# Pneumonia as a Secondary Complication Related to Inhaled Corticosteroid Combination Treatment for Chronic Obstructive Pulmonary Disease with Eosinophilic Phenotype Patient

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**Abstract**

Chronic obstructive pulmonary disorder (COPD) is a progressive respiratory condition characterized by chronic inflammation, proteases and antiproteases imbalance, and airway remodeling. Several hypotheses, including immune dysregulation, microbial colonization, and environmental triggers, explain the underlying cause of the deteriorating state and recurrence of exacerbations in COPD. Eosinophils, one of the inflammatory mediators, are involved in about 30% of cases of COPD. In COPD with an eosinophilic phenotype, specific therapy recommendations include inhaled corticosteroids (ICS) combined with a long-acting bronchodilator therapy typically includes the combination of inhaled corticosteroids (ICS) (e.g., fluticasone, budesonide) and a long-acting bronchodilator (LABA) (e.g., formoterol, salmeterol) to improve airflow and reduce inflammation. While ICS therapy is beneficial, side effects of pulmonary infections become more likely as the dose increases, particularly with prolonged use. The risk of pneumonia can be managed through dose optimization and careful patient monitoring.

**Keywords**: COPD, eosinophilia, ICS, pneumonia

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## Introduction

Chronic obstructive pulmonary disease is a chronic respiratory disease characterized by persistent airflow limitation combined with chronic inflammation, resulting in permanent lung structure remodeling.[1] Neutrophils, CD8+ T lymphocytes, and alveolar macrophages are the main mediators of inflammation in COPD. In some cases of COPD, particularly those with an eosinophilic phenotype, eosinophils also contribute to airway inflammation.[2] For several periods, eosinophilic inflammation is commonly been used to distinguish asthma from COPD. Still, the latest studies found that nearly 30% of COPD patients have a high eosinophil count which contributed to the treatment modality chosen.[3]

During exacerbations, some COPD patients have elevated sputum eosinophil levels. Eosinophil counts were higher during exacerbations compared to stable disease periods, and there was an association between higher eosinophil counts and increased exacerbation frequency. Eosinophils contribute to inflammation in acute exacerbations in nearly one-third of cases causing worsened airway obstruction and induced asthma-like symptoms (prominent expiration wheezing).[4] The eosinophil threshold is related to clinical symptoms in COPD patients and has been investigated as a potential biomarker for targeting specific medication. High Sputum and/or blood eosinophilia in COPD (≥2% or ≥300 cells/µL) may predict response to inhaled corticosteroids (ICS) as maintenance therapy and systemic corticosteroids (CS) for treatment of exacerbations. A randomized double-blind study investigated the higher level of blood eosinophil affected different results such as the risk of exacerbations over 48 weeks and lower results in $FEV_1$ pre-treatment. The combination of ICS and LABA was known to show a better effect on increasing $FEV_1$ in patients in the highest blood eosinophil groups. These findings were used as the guideline for treating patients with high eosinophil count due to the good evidence-based results.[5]

Long-term use of ICS, on the other hand, has been linked to secondary pulmonary infection in COPD patients. The most common infection seen in COPD patients receiving ICS treatment is pneumonia. COPD patients hospitalized with pneumonia comorbidities increased in frequency over the observation period and became the most prevalent comorbidity among people over the age of 65 years old.[6] The annual rate of hospitalization for COPD patients with concurrent pneumonia increased by more than 25%. The mortality rate

from COPD and pneumonia has also been reported to be higher in elderly patients. Age, as one of the parameters in pneumonia severity index scoring, has also contributed to the severity degree of pneumonia infection in COPD patients. Several studies found that COPD patients with pneumonia had a more severe degree of illness, a greater need for intensive care treatment, and an increased mortality rate following support with mechanical ventilation.[7]

