials and Methods

126 patients with COPD were included in the study to investigate the role of viral pathogens in the course of chronic obstructive pulmonary disease and to optimise the diagnosis, treatment and prevention of infectious exacerbation of this disease.

The main criteria for patient inclusion in the study were:

- Consent of the patient and opportunity to participate in the study confirmed by the signature on the patient's written informed consent;
- Presence of COPD according to the criteria specified in the order of the Ministry of Health of Ukraine № 555 of 27.06.2013;
- Presence of infectious exacerbation phase confirmed by clinical and/or laboratory studies;

Exclusion criteria were:

- Presence of severe concomitant diseases: tuberculosis, cancer, HIV infection, non-compensated heart, liver or renal failure, etc.;
- Known or suspected intolerance to the study drug;
- Occurrence of serious adverse events during the study drug administration;
- Patient's refusal to participate in the study.

The group of patients who were diagnosed with infectious exacerbations of COPD (126 patients) consisted of 90.5 % of men and 9.5 % of women aged 42 - 87 years (mean age - (67,9 ± 7.8) years). The average frequency of COPD exacerbations during the previous year in examined patients was (2.9 ± 0.3) times with a mean duration time of each (12.5 ± 1.7) days. In 43.2 % of patients with COPD, exacerbation occurred for the third time, in 15.4% for the fourth time and in 8.6% for the fifth time during the year.

Among risk factors that lead to exacerbations, the most frequently mentioned by the patients were ARVI or contact with ARVI patients in 67.9 % of cases. Hypothermia and increased impact of aggressive environmental factors (paint, dust, etc.) were reported by 18.5 % of patients.

To identify major etiologic agents of infectious COPD exacerbation, microbiological studies of biological material from 126 patients were conducted as required by the order of the Ministry of Health of Ukraine № 30 of 02.09.98 and № 535 of 22.04.1985 of the Ministry of Health of the USSR adapted according to the rules of GLP [15, 16].

Materials for microbiological examination were sputum, swabs or smears from the nasal cavity and the blood obtained by venipuncture. During sample selection, in each case the peculiarities of infection, site of the maximum pathogen localisation, route and time of its release to the environment were taken into account. Materials were obtained at the earliest time of onset.

During sampling, precautions regarding contamination of the medical personnel, material contamination limitations and pathogen viability were strictly observed. Sputum obtained from the lower respiratory tract with a deep cough before meals was used for bacteriological studies. Materials were collected in sterile containers before the start of antibiotic therapy. Material storage time from collection to further study did not exceed 1-2 hours at room temperature.

Before bacteriological examination, sputum was studied under a microscope in its native state to determine the feasibility of further microbiological analysis. Sputum smears stained by Gram were considered informative if they contained at least 25 leukocytes and less than 10 epithelial cells in the field of view (x 100) [60].

Quantitative assessment of microbial population, which vegetate in sputum, was conducted using a quantitative method by Dixon and Miller modified by L.G. Selina by seeding to the appropriate solid culture media. Sputum results were considered diagnostically important if a potential pathogen showed a titer of not less than 106 colony forming units (CFU) in 1 ml [16].

Primary sputum seeding on blood and chocolate agars (the basis of which was Columbia Agar) was performed using a quantitative method. To isolate pathogenic microorganisms (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*), a 5 % red cell mass was added to blood or chocolate agar. To isolate commensal microorganisms (*S. aureus*, *Enterobacter spp.*, yeasts and moulds) seeding was performed on Sabouraud agar, EYSA and Endo agar. Seeding to these media was carried out by traditional methods (by sector seeding, volumetric method with material dilution, etc.) in order to obtain isolated colonies which were used for obtaining pure cultures with their differentiation and subsequent identification [17]. At the same time the investigated material was seeded to liquid culture media (glucose broth and serum broth). Cultures were incubated at 37° C in an atmosphere containing 5.0 % carbon dioxide (CO_2 incubator).

Isolated microorganism cultures were identified using the API test systems manufactured by «bioMariae», France.

Sensitivity of the isolated microorganisms to antibiotics was determined using a disk diffusion method on Mueller-Hinton agar manufactured by «bioMariae», France. Disks manufactured by Russian and American companies (BBL) were used. To determine sensitivity, the NCCLS reference strains (*S. pneumoniae* ATCC 49619, *H. influenzae* ATTC 49247, *S. aureus* ATC 25923, *E. coli* ATC 25922, *P. aeruginosae* ATC 27 953, etc.) were used.

