ORIGINAL ARTICLE

# ASSESSMENT OF THE IMPACT OF ANTIREFLUX THERAPY ON THE COURSE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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## ABSTRACT

**The aim:** To examine the effect of antireflux therapy on the course of COPD.

**Materials and methods:** Under observation were 60 patients who were hospitalized in the «Transcarpathian Regional Clinical Hospital named after Andrei Novak» with a diagnosis of COPD II gr B in combination with GERD and 36 patients diagnosed with GERD who were treated on an outpatient basis.

To study the effectiveness of antireflux therapy and its impact on the course of COPD, patients are divided into 2 groups: 1 group (main) (n = 60) – patients with COPD in combination with GERD, group 2 (control) (n = 36) – patients with isolated GERD. Patients with positive Helicobacter pylori status received antihelicobacter therapy.

Patients in group 1 were divided into subgroups: 1a (n = 34) – COPD in combination with esophageal manifestations of GERD and 1b (n = 26) – COPD in combination with extraesophageal manifestations of GERD. Group 1a received complex therapy, which consisted of basic therapy of COPD in combination with antireflux and with rebapimide, group 1b – only basic therapy of COPD in combination with antireflux.

**Results:** After treatment, the clinical signs of GERD significantly decreased in all patients receiving complex therapy, improved the course of respiratory symptoms of COPD. After treatment, patients showed a clinically significant reduction in systemic inflammation, which is best seen in the group with the use of rabipimide.

**Conclusions:** Comprehensive treatment of combined pathology with the use of antireflux therapy has a positive effect not only on the clinical symptoms of the disease, but also on the indicators of external respiratory function in patients with combined COPD and GERD.

**KEY WORDS:** rabipimide, function of external respiration, influence

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an extremely common medical and economic problem not only in Ukraine but also worldwide, due to its high prevalence, severity, high risk of death and huge costs for the management of patients [1-3]. Modern scientific research is paying increasing attention to the prevalence of development and progression of combined pathology of the digestive and respiratory systems [4,5]. The problem of managing patients with a combination of gastroesophageal reflux disease (GERD) and chronic obstructive pulmonary disease is especially relevant [6,7]. GERD is an independent risk factor for exacerbations of COPD and is associated with deteriorating health of patients [8].

In the modern literature the question of treatment of patients with GERD [9] is sufficiently studied, but there are no data concerning treatment of GERD connected with COPD. Proton pump inhibitors (PPIs), which are also used to treat GERD in patients with COPD, are undoubtedly the drugs of choice in the treatment of GERD. However, the question of the importance of PPIs in reducing the frequency of COPD exacerbations and the possibility of preventing these events remains not fully studied and somewhat controversial [10]. Therefore, the study of the impact of antireflux therapy on the course of COPD is promising.

## THE AIM

The aim of the research was to examine the effect of antireflux therapy on the course of chronic obstructive pulmonary disease in the period of exacerbation.

## MATERIALS AND METHODS

Under observation were 60 patients who were treated in the pulmonology department of the Municipal Non-Profit Enterprise «Transcarpathian Regional Clinical Hospital named after Andrei Novak» with a diagnosis of COPD II gr B in combination with GERD and 36 patients diagnosed with GERD were treated by a gastroenterologist. The mean age of the subjects was 55 ± 1.64 years. Among the examined patients, men predominated by sex – 78.1% (75 out of 96).

All subjects signed an informed consent, the methodology of which was in line with the Helsinki Declaration of 1975 and its revision in 1983 and was approved by Uzhhorod National University's Commission on Bioethics (Protocol №1 of 10.01.2020). The inclusion criteria confirmed the diagnosis of chronic obstructive pulmonary disease (GOLD II) and age over 40 years and less than 70 years. Exclusion criteria: age under 18 and over 70 years, taking corticosteroids per os, the presence of concomitant diseases of the respiratory, digestive,

cardiovascular system, malignant neoplasms, the patient's refusal to study.

The diagnosis of COPD was confirmed in accordance with the order of the Ministry of Health of Ukraine №555 dated 27.06.2013 «On approval of clinical protocols for medical care in the specialty «Pulmonology « and the provisions set out in the document GOLD [2017] [5].