**Case Presentation**

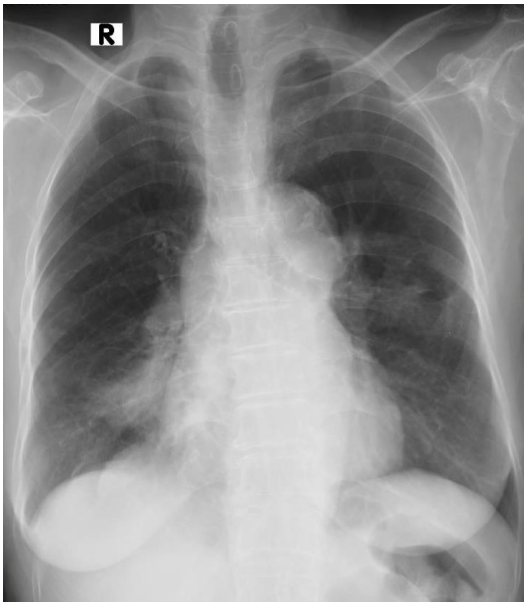


**Image 1.** Chest x-ray showed an emphysematous lung with consolidation in the lower right lobe suggesting pneumonia.

A 91-year-old female patient arrived at the emergency department with a chief complaint of exertional dyspnea, which started two days prior to hospital admission and worsened within four hours. The complaints were associated with a four-day history of productive cough, yellowish purulent sputum, and a high body temperature. The patient had persistent recurrent dyspnea for two years and was diagnosed with group D COPD managed using a combination of controller inhaler therapy consisting of ICS and a long-acting beta-adrenergic (LABA). The patient was reported to have no known cardiac or metabolic comorbidities such as diabetes mellitus, hypertension, and systemic diseases related to his condition. The patient is a passive smoker, worked as a farmer, and lived near the rice field potentially exposed to environmental pollutants and agricultural dust that may exacerbate her respiratory condition.

The patient's clinical condition was completely conscious, with vital signs indicating an increasing body temperature of 38.7°C, a heart rate of 114 beats per minute, a blood pressure of 132/72 mmHg, and a respiratory rate of 28 times per minute with pursed-lip breathing and peripheral oxygen saturation 90% without supplemental oxygen. The physical examination showed a sternocleidomastoid muscle involvement during the dyspnea without any sign of cyanosis. Thoracic examination revealed symmetrical lung expansion, Sonor percussion, wheezing auscultation in the bilateral lung, and crackles in the lower-middle part of the right chest. The heartbeat was regular, without abnormal heart sounds.

Peripheral blood examination results confirmed leukocytosis (15.300/µL), neutrophilia (82%), and hypereosinophilia (10%). The chest X-ray revealed inhomogenous consolidations in the middle and lower right lung (Figure 1), without signs of cardiac enlargement. There was no sign of abnormal cardiac rhythm from the electrocardiography. The patient was admitted with a working diagnosis of COPD exacerbation with hypereosinophilic features and community-acquired pneumonia.

Since the early hours in the emergency room, the patient had received supplemental oxygenation via a 3-liter nasal cannula, with peripheral oxygen saturation improvement to 95%. The preferred treatment for this patient's bronchospasm was nebulized ipratropium bromide and salbutamol. To treat the systemic inflammation caused by the COPD exacerbation, 30 mg of methylprednisolone was administered intravenously three times a day. The patient received intravenous antibiotics for the treatment of community-acquired pneumonia, using levofloxacin 1x750mg. Cetirizine 1x10mg per oral is given as an antihistamine to treat the allergy that may have caused eosinophilia.

Clinical improvements were monitored every 12 hours during the first 24 hours of admission and continued every 24 hours afterward. Because the infection had not been eradicated, the combination of inhalation

medicines was continued 24 hours after the bronchospasm stopped occurring. After three days of treatment, a follow-up test indicated considerable clinical improvement, as well as a reduction in leucocyte count to 10.430/µL and blood eosinophil count to 5%.

**Discussion**

Chronic Obstructive Pulmonary Disease is a heterogeneous pulmonary disorder defined by chronic respiratory symptoms (dyspnea, cough, and exacerbations) caused by abnormalities in the airways that result in progressive airflow obstruction. This condition developed involving small airway anomalies, emphysema, and systemic effects caused by inflammation.[8] The management of these issues, along with comorbidities such as pulmonary hypertension and metabolic disorders, is crucial, as they significantly affect the patient's prognosis. Some phenotypes exhibit distinct molecular and clinical characteristics that require specific treatments.[9]

