

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a leading cause of disability and death. Prevalence rates are related to tobacco smoking and indoor air pollution, and are expected to rise as smoking rates continue to increase among women and in developing countries. By 2030, COPD is expected to represent the third leading cause of death. Caring for patients with advanced disease who experience frequent exacerbations places a significant burden on health care resources. Evidence on the natural history of COPD demonstrates early institution of long acting bronchodilator therapy slows the rate of lung function decline and reduces frequency of exacerbations that can lead to further functional decline. The goals of therapy are symptom control, reduce exacerbations, and maintain quality of life. Smoking cessation, pharmacotherapy with long acting bronchodilators, inhaled corticosteroids, pulmonary rehabilitation, and palliative care are important components. This review highlights current guidelines and management strategies for COPD.

Keywords:

Symptom control, Reduce exacerbations, Lung volume reduction surgery, Triple therapy, Lung function decline, Endobronchial valve

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INTRODUCTION

COPD is characterised by airflow limitation and inflammation, resulting in progressive decline in respiratory function and quality of life (QoL). COPD affects proximal and peripheral airways, lung parenchyma and pulmonary vasculature.¹ It is punctuated by exacerbations that can be life-threatening and associated with worsening lung function, increased mortality and resource utilisation.^{2, 3} Comorbidity such as cardiovascular disease, diabetes mellitus and depression as well as weight loss and muscle dysfunction from inactivity and deconditioning add considerably to the overall burden of disease.⁴ COPD is preventable and treatable, however, despite its high prevalence and significant burden, it remains substantially underdiagnosed and undertreated. Undiagnosed early-stage patients if symptomatic are more likely to progress to a more severe form of COPD.⁵ Reports highlight gaps between guideline-recommended, actual treatment and follow-up care of COPD patients.⁶

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LUNG FUNCTION DECLINE

The progressive deterioration in COPD has traditionally been illustrated by the Fletcher-Peto curves which suggest smooth continuous accelerated decay in lung function over time.⁷ Such a gradual decay in forced expiratory volume in 1 s (FEV₁) implies that exacerbations do not alter this natural history. Results from Framingham cohort⁸ however demonstrate that annual FEV₁ decline rates are greater during the earlier disease stages, and symptomatic patients represent a susceptible group for progressive lung function decline, thereby reinforcing current thinking that multidimensional influences impact COPD progression and early diagnosis and intervention are critical. Exacerbation frequency also exerts a negative impact on lung function decline. Among a cohort of 109 COPD patients, frequent exacerbators show faster decline in FEV₁ (-40.1 mL/year) and peak expiratory flow (-2.9 L/min/year) compared with infrequent exacerbators (-32.1 mL/year and -0.7 L/min/year respectively).⁹

ROLE OF EXACERBATIONS

Exacerbation-prone individuals are negatively affected by decreased quality of life, increased hospitalisation, and premature deaths. Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) initiative suggests that there is a frequent-exacerbation phenotype independent of disease severity. History of exacerbations is the single best predictor of future exacerbations,¹⁰ duration of exacerbation may be variable, its impact on COPD prolonged or permanent, and patients experiencing acute exacerbations remain at increased risk for subsequent exacerbations during the 8-week recovery period.¹¹ Besides impact on societal health is the staggering cost of treating acute exacerbations if severe and warrant hospitalisation. Notably, the total cost of caring for COPD in the United States is rapidly approaching US\$50 billion per year, and 70% relates to treating exacerbations.¹²

CURRENT APPROACH TO COPD MANAGEMENT**Pharmacological Interventions**

GOLD guidelines aim to increase awareness of COPD and to advise on management which is patient centered and step-wise depending on disease severity (Figure 1).¹ However GOLD guidelines are poorly implemented in both primary and secondary care settings¹³ as diagnosis is hampered by limited use of spirometry at the primary care level due to lack of access, cost, inaccurate interpretation of results and inadequately trained staff. In fact a recent study reported that only 30% of patients were diagnosed by spirometry,¹⁴ and drugs prescribed were not in accordance with recommendations based on severity.¹⁵

