

Managing Acute Exacerbation of Chronic Obstructive Pulmonary Disease: What's New?

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third-leading cause of death worldwide causing a major health-care burden. With a global prevalence of 10.1%, it not only affects low/middle-income countries but also wealthy countries.^[1] COPD is a constellation of clinical entities such as chronic respiratory symptoms, structural pulmonary abnormalities, and airflow limitation, which is poorly reversible.^[2] A COPD exacerbation event can be defined as a worsening of respiratory symptoms that warrants additional therapy.^[3] Exacerbations are significant events in COPD management due to their negative impact on health status and disease progression. COPD can be categorized as “stable” when symptoms are well controlled with minimal pulmonary decline and “unstable” when there are frequent/severe exacerbations with a faster pulmonary decline.^[4] Acute exacerbation of COPD requiring hospitalization is associated with an increased 1-year mortality risk of at least 18%.^[5] This review will focus on the management of acute exacerbation of COPD, recent advances in management, and newer emerging therapies.

EXACERBATION AND ITS IMPACT

Exacerbations in COPD patients are associated with increased airway inflammation, increased mucus production, and increased gas trapping. These changes contribute to dyspnea, which is the predominant complaint of these patients. Numerous studies have documented the association between exacerbation history and future exacerbation events.^[6,7] The prevention of acute exacerbation plays a vital role in COPD management as it is associated with an increase in mortality.^[8] Many of these exacerbation events are not reported to the health-care personnel. Although some events are shorter in duration, their impact on health status is huge.

EXACERBATION-HOW TO APPROACH

Exacerbations are classified^[3] as:

- Mild – Treated with short-acting bronchodilators only
- Moderate – Treated with short-acting bronchodilators + antibiotics and/or oral corticosteroids
- Severe - Requiring hospitalization/visit to the emergency room.

Triggers for exacerbation mainly include respiratory viral infections, bacterial infections, and environmental factors such as pollution and ambient temperature. Sudden worsening of respiratory symptoms, hypoxemia, acute mental changes,

nonresponders to initial medical management, insufficient home support, and the presence of serious comorbidities are indications of hospitalization during an acute exacerbation episode. In COPD patients, other comorbidities which can worsen respiratory symptoms should also be ruled out, before labeling them as acute exacerbation, such as pulmonary embolism, pneumothorax, pulmonary edema due to cardiac causes, and pneumonia.

Pharmacological management

The cornerstone of treatment of an acute exacerbation event is the administration of short-acting inhaled beta-2 agonists with or without short-acting anticholinergics. The mode of delivery of these agents should be individualized to each patient, as studies demonstrate that there is no significant difference in benefit between metered dose inhalers and nebulizers.^[9] In cases where nebulizer is preferred, air-driven nebulization is more beneficial than oxygen-driven nebulization as PaCO₂ levels always increase with the latter one.^[10]

Systemic glucocorticoids shorten recovery time, improve forced expiratory volume in 1 s (FEV₁), improve oxygenation, and decrease the length of hospitalization.^[11,12] Treatment for 5 days with 40 mg of prednisone or its equivalent daily is equally effective as a 10-day course.^[13] Nebulized budesonide is also an alternative, which can be used comfortably in some patients. Recent studies demonstrate that corticosteroids may be ineffective in treating acute exacerbation in COPD patients for whom blood eosinophil count is lower,^[14,15] and thus, more steroid-sparing regimens are needed to treat them. Methylxanthines are not recommended in these patients due to their significant side effects, such as nausea, vomiting, frequent tremors, palpitations, and arrhythmias.^[16]

Antibiotics are beneficial in patients with purulent sputum and severe exacerbation requiring mechanical ventilation and duration of 5–14 days will suffice in most of the cases.^[13] Other adjunctive therapeutic measures include maintaining fluid balance, thromboembolism prophylaxis, ensuring adequate nutrition, and treatment of other comorbidities.

Respiratory support

Oxygen supplementation is crucial in patients with hypoxemia, and a target saturation of 88%–92% is accepted. The high-flow nasal cannula did not exhibit any benefit in these patients.^[17] Noninvasive ventilation (NIV) has been the preferred mode of ventilation to treat acute respiratory failure in these patients. NIV improves oxygenation, decreases tachypnea, decreases the work of breathing, and decreases mortality and intubation rates in these cases.^[18,19] Invasive ventilation is only used as a

rescue therapy in those who do not respond to NIV, patients in shock, and in those unable to protect the airway.