Laboratory diagnostics of viral infections were performed at the Virology Department of the P.L. Shupik National Medical Academy of Post-Graduate Education (Head of Department - Professor Dzyublik I.V.). Samples were tested for A and B human influenza viruses, 4 types of parainfluenza virus, type I and II coronaviruses, 32 serotypes of adenovirus and RS-virus.

To prevent virus inactivation, a nasal smear was placed in a test tube with 2.0-3.0 ml of a special viral transport medium (VTM) or saline. Test materials (swabs or smears from the

nasal cavity and blood) were transported to the laboratory in containers with refrigerants at a temperature of 4 °C.

In this study comprehensive methods including classical virological studies (hemagglutination inhibition test (HIT), hemadsorption reaction (HAR)) and modern methods for rapid virus detection and viral antigen detection in clinical materials and in cell cultures (enzyme-linked immunosorbent assay (ELISA), indirect fluorescent antibody (IFA) method in direct version and simple/rapid tests based on immunochromatographic assay (ICA)) were used.

Isolation and identification of A and B influenza virus isolates were carried out in full compliance with the order of the Ministry of Health of Ukraine №30 of 09.02.1998.

The test algorithm for influenza viruses included the following steps:

- Centrifugation of the material taken from the patient in order to obtain sediment cells which were later used for the preparation of smears with fluorescent immunoglobulins and IFA;
- Identification of the isolated influenza virus in HIT with type-specific or strain-specific sera to establish virus type or strain[15].

Specific diagnostics of RS-virus were performed by isolation of the pathogen in the susceptible cell culture (Hep-2) followed by virus indication using HAR or according to characteristic cytopathic effect (CPE), or by the presence of intranuclear inclusions found using IFA.

In this study, type-specific immune sera for influenza viruses A(H1N1), A(H3N2), B and the RS-virus manufactured by the Research Institute of Influenza of the RAMS (Russia) were used.

Enzyme-linked immunosorbent assay (ELISA) was only used in patients for etiological diagnostics of influenza to identify a type-specific ribonucleoprotein antigen of the influenza virus in nasopharyngeal secretions (swabs) of the patients. Nasal smears were also used as test materials (which is permitted); cotton wipes with mucous cells were re-suspended in 2 ml of PBS with 0.05% Tween-20, frozen and thawed twice to remove viral antigens from cells before testing. Prepared materials were stored at -20 °C before ELISA. For A and B influenza, two test systems manufactured by the Research Institute of Influenza of the RAMS (Russia) were used simultaneously. The ELISA studies were carried out according to instructions for the test system. Plate washing was carried out using a «WELLWASH 4 MK-2» («TERMO ELECTRON», Finland) automatic washer. The ELISA results were recorded in a two-wave mode 450/620 nm with a «Multiscan-ascent» («TERMO ELECTRON», Finland) spectrophotometer.

IFA was used to detect viral antigens in smears from the nasal cavity using fluoro-chrome-labelled specific antiviral globulins. Immune sera for influenza viruses A(H1N1), A(H3N2), B; parainfluenza 1, 2, 3, 4; RS-virus, rhinovirus and adenovirus manufactured by the Research Institute of Influenza of the RAMS (Russia) were used. Preparations were analysed under a «Lyumam R-3» fluorescent microscope using an immersion lens 90x 1.25 L, ocular lens x5, CF1-2 blue-violet excitation filters and SZS 7-2 and SZS 14-4 thermal lens filters. Study results were considered diagnostically significant if a specific diffuse or granular glow was detected in the cytoplasm or nucleus of 3-4 cells in cylindrical epithelium with brightness of not less than (2+) measured by four plus system (4+) [18].

For rapid diagnostics of type A and B influenza, «Cito Test Influenza A & B» commercial simple/rapid tests by Pharmasco, registered in Ukraine in 2005, were used. They are based on the immunochromatographic assay (ICA), a specific interaction between antigens and antibodies on a chromatographic membrane of the test after wetting it with a fluid sample from a patient. This interaction is due to the diffuse movement of the indicative immune component stained with colloidal gold (CG), previously placed on the membrane, and test sample antigens after placing them on the membrane. For visual detection of a specific immune response, the necessary components which concentrate the dye in the form of a coloured band are strictly enclosed in a particular area-band of the chromatographic membrane. Study materials included nasal smears, nasopharyngeal swabs or nasal discharge. Study results were collected in 5-15 minutes. In the presence of influenza virus antigens, two (one pathogen) or three (two pathogen) red bands were detected, one of which was a control.