The diagnosis of gastroesophageal reflux disease (GERD) was made in the presence of relevant complaints and the results of instrumental studies – a positive test with rabeprazole, fibrogastroduodenoscopy (FGDS) and intragastric pH-metry, taking into account the Montreal Consensus (2006), 10H as well as in accordance with domestic protocols for medical care (order of the Ministry of Health of Ukraine № 943 of 31.10.2013).

Positive Helicobacter pylori status (Hp +) was registered in 69.8% (67 out of 96), with a distribution by groups of 47.9% (46 out of 96) in group 1 and 21.9% (21 out of 96) in group 2 respectively.

To study the effectiveness of antireflux therapy and its impact on the course of COPD, patients are divided into 2 groups: 1 group (main) (n = 60) – patients with COPD in combination with GERD, group 2 – (control) (n = 36) – patients with isolated GERD. Groups of patients were homogeneous in age and sex. The study evaluated the effectiveness of complex therapy of patients with COPD in combination with GERD. All patients received basic treatment for COPD according to existing national and international guidelines, which included long-acting beta-2 agonists, long-acting anticholinergics, inhaled glucocorticosteroids, and short-acting beta 2-agonists as needed.

Patients in group 1 were divided into subgroups: 1a (n = 34) – COPD in combination with esophageal manifestations of GERD and 1b (n = 26) – COPD in combination with extraesophageal manifestations of GERD. All patients with positive *Helicobacter* status (Hp +) received antihelicobacter therapy, which included amoxicillin 1000 mg, clarithromycin 500 mg, rabeprazole 20 mg – 1t x 2 times a day with each drug – 14 days and probiotic Saccharomyces boulardii 2 times 1 capsule per day – 10 days. After successful eradication of Helicobacter pylory (Hp), all patients were prescribed antireflux therapy, which included: measures to change lifestyle; appointment of rabeprazole at a dose of 20 mg in the morning 30 minutes before meals for 8 weeks with the transition to therapy «on demand» and itopride hydrochloride 50 mg 3 times a day for 1 month. Therapy «on demand» included – in the case of recovery of heartburn in a patient after a course of PPIs, taking rabeprazole at a dose of 20 mg for 7 days, with the transition to 10 mg for another 14 days.

Patients of subgroup 1a on the background of basic COPD therapy received antireflux therapy with additional inclusion of rebapimide 100 mg 3 times a day for 1 month, and patients of subgroup 1b received basic therapy of COPD in combination with antireflux without the use of rebapimide. The effectiveness of the therapy was evaluated by the dynamics of the following indicators: assessment of clinical manifestations of GERD, assessment of dyspnea by mMCD, indicators of inflammation (CRP, leukocytes, neutrophils, ESR, procalcitonin), cytokine activity (IL-4, IL-6, IFNγ, IFN 4), the parameters of the function of external respiration (FEV 1%, FVC, FEV1 / FVC). Statistical analysis of the data was performed using Jamovi, version 2.0.0 using the paired Student's t test, Pearson's $\chi^2$ test and Fisher's exact test, depending on the type of source data. The average values of the numerical data were represented as M ± SD. The normality of the distribution was evaluated by the Shapiro-Wilk test. The critical level of reliability was considered to be $\alpha = 0.05$.

## RESULTS

Analysis of the results showed that the leading clinical symptom in patients of group 1a and group 2 was heartburn and acid regurgitation, in 50% (30 of 60) and 55% (33 of 60), respectively,