Long-acting beta2-agonists VS long-acting muscarinic antagonists

Ultra-long-acting beta2-agonists (LABAs) improve lung function, decrease symptoms, and help in preventing exacerbations.^[20,21] Many “once-daily dosing LABA” have been available over the past years and indacaterol, olodaterol and vilanterol are the newest drugs available. In symptomatic individuals, there is no significant difference between LABA and long-acting muscarinic antagonists (LAMA). Whereas in frequent exacerbators, LAMA is more effective than LABA.^[22,23]

Tiotropium was the only available LAMA worldwide, of which effectiveness is supported by a multitude of studies. Over the years, new drugs have emerged with efficacy being established by various trials such as aclidinium (ACCLAIM trial^[24] and ATTAIN trial).^[25] Similarly, umeclidinium also had promising results with increase in FEV₁, dyspnea, and quality of life scores.^[26] Another promising agent was glycopyrronium, of which efficacy was established by the GEM study.^[27]

LONG-ACTING BETA2-AGONISTS LONG-ACTING MUSCARINIC ANTAGONISTS

Aclidinium + formoterol combination helped in reducing exacerbations, as demonstrated by AUGMENT and ACLIFORM studies.^[28] Umeclidinium + vilanterol combination also had a favorable outcome in some studies.^[29,30] Similarly, glycopyrronium/indacaterol reduced the rate of mild-to-severe COPD exacerbations compared to fluticasone/salmeterol.^[31] Recent studies suggest that single-inhaler triple therapy (LABA + LAMA + inhaled corticosteroids [ICS]) provides a significant symptom relief and decreased rate of exacerbation compared to single-inhaler separate therapy.^[32,33]

THE “GOLD” GUIDELINES

The global initiative for chronic obstructive lung disease suggests the flowchart [Figure 1] for the management of exacerbation in COPD.^[34] The withdrawal of inhaled corticosteroids (ICS) is recommended in cases where eosinophil counts are less than 100, there is a poor response and occurrence of pneumonia. Roflumilast (PDE4 inhibitor) can be added in patients with FEV₁ <50% and chronic bronchitis.^[35,36] Adding a macrolide antibiotic like azithromycin to the treatment can decrease the rate of exacerbations in a year and improve the quality of life in patients, especially who are not current smokers.^[37]

PREVENTION AND FOLLOW-UP

After an episode of exacerbation, measures should be taken for the prevention of further episodes. Smoking cessation, rehabilitation, Vitamin D supplementation, and shielding

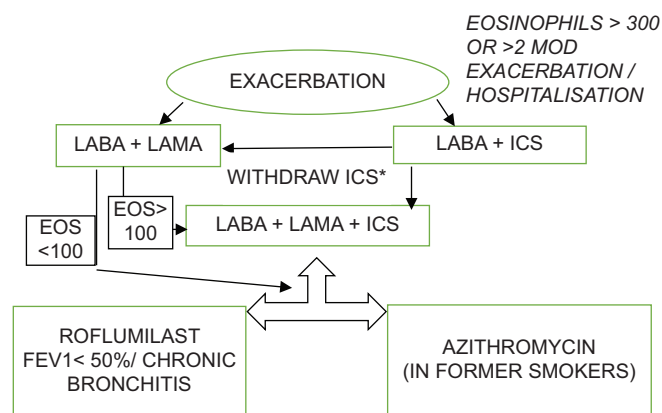


Figure 1: *Withdraw ICS: Pneumonia, lack of response. ICS: Inhaled corticosteroids. The Global Initiative for Chronic Obstructive Lung Disease Guidelines on exacerbation management

measures (masks, social distancing and frequent hand washing) are some of the methods which can prevent further exacerbation episodes.^[34]

At the time of discharge, ensure adequate patient education, optimize medication, correct technique of using inhalers, optimize other comorbidities, and continue patient contact. Early follow-up (within 4 weeks) is associated with less exacerbation-related readmissions.^[38] Additional follow-up at 12 weeks to review patient’s lung function, assessment of long-term oxygen therapy, the status of other comorbidities, and prognostication is recommended.^[34]

EMERGING THERAPIES

Lung volume reduction surgeries are the only surgical option available for patients with severe emphysema. Recent years saw the development of novel bronchoscopic interventions to treat severe emphysema, such as coils and endobronchial valves. The REVOLENS^[39] and RENEW^[40] randomized controlled trials evaluated the effect of bronchoscopic lung volume reduction in severe emphysema patients; however, further studies are required in this to establish a definitive clinical role. Bronchoscopic lung volume reduction with the use of one-way endobronchial valves is another potential treatment for patients with severe emphysema with modest results, but it needs further studies in the future.^[41]

CONCLUSION

COPD exacerbations, particularly those that require hospitalization, lead to substantial financial burden. Patients who are frequent exacerbators have decreased quality of life and quick disease progression. Appropriate therapy with maintenance bronchodilators has been shown to reduce exacerbation frequency but is underused, highlighting a need for increased awareness of treatment recommendations among treating patients, physicians, and health-care organizations. Emerging evidence of LAMA + LABA therapy, single inhaler with dual/triple medication, and withdrawal of ICS is showing

promising results in managing acute exacerbations. Proper patient education, appropriate training to use inhalers, and pulmonary rehabilitation improve patients' quality of life of those with frequent exacerbation.

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