Studies were performed using state budget funds.

Results and conclusions

In 106 patients (84.1 %), 115 bacterial strains were isolated from the sputum. The main etiopathogen of IE in COPD patients was *H. influenzae*, which was found in (49.1 ± 4.9)% of cases. Resistant to penicillins, aminopenicillins and chloramphenicol were (5.8 ± 3.2)% of these pathogen strains (Table. 3.1). In (22.6 ± 4.1) % of cases the IE pathogen was *S. pneumoniae;* (8.3 ± 5.6) % of the isolated strains were resistant to penicillins, aminopenicillins and protected aminopenicillins due to modification of the penicillin-binding protein in the cell membrane of the pathogen; resistant to chloramphenicol were (125 ± 6.8) %. It should be noted that (4.2 ± 4.1) % of *S. pneumoniae* strains also had associated resistance to macrolides, II generation cephalosporins and II generation fluoroquinolones. At the same time, all strains of this pathogen were sensitive to III generation fluoroquinolones (levofloxacin). In (13.2 ± 3.3) % of patients *M. catarrhalis* was isolated. 85.7 ± 9.4% of the isolated strains were resistant to penicillins and aminopenicillins. In 7.9 % of patients *K. pneumoniae* was isolated. (50.0 ± 15.8) % of the isolated strains were resistant to penicillins, cephalosporins and II generation aminopenicillins. In (7.6 ± 2.6) % of patients *S. aureus* was isolated. (87.5 ± 11.7) % strains were resistant to natural and synthetic penicillin. *E. coli* was the cause of IE in (6.6 ± 2.4) % of COPD patients which had a clinically significant level of resistance (57.1 ± 18.7) % to penicillins, aminopenicillins and chloramphenicol but a lesser level of resistance to II generation cephalosporins.

During virological studies of the nasal swabs and smears in 126 patients using fluorescent antibodies, viral antigens were detected in 40 individuals corresponding to (31.8 ± 4.1) %.

Respiratory adenovirus antigens (1-39 types) were detected using IFA in (30.0 ± 7.2) % of patients; influenza A(H1N1), (H3N2), B in (37.5 ± 7.7)%; parainfluenza I, II, III type in (25.0 ± 6.8) % and RS-virus in (7.5 ± 4.2) %.

ELISA was used in all 126 cases for etiologic diagnostics of influenza. Collected and processed as described in Section 2, material was stored until simultaneous ELISA on two test systems. 20 positive results were obtained: 15 for influenza A and 5 for influenza B.

Identification of the influenza virus was performed using HIT with type-specific sera. It was established that influenza A(H3N2) was isolated in 6 patients, influenza A(H1N1) in 2 patients, influenza B in 5 patients and influenza A (not yet identified) in 5 patients. A total of 18 influenza virus strains were isolated.

In parallel testing for the influenza virus using ELISA and simple/rapid tests it was found that all 18 positive samples in ELISA were confirmed by ICA tests. The presence of a clear bright line was observed in 100 % of cases. During the study of negative influenza samples from patients, the results were consistent and were interpreted as «negative» in 100 % of cases.

Therefore, in the vast majority (84.1 ± 3.3) % of patients the infectious exacerbations of COPD were caused by bacteria and in (31.8 + 4.1) % by viruses, (69.8 ± 4.1) % of cases were caused by bacterial pathogens only and (15.9 ± 3.3) % by viruses only and (14.3 ± 3.1) % by their combination.

The highest etiologic significance among bacterial pathogens belonged to *H. influenzae* - in (49.1 ± 4.9) % of cases, *S. pneumoniae* - in (22.6 ± 4.1) %, *M. catarrhalis* - in (13.2 ± 3.3) % and to a lesser extent to *K. pneumoniae* - in (9.4 ± 2.8) %, *S. aureus* - in (7.6 ± 2.6) %, *E. coli* - in (6.6 ± 2.4) %. In 5.8-87.5 % of selected strains a resistance to natural and semisynthetic penicillins was found.

It was found that the most common viral pathogens were influenza A and B - in (37.5 ± 7.7) % of cases, respiratory adenoviruses - in (30.0 ± 7.2) %, parainfluenza - in (25.0 ± 6.8) % and rare RS-virus - in (7.5 ± 4.2) %.