**Table I.** Dynamics of clinical symptoms in the examined patients before and after treatment

| Indication | Groups | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 COPD + GERD (n=60) | | | | Control group GERD (n=36) | |
| | 1a (n=34) | | 1b (n=26) | | | |
| | before | after | before | after | before | after |
| Heartburn (abs /%) | 30/50,0* | 6/10,0 | 0/0 | 0/0 | 29/80,5 | 5/13,9 |
| Sourbelching (abs /%) | 33/55,0* | 7/11,7 | 0/0 | 0/0 | 33/91,6 | 10/27,8 |
| Dysphagia (abs /%) | 28/46,7 | 11/18,3 | 0/0 | 0/0 | 17/47,2 | 7/19,4 |
| A lump in the throat (abs /%) | 31/51,7 | 9/15,0 | 0/0 | 0/0 | 12/33,3 | 3/8,3 |
| Itching in the throat (abs /%) | 0/0 | 0/0 | 7/11,7** | 1/1,6 | 2/5,5 | 1 / 2,7 |
| Hoarseness of voice (abs /%) | 0/0 | 0/0 | 4/6,6 | 2/3,3 | 0/0 | 0/0 |
| Dry, barking cough that worsens at night (abs /%) | 0/0 | 0/0 | 14/23,3** | 4/6,6 | 3/8,3 | 0/0 |
| Chest pain along the esophagus (abs /%) | 0/0 | 0/0 | 2/3,3 | 0/0 | 3/8,3 | 0/0 |
| Irregular heart rhythm (abs. / %) | 0/0 | 0/0 | 2/3,3 | 1/1,6 | 1/2,8 | 1 /2,8 |

Note. Significance of the difference: * - incomparison with patients of group 1b and 2 at p <0,05, ** - incomparison with patient of group

**Table II.** Assessment of the degree of dyspnea and the need for SAB in patients of both groups before and after treatment

| Indication | Group 1a (n=34) | | Group 1b(n=26) | |
|---|---|---|---|---|
| | before | after | before | after |
| The degree of shortness of breath in points | 3±0,88* | 2±0,4 | 3±0,91** | 2±0,6 |
| The need to use short-acting bronchodilators per day | 4±0,7* | 2±0,4 | 4±0,9** | 2±0,5 |

Note. Significance of the difference: * - in comparison with patients of group 1b at p <0,05, ** - in comparison with patients of group 1a at p <0,05

**Table III.** Dynamics of spirometry before and after treatment

| Indication | Group 1a (n=34) | | Group 1b (n=26) | | Group 2 (n=36) | |
|---|---|---|---|---|---|---|
| | before | after | before | after | before | after |
| FEV 1 % | 63,2 ± 1,8* | 68,4 ± 1,7 | 66,1 ± 1,4 | 67,3 ± 1,5 | 81,4±0,4 | 84,8 ± 1,1 |
| FVC % | 73,3 ± 1,9* | 79,2 ± 3,1 | 75,4 ± 1,7 | 78,1 ± 3,1 | 85,3±1,2 | 88,8 ± 2,3 |
| FEV 1/ FVC % | 63,2 ± 0,9* | 71,7 ± 2,14 | 65,2 ± 0,7 | 69,8 ± 2,1 | 88,3±1,2 | 87,8 ± 0,9 |

Significance of the difference: * - in comparison with patients of groups 1b and 2 at p <0,05.

**Table IV.** Dynamics of laboratory parameters as a result of treatment

| Indication | Before/ After (1/2) | Group 1a (n=34) | Group 1b (n=26) | Group 2 (n=36) |
|---|---|---|---|---|
| Leukocytes 10 * 12 / l | 1 | 12,1±0,6 | 13,2±1,1 | 6,5±1,3 |
| | 2 | 7,3±0,7 | 9,2±0,8 | 6,3±1,2 |
| Neutrophils % | 1 | 73,2±2,4 | 74,1±2,6 | 67,2±3,1 |
| | 2 | 67,2±1,7 | 68,1±1,6 | 69,1±2,8 |
| Neutrophils in sputum in p / s | 1 | 30,6±1,3 | 34±1,4 | - |
| | 2 | 22±1,4* | 24±2,8** | - |
| ESR mm / year | 1 | 16 ±3,2 | 15 ±3,7 | 6±4,1 |
| | 2 | 11 ±1,2 | 10 ±2,5 | 5±3,5 |
| CRP mg / l | 1 | 14,3±2,8* | 16,2±2,5** | 3,3 ±1,5 |
| | 2 | 3,3±0,6 | 3,4±0,8 | 2,1 ±1,9 |
| Procalcitonin ng / ml | 1 | 0,1±0,04 | 0,1±0,05 | 0,03 ±0,01 |
| | 2 | 0,04±0,03 | 0,04±0,04 | 0,04±0,01 |
| IL-4, pg / ml | 1 | 10,4±2,1* | 13,5±0,5** | 4,1±0,6 |
| | 2 | 7,4±1,1 | 8,5±0,7 | 3,2±0,4 |
| Interferon gamma (IFNγ) pg / ml | 1 | 318,2±11,8* | 359,1±11,9** | 126,9±12,4 |
| | 2 | 201,1 ±6,8 | 213,1±5,5 | 124,5±12,4 |
| IFNγ/ ІЛ-4 | 1 | 23,7±11,2* | 29,3±9,2** | 7,1±1,4 |
| | 2 | 6,6±3,2 | 9,2±2,2 | 6,7±1,3 |
| IL-6, pg / ml | 1 | 17,4 ±1,3* | 18,5 ±0,8** | 6,8±1,7 |
| | 2 | 7,1±0,9 | 8,2±1,3 | 5,3±1,4 |