FIGURE 1. CURRENT APPROACH TO COPD ACCORDING TO DISEASE SEVERITY

I: Mild	II: Moderate	III: Severe	IV: Very severe
FEV ₁ /FVC <0.70 FEV ₁ ≥80% predicted	FEV ₁ /FVC <0.70 50% ≤FEV ₁ <80% predicted	FEV ₁ /FVC <0.70 30% ≤FEV ₁ <50% predicted	FEV ₁ /FVC <0.70 FEV ₁ <30% predicted, or FEV ₁ <50% predicted plus chronic respiratory failure
Active reduction of risk factor(s): influenza, pneumococcal vaccination Add short-acting bronchodilator (when needed)			
		Add regular treatment with one or more long-acting bronchodilators (when needed); add rehabilitation	
		Add inhaled glucocorticosteroids if repeated exacerbations	
		Add long-term oxygen if chronic respiratory failure. Consider surgical treatment	

Short-acting bronchodilators (SABAs) can be used to relieve intermittent symptoms on top of maintenance therapy which comprises of medications administered regularly to improve symptoms not controlled by SABAs. These include long-acting antimuscarinic antagonist (LAMA), long-acting β₂ agonist (LABA), LABA-inhaled corticosteroid (ICS) combinations, and methylxanthines (e.g., theophylline). Twice daily LABA (salmeterol, formoterol) and once daily LAMA (tiotropium) are preferred drugs for maintenance treatment with bronchodilation achieved through different mechanisms.¹ Which agent to use first has not been evaluated but tiotropium has been shown to provide better bronchodilation and clinical outcomes than the twice-daily LABA.¹⁶ Initial treatment with LAMA is sensible since there is heightened cholinergic airway tone in COPD.¹⁷ LABA can be added to initiate an alternative pathway of bronchodilation without increased side effects.¹⁸ ICS is not recommended as monotherapy but its combination with LABA leads to reduced exacerbation frequency in patients with moderate to severe COPD, and those with history of exacerbations.¹⁹ Some ICS such as fluticasone are more likely to be associated with pneumonia than others (budesonide).¹⁸

“Triple therapy” (LAMA, LABA-ICS) may achieve better symptom control and quality of life in patients with severe COPD, improve lung function and reduce exacerbations however cost constraints may limit its use.²⁰ Methylxanthine (theophylline) is reserved as third-line option due to side effect profile, and only recommended for very severe disease.¹ At low doses they may enhance the anti-inflammatory effects of

corticosteroids and useful in combination regimens.²¹ Long-term oral glucocorticosteroid therapy is not recommended but may be necessary to treat exacerbations in patients with severe COPD.

Patients with viscous sputum may benefit from mucolytic therapy although routine use is not recommended. Other chronic therapies, such as antioxidants, carbocysteine, N-acetylcysteine, may reduce COPD exacerbations but evidence is conflicting.²² For inhaled drugs, inspiratory flow rate is important especially in patients with severe disease. Technique, delivery systems as well as patient adherence should be checked regularly since adherence declines over time contributed in part by the inhaler device.

Non-pharmacological Interventions

Optimal COPD management plans integrate both pharmacologic and non-pharmacologic interventions that include education, smoking cessation, oxygen therapy, exercise, vaccination, pulmonary rehabilitation and management of endocrine and cardiovascular diseases.²³ Pulmonary rehabilitation should be considered for all patients with COPD to overcome exercise deconditioning, muscle wasting, weight loss, social isolation and depression not adequately addressed by pharmacologic interventions as well as reduce recurrent exacerbations.

In a multicenter study, patients managed with tiotropium plus pulmonary rehabilitation experienced fewer exacerbations and

exacerbation days, and improvements in health-related QOL, relative to the tiotropium-only group.²⁴ Influenza and pneumococcal vaccinations should be recommended to all COPD patients as important risk reduction strategy.¹

Lung Volume Reduction

Lung-volume-reduction surgery (LVRS) was initially proposed as a palliative treatment for those with severe emphysema. The National Emphysema Treatment Trial (NETT) found a survival advantage among former smokers with upper lobe predominant emphysema and low baseline exercise capacity. Exercise capacity was improved by 10W in 28, 22, and 15% of LVRS patients at 6-, 12-, and 24-month follow-up versus 4%, 5%, and 3% of patients in the medical therapy group. The LVRS group also showed improved 6-minute walk distance, FEV₁% predicted, level of dyspnoea, and disease-specific and general quality of life (QOL) scores.