In patients with infectious exacerbation of COPD the viral pathogens were mainly isolated in winter, spring and autumn: influenza viruses A and B in February, 7 (17.5 ± 6.1) %, March, 5 (12.5 ± 5.3) %, April, 3 (7.5 ± 4.2) %; parainfluenza in May, 3 (7.5 ± 4.2) %, October, 7 (17.5 ± 6.1)%; adenoviruses in February, 6 (15.0 ± 5.7) %, April, 1 (2.5 ± 2.5) %, October, 5 (12.5 ± 5.3) %; RS-viruses in May, 3 (7.5 ± 4.2) %, which generally corresponded to the seasonal prevalence of ARVI, caused by these pathogens.

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ХРОНИЧЕСКОЕ ОБСТРУКТИВНОЕ ЗАБОЛЕВАНИЕ ЛЕГКИХ: ЗНАЧЕНИЕ ИНФЕКЦИОННОГО АГЕНТА В ВОЗНИКНОВЕНИИ ОБОСТРЕНИЯ ПРОЦЕССА

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Резюме

Цель исследования – *изучение роли бактериальных и вирусных возбудителей в возникновении обострений ХОЗЛ, методы выявления патогенных возбудителей, определение чувствительности их к различным группам антибактериальных препаратов.*

Объект исследования: *126 пациентов с обострением ХОЗЛ, вызванным инфекциями бактериальной, вирусной и смешанной этиологии, в возрасте от 42 до 87 лет.*

Материалы и методы исследования: *клинико-функциональные, микробиологические, вирусологические, биохимические, бактериологические, статистические.*

Результаты и их обсуждение

Основными причинами возникновения обострений ХОЗЛ являются бактериальные и вирусные инфекции. В работе применены современные методы выявления возбудителей обострений ХОЗЛ, проведен анализ определения чувствительности патологических агентов, вызывающих обострения, к различным группам антибактериальных препаратов.

Установлено, что основным проблемным этиопатогеном была H. influanzae. Резистентность к пенициллинам, аминопенициллинам и хлорамфениколу выявлена у 5,8 % штаммов этого возбудителя. В 22 % случаев возбудителем являлся S. pneumoniae, 8,3 %

штаммов из них резистентны к пенициллинам, аминопенициллинам и защищенным аминопенициллинам. В то же время все штаммы этого возбудителя были чувствительны к фторхинолонам III поколения(левофлоксацину).

Таким образом, в большинстве случаев (84,1 %) обострение ХОЗЛ было вызвано бактериями, у 31,8 % – вирусами, у 14,3 % – совместно бактериально–вирусным инфицированием.

Ключевые слова: *хроническое обструктивное заболевание легких (ХОЗЛ); обострение, бактериальные, вирусные возбудители, резистентность.*

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ХРОНІЧНЕ ОБСТРУКТИВНЕ ЗАХВОРЮВАННЯ ЛЕГЕНЬ: ЗНАЧЕННЯ ІНФЕКЦІЙНОГО АГЕНТА У ВИНИКНЕННІ ЗАГОСТРЕННЯ ПРОЦЕСУ

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Резюме

Мета дослідження – вивчення ролі бактеріальних і вірусних збудників у виникненні загострень ХОЗЛ, методи виявлення патогенних збудників, визначення чутливості їх до різних груп антибактеріальних препаратів.

Об'єкт дослідження: 126 пацієнтів із загостренням ХОЗЛ, викликаним інфекціями бактеріальної, вірусної і змішаної етіології, у віці від 42 до 87 років.

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

Результати та їх обговорення

Основними причинами виникнення загострень ХОЗЛ є бактеріальні та вірусні інфекції. У роботі застосовані сучасні методи виявлення збудників загострень ХОЗЛ, проведено аналіз визначення чутливості патологічних агентів, що викликають загострення, до різних груп антибактеріальних препаратів.

Встановлено, що основним проблемним етіопатогеном була H. influanzae. Резистентність до пеніцилінів, амінопеніцилінів і хлорамфеніколу виявлена у 5,8 % штамів цього збудника. У 22 % випадків збудником був S. pneumoniae, 8,3 % штамів з них резистентні до пеніцилінів, амінопеніцилінів і захищеним доамінопеніцилін. У той же час всі штами цього збудника були чутливі до фторхінолонів III покоління (левофлоксацину).

Таким чином, у більшості випадків (84,1 %) загострення ХОЗЛ було викликано бактеріями, у 31,8 % – вірусами, у 14,3 % – спільно бактеріально-вірусним інфікуванням.

Ключові слова: *хронічне обструктивне захворювання легень; загострення, бактеріальні, вірусні збудники, резистентність.*

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