Notes: * - the difference is significant (p <0,05) in comparison with group 1b and 2; the difference is significant (p <0,05) in comparison with group 1a and 2; a - before treatment; b - after treatment.

and 81% (29 of 36) and 92% . (33 of 36) at p <0.05, compared with group 1b, where dry cough and sore throat prevailed – in 23% (14 of 60) and 12% (7 of 60), respectively, at p <0.05 . After the treatment, a significant decrease in the intensity of clinical signs of combined pathology was registered in both groups, with a predominance in group 1a (table I).

When assessing the severity of shortness of breath on the scale of mMKD and the use of short-acting bronchodilator (SAB) «on demand» before and after treatment, the following data were obtained (table II) .

When assessing the degree of shortness of breath in both groups of patients before and after treatment, there was a significant decrease in 1.5 ± 0.3 or the severity of the symptom of shortness of breath, and antireflux therapy reduced the frequency of short-acting bronchodilators «on demand» 2 times at p <0.05.

When measuring the function of external respiration before and after treatment, the following results were obtained (table III).

Spirometric monitoring revealed improvements in key indicators of external respiratory function, such as FVC, FEV1 / FVC % – and FEV1 in patients of all groups. However, patients who received complex treatment with rabipimide had a more pronounced positive dynamics of the mean: FEV1 increased from 63.2 ± 1.8% to 68.4 ± 1.7% ($p < 0.05$), FVC – from 73 , 3 ± 1.9% to 79.2 ± 3.1% ($p < 0.05$) and FEV1 / FVC % – from 63.2 ± 0.9% to 71.7 ± 2.14% compared with patients of group 1b, where these indicators were: from 65.2 ± 1.8% to 67.3 ± 1.5% ($p < 0.05$), FVC – from 74.3 ± 1.7% to 78.1 ± 3.1% ($p < 0.05$) and FEV1 / FVC % – from 64.1 ± 0.9% to 69.8 ± 2.1%. In group 2 with isolated GERD significant changes in ERF were not detected at $p < 0,05$.

Patients also underwent laboratory evaluation of inflammation according to the general analysis of blood, the level of ESR, C-reactive protein (CRP), procalcitonin and cytokine profile (table IV).

As can be seen from table IV, patients in groups 1a and 1b after treatment showed a significant decrease in acute phase parameters in the serum (CRP), the level of neutrophils in the sputum, levels of IFNγ, IFNγ / IL-4 and IL-6 at $p < 0.05$. Procalcitonin levels in patients of all groups are not prognostically significant at $p < 0.05$.

## DISCUSSION

Therefore, in patients with combined pathology there is leukocytosis and an increase in acute phase parameters in the serum (ESR and CRP), indicating active systemic inflammation [11].

The presence of increased levels of neutrophils in the sputum of patients indicates the presence of an inflammatory process in the bronchi [12]. Also in patients of the above groups there is an increase of almost 2 times the level of IFNγ, which involves the activation of the cellular immune system in combined pathology. Increased, almost 3 times compared with the control group, the ratio between IFNγ / IL-4 indicates the presence of an imbalance in the immune system in patients with concomitant GERD [13]. Elevated pro-inflammatory cytokine IL-6 in these patients in the pro-inflammatory cytokine IL-6 stimulates an excessive and unregulated immune response, which in turn maintains chronic inflammation even in remission [14].

After treatment, all patients showed a clinically significant reduction in systemic inflammation, in clinical symptoms of GERD and respiratory symptoms, improved respiratory function which is more pronounced in patients taking rabipimide. Thus, antireflux therapy in patients with COPD in combination with GERD eliminates the main pathogenetic factor (acid reflux), which is an activator of the inflammatory process in the esophagus and airways.