However overall mortality within 90 days was 7.9% (95% CI, 5.9–10.3) in the surgery group compared with 1.3% (95% CI, 0.6–2.6) in the medical therapy group (P < .001). A predictor of mortality was non upper lobe predominant emphysema. Morbidity was also higher among older patients, those with low FEV₁ (<20%) and DLCO (<20%). Post-operative complication rate within 30 days was 58.7% with arrhythmias, pneumonias, reintubations and persistent air leaks accounting for the majority. About 28% of patients remained in hospital, nursing home or rehabilitation facility for a month after LVRS.²⁵ LVRS may be beneficial for a subgroup of patients with severe COPD, but its risks outweigh the benefits and use of endobronchial blockers, bypass methods, valves and sealants have been attempted.²⁶

We reviewed endobronchial valve as it is available in Singapore. The intrabronchial valve (IBV, Spiration, Inc, Redmond, Washington, USA) and Zephyr endobronchial valve (EBV, Pulmonx, Inc, Palo Alto, California, USA) are one-way valves that limit air flow to the target lobe during inspiration but allow air to escape during expiration. In a multicenter trial of 91 patients with heterogeneous emphysema underwent bilateral IBV therapy. One patient died of tension pneumothorax, another had non-fatal myocardial infarction, 8 developed pneumothoraces, and 7 bronchospasm. Removal of IBV was necessary in 16 patients due to unresolving pneumonia, persistent bronchospasm and air-leak. FEV₁, 6 minute walk test and total lung volume did not change but better health-related QOL scores which could be explained by reduction of lung volume (without atelectasis) on CT, and better ventilation-perfusion matching.²⁷

A prospective, multicenter trial where 220 were randomised to EBV and 101 to medical therapy, all underwent pulmonary rehabilitation, high resolution CT (HRCT) used to score disease severity and interlobar fissure integrity before target lobe selection. Differences between 2 groups favouring EBV were 6.8% increase in FEV₁ and 5.8% in 6 minute walk test. These improvements were more marked in those with higher HRCT heterogeneity scores (>15% between targeted and adjacent

lobes) and presence of complete fissures. Lobar atelectasis was observed in less than 25% of patients undergoing EBV, but highly desirable as it led to physiologic improvements akin to LVRS.

Lobar occlusion and atelectasis is emerging as an important predictor of good outcome, which in turn depends on the presence of complete fissure on HRCT.²⁸ Collateral ventilation to the target lobe can be measured by a balloon catheter (Chartis System, Pulmonx, Inc, Palo Alto, California, USA) inserted through 2.8mm working channel of a flexible bronchoscope. The balloon is first inflated to seal the airway. This prevents air from entering the target lobe but allows air to escape through the central lumen of the catheter. Airflow resistance is calculated and represented in a graphic format. Higher values were found to correlate with lobar atelectasis with EBV. This device appears to be the only sensitive method of measuring collateral ventilation that is currently available.²⁹

NEW AND EMERGING DRUGS FOR MAINTENANCE THERAPY

New respiratory medications focus on once-daily agents as monotherapy or in combination. These include indacaterol (once daily LABA), and roflumilast (selective once-daily oral phosphodiesterase (PDE)-4 inhibitor).³⁰

CONCLUSION

To date only smoking cessation and oxygen therapy have been shown to alter the clinical course of COPD although improvements in dyspnoea and exercise capacity as well as reductions in recurrent exacerbations can be achieved through pulmonary rehabilitation. Identification of early-stage patients is crucial since emerging evidence supports early administration of pharmacotherapies which aim at slowing down lung function decline and reducing risk of acute exacerbations. Early recognition requires heightened COPD awareness among both patients and physicians, and proper use of spirometry. By helping to prevent, recognise, and appropriately treat acute exacerbations, clinicians can make a major impact on the course of COPD.

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LEARNING POINTS

- **The goals of therapy are symptom control, reduce exacerbations, and maintain quality of life. Smoking cessation, pharmacotherapy with long acting bronchodilators, inhaled corticosteroids, pulmonary rehabilitation, and palliative care are important components.**
- **To date only smoking cessation and oxygen therapy have been shown to alter the clinical course of COPD although improvements in dyspnoea and exercise capacity as well as reductions in recurrent exacerbations can be achieved through pulmonary rehabilitation.**
- **Identification of early-stage patients is crucial since emerging evidence supports early administration of pharmacotherapies which aim at slowing down lung function decline and reducing risk of acute exacerbations.**
- **Early recognition requires heightened COPD awareness among both patients and physicians, and proper use of spirometry.**
- **By helping to prevent, recognise, and appropriately treat acute exacerbations, clinicians can make a major impact on the course of COPD.**