According to multiple studies, neutrophilic inflammation is a prominent feature of COPD, with several inflammasomes involved including IL-1 and IL-18 that resulted from the formation of Th1-type cytokines. A smaller percentage of subjects had an eosinophilic phenotype, with type 2 innate lymphoid cells acting as inducers of eosinophilia via non-IL-5-dependent or IL-33 mechanism.[2] Eosinophils develop from progenitor cells and require specific cytokines and receptors for maturation in the bone marrow. Eosinophils enter the peripheral circulation, mediated by IL-5 and chemokines, and subsequently migrate to the airways, affecting the inflammation and immunoregulatory cells enter the airways.[10]

Eosinophil infiltration into the airway occurs when inflammatory signals activate adhesion molecules on the bronchial vascular endothelium and epithelium, allowing eosinophils to migrate into the airways. This chemokine-receptor interaction is essential for eosinophil recruitment, along with the chemoattractant receptor molecule expressed on T helper type 2 cells and prostaglandin D2 as a ligand, to induce airway inflammation. These cells contain a variety of preformed granules capable of up-regulating inflammation and causing injury to lung epithelium.[10]

Epidemiological studies indicate that circulating blood eosinophils are associated with various significant clinical outcomes. Normally, the percentage of eosinophils in the peripheral circulation ranges from 1% to 6%.[11] COPD with eosinophilic phenotype can be defined as having an eosinophil count of more than 2% of total cells or 150 cells/µl and is known to be beneficial with the treatment using an inhaled corticosteroid. One study stated that COPD with an eosinophilic phenotype defined as a peripheral blood eosinophil counts above 275 cells/µL, has been correlated to an elevated risk of all-cause mortality. Another study concluded that having a circulating eosinophil level above 340 cells/µL increased the probability of severe exacerbations due to bronchospasm and airway edema.[10]

Global Initiative for Chronic Obstructive Lung Disease (GOLD) established the blood eosinophil count as a biomarker to determine the efficacy of inhaled corticosteroids (ICS) in preventing exacerbations. GOLD suggests considering ICS treatment for COPD patients having recurrent exacerbation despite LAMA/LABA treatment (eosinophil count ≥100 cells/µL).[12] ICS combination treatment in recurrent exacerbations patients with more than 2% eosinophils showed a significant reduction compared to the lower eosinophil group. The INSPIRE and TRISTAN study comparing an ICS combination to a single non-ICS treatment in a high eosinophil group of patients showed a significant benefit in lowering exacerbations.[13]

Despite many favorable effects of ICS therapy in COPD with an eosinophilic phenotype, one adverse effect to consider is the development of pneumonia with extended treatment. The risk of pneumonia increased with the cumulative ICS dose. A study comparing ICS and non-ICS patients after a duration of treatment period discovered a risk of pneumonia. Daily ICS doses, defined as low, medium, and high, were identified as significant risk factors for pneumonia.[4] According to observational research, the risk of pneumonia increased upon increasing daily ICS doses. Given that the cumulative dose of ICS is another risk factor for pneumonia, ICSs should be withdrawn if pneumonia or a lack of treatment response is present. Study found that

following discontinuing ICS, the risk of pneumonia significantly declined to 50% during our months and subsequently disappeared after six months.[14]

The suggested mechanism for assessing the risk of pneumonia in COPD is caused by persistent bacterial colonization of the airways. Developments in molecular microbiology have revealed the existence of a normal pulmonary microbiota, and its displacement by other species may be harmful to host health. COPD patients have lung microbiome changes that may lead to persistent infection with potentially harmful microorganisms. Additionally, the use of ICS may affect the lung microbiota.[15] One potential reason for ICS's therapeutic impact in COPD is its inhibitory effect of nuclear factor kappa B (NF-ƙB), which may reduce normal host responses to bacterial infections. Previous use of ICS in patients hospitalized for CAP was related to a decreased systemic inflammatory response, as shown by lower levels of IL-6 and TNF-α. This low amount of pro-inflammatory cytokines leads to a considerable deterioration in the lung's protective mechanism against pathogens.[16]

**Conclusion**

ICS medication is recommended for COPD patients with eosinophilia ≥300 cells/µL or ≥100 cells/µL with a history of frequent exacerbations despite appropriate dual bronchodilator therapy (LAMA/LABA combination). Long-term use of ICS, particularly at high doses or when combined with LABA or LAMA in triple therapy, has been associated with an increased risk of pneumonia. The risks and benefits should be considered to achieve better control of the clinical improvement.

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