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Optimizing Management of Exacerbations and Premature Death Risks in Patients with COPD (Review)

Data analysis of numerous studies was carried out and trends and directions in the management of patients with chronic obstructive pulmonary disease (COPD) were analysed. Studying the characteristics of factors contributing to disease development без коми allows us to understand that the smoking epidemic, the aging of the world population and the lack of disease-modifying therapy will lead to a further increase in mortality from COPD. Each COPD exacerbation increases both the risk and frequency of subsequent exacerbations, and the development of local or systemic changes and complications has also been established. Not only severe but also moderate COPD exacerbations (those that do not require hospitalization and could be treated on an outpatient basis) also increased the risk of subsequent exacerbations and death. The degree of increase in risk was proportional to the number of exacerbations per year. Thus, two moderate exacerbations per year increased the risk of death by 80 % (hazard ratio — 1.80 (95 % confidence interval (CI): 1.19—2.70)), while increased frequency of exacerbations to 5 increased the hazard ratio to 2.33 (95 % CI: 1.45—3.76).

The effectiveness of the treatment of patients with COPD and the dependence of the latter on various factors were evaluated. Based on the received data, the specialists have concluded that the presence of one severe or two or more moderate COPD exacerbations during one year indicates a high risk of exacerbations in the future and is associated with an increased risk of premature death. Therefore, a high-risk group patient requires special attention when choosing the tactics of his management. This is reflected both in international and national consensus documents. A single-inhaler triple therapy (specifically a fixed combination of budesonide/glycopyrronium/formoterol), administered within the first 30 days after an exacerbation, is currently the only pharmacotherapeutic option that has been proven to reduce mortality in COPD patients.

Keywords

Chronic obstructive pulmonary disease, modifying factors of exacerbations, effective three-component therapy, mortality prevention.

COPD is one of the leading causes of death and disability worldwide. In 2019, 3.23 million deaths from COPD were recorded. This accounts for about 6 deaths every minute. More than 80 % of these deaths occur in low-income and middle-income countries [9, 32]. The growing smoking epidemic, the aging of the world population and the lack of disease-modifying therapy are factors that will lead to a further increase in mortality from COPD [10].

That is why therapy goals for COPD patients, defined by GOLD (Global Initiative for Chronic Obstructive Lung Disease) experts are reducing the risk of premature death and reducing the risk of exacerbations, which are key factors in the progression of this currently incurable disease [10].

A Canadian cohort study evaluated data from more than 73,000 patients who were first hospitalized with a COPD exacerbation [27]. It was found that the probability of survival within 5 years after the first hospitalization with COPD exacerbation was only about 40 %. Such a low 5-year survival rate is comparable to that of heart failure, myocardial

infarction, and even some cancers (e.g., bladder cancer) [7, 23, 29].

Each COPD exacerbation increases both the risk and frequency of subsequent exacerbations and the development of local or systemic changes and complications, both in the respiratory system and in other body systems [3, 16, 22]. Thus, the interval between the first and second severe exacerbations, according to the Canadian cohort study, is about 5 years, but over time the period between exacerbations reduces and lasts less than 4 months between the 9th and 10th exacerbations. The risk of a subsequent severe exacerbation increases threefold after the second severe exacerbation and 24-fold after the tenth [27]. Thus, with each subsequent exacerbation, the course of COPD is accompanied by a rapid deterioration in the health of patients and a significant increase in the risks of subsequent exacerbations and death.

But the prognosis for COPD patients is worsened not only by severe exacerbations. A trial involving 99,574 COPD patients who were followed for 10 years, states that moderate COPD exacerbations (those that do not require hospitalization and could be treated on an outpatient basis) also increased the risk of subsequent exacerbations and death [21]. The degree of increase in risk was proportional to the number of exacerbations per year. Thus, two moderate exacerbations per year increased the risk of death by 80 % (hazard ratio (HR) — 1.80 (95 % confidence interval (CI): 1.19—2.70)), while increased frequency of exacerbations to 5 increased the HR to 2.33 (95 % CI: 1.45—3.76). Severe exacerbations increase this risk even more.

Based on such data, COPD-treating specialists have concluded that the presence of one severe or two or more moderate COPD exacerbations during one year indicates a high risk of exacerbations in the future and is associated with an increased risk of premature death. Therefore, a high-risk group patient requires special attention when choosing the tactics of their management. This is reflected both in international consensus documents [10] and in the Unified Clinical Protocol for Primary, Specialized and Emergency Medical Care «Chronic Obstructive Pulmonary Disease» approved by the Order of the Ministry of Health of Ukraine No. 1610 dated 20.09.2024 [1].

Often, COPD patients do not report their exacerbations which presents a significant problem. According to studies, patients with COPD exacerbations do not seek any medical help in 50 to 70 % of cases [11, 12]. Thus, according to a diary study of exacerbations frequency in COPD patients, the total frequency of exacerbations was 2.7 cases per person per year, but only 0.8 cases per person per year were reported [11]. However, both reported and unreported exacerbations impact health condition.