## CONCLUSIONS

1. Complex treatment of combined pathology with the use of antireflux therapy has a positive effect not only on the clinical symptoms of reflux, but also on the indicators of the function of external respiration in patients with combined COPD and GERD.
2. Addition of rabipimide to antireflux therapy in patients with combined pathology normalizes the indicators of systemic inflammation, which indicates a pronounced anti-inflammatory effect of the applied therapeutic complex.

## REFERENCES


1. Feshchenko Yu. I., Gavrysyuk V. K., Dzyublyk O. Ya. et al. Adaptovana klinichna nastanova: khronichne obstruktyvne zakhvoryuvannya legen. [Adapted clinical guideline: chronic obstructive pulmonary disease]. Ukrainian Pulmonology Journal 2020;(3):5–36. (In Ukrainian)
2. Halpin D. M. G., Criner G. J., Papi A. et al. Global initiative for the diagnosis, management, and prevention of chronic obstructive lung disease. The 2020 GOLD science committee report on COVID-19 and chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2021;203(1):24–36.
3. Iheanacho I., Zhang S., King D. et al. Economic burden of chronic obstructive pulmonary disease (COPD): a systematic literature review. International journal of chronic obstructive pulmonary disease. 2020;15: 439.
4. Bobyk L.R., Levynska N.I., Piddubna A.A. et al. Metabolichni osoblyvosti erozyvno-vyrazkovykh urazhen shlunka ta dvanadtsyatypaloyi kyshky u khvorykh na khronichne obstruktyvne zakhvoryuvannya legen. [The pathogenetic features of erosive-ulcerative damages of stomach and duodenum in patients with chronic obstructive lung's disease]. Young. 2018;63(11) (in Ukrainian)
5. Shevchuk-Budz U.I.Clinical and functional features of chronic bronchitis development admixed with a gastroesophageal reflux disease during an additional prescription of lecithine. 2018. https://www.thepharmajournal.com/archives/2018/vol7issue4/PartH/7-3-131-796.pdf Date access 20.08.2021
6. Shevchuk-Budz U. I. The study of clinical and pathogenetic characteristics of the chronic bronchitis course on the background of the aggravating concomitant gastroesophageal reflux. 2018. https://www.thepharmajournal.com/archives/2018/vol7issue10/PartB/7-9-26-921.pdf Date access 20.08.2021
7. Lin Y. H., Tsai C. L., Tsao L. I., Jeng C. Acute exacerbations of chronic obstructive pulmonary disease (COPD) experiences among COPD patients with comorbid gastrooesophageal reflux disease. Journal of clinical nursing. 2019;28(9–10):1925–35.
8. Hasegawa K., Sato S., Tanimura K. et al. Gastroesophageal reflux symptoms and nasal symptoms affect the severity of bronchitis symptoms in patients with chronic obstructive pulmonary disease. Respir Investig. 2018;56(3):230–7.
9. Lee A. L., Goldstein R. S. Gastroesophageal reflux disease in COPD: links and risks. International journal of chronic obstructive pulmonary disease. 2015;10:1935.
10. Kikuchi S., Imai H., Tani Y. et al. Proton pump inhibitors for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2020;(8).
11. Golpe R., Martín-Robles I., Sanjuán-López P. et al. Differences in systemic inflammation between cigarette and biomass smoke-induced COPD. International journal of chronic obstructive pulmonary disease. 2017;12: 2639.
12. Eapen M. S., Myers S., Walters E. H., Sohal S. S. Airway inflammation in chronic obstructive pulmonary disease (COPD): a true paradox. Expert review of respiratory medicine. 2017;11(10): 827-839.

13. Chang C. H., Chen T. H., Chiang L. L. L., Ma C. C. Risk factors for diabetes mellitus in patients with gastroesophageal reflux disease. International Journal of Diabetes in Developing Countries. 2021;1-7.
14. Giraldez M. D., Carneros D., Garbers C. et al. New insights into IL-6 family cytokines in metabolism, hepatology and gastroenterology. Nature Reviews Gastroenterology & Hepatology. 2021;1-17.

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