Another challenge is the timely provision of adequate maintenance therapy, taking into account the patient's history of exacerbations. Data from actual clinical practice (n = 250,723) over an 8-year period, published in 2024 [31], confirm this problem. The highest risk of death in this trial was among COPD patients with a history of more than one moderate or severe exacerbation. In the 3 months before death, 17.2 % of patients experienced a severe exacerbation and 34.8 % experienced a moderate exacerbation. Despite the increased frequency of exacerbations in the year before death, more than half of the patients did not receive recommended pharmacological COPD therapy. This indicates the critical need to pay special attention to the assessment of exacerbation anamnesis and the adjustment of maintenance therapy based on its results during COPD patient surveillance.

GOLD experts proposed changes to the algorithm for the initial assessment of symptoms and exacerbation risk following the ABE scheme which specifically recognizes the importance of COPD exacerbations regardless of the level of symptoms [10]. These changes are also reflected in the national industry standards for COPD patients' surveillance [1, 2]. According to these documents, group E includes patients who have had one or more severe (requiring hospitalization) or 2 or more moderate exacerbations in the previous 12 months. For such patients, treatment with a dual long-acting bronchodilator is recommended as basic therapy. The combination of a long-acting beta-agonist + a long-acting muscarinic antagonist + an inhaled corticosteroid (LABA + LAMA+ICS) should be considered if the blood eosinophil count is ≥ 300 cells/μL, since the effect of ICS on preventing exacerbations correlates with the blood eosinophil count.

Regarding further therapy for patients with exacerbations, the algorithm is applied regardless of the ABE scheme group [1]:

- Patients with persistent exacerbations who receive long-acting bronchodilator monotherapy are recommended to increase the scope of therapy to LABA + LAMA.
- Patients with exacerbation progression under long-acting bronchodilator monotherapy whose blood eosinophil level is ≥ 300 cells/μL are recommended to increase the scope of therapy to LABA + + LAMA + ICS. Evaluation of the number of eosinophils in the blood can identify patients with a higher probability of a good response to ICS.
- Patients with additional exacerbation progression under LABA + LAMA therapy are offered two alternatives:

Table. **Factors to consider when adding ICS to long-acting bronchodilators (Note that the scenario is different when considering discontinuation of ICS)**

Prescription is recommended	Availability of COPD hospitalizations in the anamnesis
	≥ 2 moderate COPD exacerbations per year*
	Blood eosinophil count > 300 cells/μcL
	Bronchial asthma or comorbidity in the anamnesis
Consider prescribing	1 moderate COPD exacerbation per year*
	Blood eosinophil count 100—300 cells/μcL
Contraindications	Repeated pneumonia episodes
	Blood eosinophil count < 100 cells/μcL
	Mycobacterial infection in the anamnesis

Note. * Despite appropriate supportive therapy with long-acting bronchodilators; note that blood eosinophil levels should be viewed as a continuum; these values are approximate cut-off values; blood eosinophil levels may fluctuate.

a) increase the scope of therapy to LABA + LAMA + + ICS. A good response to the addition of ICS may be seen if patients' blood eosinophil count ≥ 100 cells/μcL, and stronger response is more likely to be observed with higher eosinophil count;
b) the blood eosinophil count < 100 cells/μcL may show a low likelihood of a good response to ICS treatment. In this case, consider adding roflumilast (for patients with FEV1 < 50 % of the predicted value and chronic bronchitis) or azithromycin (if the patient is currently a non-smoker). If a patient with COPD has no signs of asthma has been treated for any reason with a LABA + ICS and their symptoms and exacerbations are well controlled, LABA + ICS may be continued. However, if the patient has:
a) further exacerbations, the scope of therapy should be increased to LABA+LAMA+ICS;
b) major symptoms, the possibility of switching to LABA+LAMA should be considered.

An ICS component should be included in the therapy of high-risk COPD patients. Factors to consider when adding ICS to long-acting bronchodilators are listed in Table.

Discontinuation of ICS should be considered in case of development of pneumonia or other significant adverse events. However, a blood eosinophil level ≥ 300 cells/μcL indicates patients at greatest risk of developing exacerbations after ICS discontinuation.

Triple therapy in a single inhaler is currently the only pharmacotherapeutic option that has been proven to reduce mortality in COPD patients [4, 12, 16]. Previous studies, such as TORCH [6] and SUMMIT [5], have not proven the efficacy of LABA + ICS in reducing mortality in patients with COPD compared with placebo. UPLIFT [28], the largest study on the treatment with LAMA, when analysing all randomized patients, that is, 30 days after the end of the study period, also did not demonstrate any reduction in mortality compared with placebo. And, recently, two large randomized clinical trials, IMPACT [13] and ETHOS [19], have provided evidence that inhaled triple combinations of LABA + LAMA + ICS in fixed doses (i. e., in one inhaler) reduce all-cause mortality compared with dual inhaled therapy with long-acting bronchodilators. These studies included patients with severe symptoms (CAT ≥ 10) and with a history of frequent (≥ 2 moderate exacerbations) and/or severe exacerbations (≥ 1 exacerbation requiring hospitalization). Thus, the ETHOS trial, which lasted 52 weeks and included 8,588 patients with moderate to very severe COPD with exacerbations, a fixed combination of budesonide/glycopyrronium/formoterol (*ed.* — registered in Ukraine under the trademark Trixeo Aerosphere, AstraZeneca) resulted in a statistically significant reduction in the risk of death compared to the combination of LAMA + LABA by 49 % (relative risk: 0.51; 95 % CI: 0.33—0.8; p = 0.0035). This effect may be implemented through the following potential mechanisms [4, 8, 14, 17, 18, 20, 24—26]:

- *Effect on hyperinflation.* ICS in combination with bronchodilators may reduce hyperinflation, potentially improving cardiac function through improved respiratory mechanics and beneficial effects on the structure and function of the heart and pulmonary veins.
- *Effects on exacerbations.* ICS-containing therapy reduces the number of exacerbations, which may lead to fewer hospitalizations, cardiovascular events, and premature death.
- *Effects on inflammation.* ICS-containing therapy may reduce various markers of systemic inflammation, potentially improving cardiac function. It may reduce lung-specific biomarkers of inflammation, leading to improved lung function and overall well-being in COPD patients.

Drug-free therapies that have been shown to reduce mortality in COPD patients include: smoking

cessation, pulmonary rehabilitation, long-term oxygen therapy, non-invasive positive pressure ventilation, and lung volume reduction surgery [2, 22].

It is also important to note that the best results of drug triple therapy are seen in patients when administered within the first 30 days of a COPD exacerbation. According to a retrospective observational study of the insurance database (USA, n = 24,770), which included patients after ≥ 2 moderate or ≥ 1 severe exacerbation in the previous year [17], the administration of triple therapy within 30 days after an exacerbation significantly reduced the risk of exacerbations by 39 % compared with its administration after 6—12 months. At the same time, every 30 days of delay in prescribing triple therapy increased the probability of a second exacerbation by 11 % during the 12-month observation period.

Conclusions

If the goal is to optimize the treatment of patients with COPD at high risk of exacerbations and premature death, triple maintenance therapy of ICS + LABA + LAMA in one inhaler is a standard approach to the treatment of such patients according to international and national guidelines. Actual clinical practice shows that a successful outcome can be achieved in 96.5 % of cases after 90 days of therapy and in 91.8 % of cases after 180 days of treatment [15]. Therapy was considered successful if the patient did not have COPD exacerbations, hospitalization due to any respiratory event, myocardial infarction, heart failure, death, and the absence of pneumonia.

Thus, preventing exacerbations and reducing the risk of premature death remains an urgent need in COPD. Early identification of patients at increased risk and timely appropriate therapeutic intervention are key to preventing COPD progression and reducing its risks. GOLD recognizes triple therapy as the only pharmacological therapy that reduces mortality in COPD. Triple therapy of ICS + LABA + LAMA in one inhaler is an effective solution for eligible COPD patients from the high-risk group.

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Оптимізація менеджменту ризиків загострень та передчасної смерті в пацієнтів із хронічним обструктивним захворюванням легень (огляд літератури)

Проведено аналіз даних багаточисленних досліджень, тенденцій та напрямів роботи з пацієнтами, що страждають на хронічне обструктивне захворювання легень (ХОЗЛ). Вивчення особливостей хворобоіндукуючих факторів розвитку захворювання дає змогу зрозуміти, що епідемія куріння, яка зростає, постаріння світової популяції та дефіцит модифікуючої терапії призведе до подальшого зростання смертності від ХОЗЛ. Встановлено, що кожне загострення ХОЗЛ підвищує як ризик, так і частоту наступних загострень та розвиток локальних чи системних змін та ускладнень. Не тільки тяжкі, але й помірні загострення ХОЗЛ (такі, що не потребували госпіталізації та могли лікуватись в амбулаторних умовах) також підвищували ризик наступних загострень та смерті. При цьому ступінь підвищення ризику була пропорційна кількості загострень на рік. Так, два помірних загострення на рік підвищували ризик смерті на 80 % (відношення ризиків — 1,80 (95 % довірчий інтервал — 1,19—2,70)), в той час, як підвищення частоти загострень до 5 збільшувало відношення ризиків до 2,33 (95 % довірчий інтервал — 1,45—3,76).

Оцінена ефективність лікування хворих на ХОЗЛ та залежність останнього від різних чинників. Базуючись на отриманих даних, фахівцями були зроблені висновки, що наявність одного тяжкого або двох і більше помірних загострень ХОЗЛ протягом року свідчить про високий ризик загострень у майбутньому та асоціюється з підвищеним ризиком передчасної смерті. Тому пацієнт із групи висо-

кого ризику потребує особливої уваги при визначенні тактики його ведення. Це знайшло своє відображення як у міжнародних, так і національних консенсусних документах. Трикомпонентна терапія в одному інгаляторі (зокрема фіксована комбінація будесоніду/глікопіронію/формотеролу), призначена у перших 30 днів після загострення, на сьогодні є єдиною фармакотерапевтичною опцією, що доведено знижує смертність пацієнтів із ХОЗЛ.

Ключові слова: хронічне обструктивне захворювання легень, модифікуючі чинники загострень, ефективна трикомпонентна терапія, профілактика смертності.

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