Chronic obstructive pulmonary disease and respiratory failure

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Abstract

Chronic obstructive pulmonary disease is a current problem for elderly patients due to diffusion, mortality, and other negative outcomes. The most complex management aspects consist of the presence of frailty, which increases the risk of complications and adverse drug events and reduces the effectiveness of treatments. In this context, to determine the best individualized treatment, it is crucial to have an excellent understanding of the medical and non-medical treatments available, the use of ventilation systems, combined with in-depth geriatric knowledge.

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Introduction

Chronic obstructive pulmonary disease: definition and mechanisms

Chronic obstructive pulmonary disease (COPD) is a common disease among elderly patients. It is characterized by high mortality, healthcare utilization, and the unmet needs of both patients and their caregivers.[1] The global initiative on obstructive lung disease (GOLD) recommends the use of a fixed ratio [the ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (<0.7)] together with exposure to noxious fumes or gases and respiratory symptoms (Figure 1). Healthy elderly people might meet the GOLD definition of airflow obstruction but not necessarily COPD due to the absence of exposure to noxious fumes or gases and respiratory symptoms.[2] The specific molecular mechanisms and functional relationship of aging in the occurrence and development of chronic obstructive pulmonary disease, or pulmonary fibrosis, are not completely clear.[3]

In older frail patients, functional and cognitive decline complicates the success of specific treatments. For example, COPD is highly prevalent in association with chronic heart failure. Appropriate decision-making must consider comorbidities, find trade-offs between desired outcomes, and the increased risk of adverse events. In this context, it is important to focus on symptom relief and function and prepare the patients and their caregivers for further declines until their end-of-life stage. Guidelines are limited when applied to older patients with dyspnea and respiratory failure for several reasons. Firstly, both acute respiratory failure episodes and chronic dyspnea are multifactorial. Secondly, guidelines may not address all the previously described patient needs resulting from frailty. Moreover, although most guidelines recognize the importance of comorbidities, they often do not account for the negative consequences of polypharmacy.[1-5] Furthermore, some specific factors, common in frail older patients, contribute to both dyspnea and respiratory failure, reducing ventilatory capacity, such as respiratory muscle weakness caused by sarcopenia,[6] or the utilization of medications like opiates and benzodiazepines. The utilization of corticosteroids can also influence chest wall configuration, reducing breathing efficiency.[7,8]

At the same time, dyspnea can also be determined by an increased ventilatory demand. Older individuals are burdened by

several common impairments that reduce aerobic capacity.[7-10] Studies have demonstrated that a higher blood eosinophil (EOS) count is a risk factor connected with the frequency and severity of COPD. In patients with stable COPD, it is associated with an increased risk of severe acute exacerbations of COPD (AECOPD).[11]

Medical treatment

Patients with high eosinophilic exacerbations were observed to respond better to inhaled corticosteroids (ICS) than patients with non-high eosinophilic exacerbations. ICS combined with long-acting β2-agonists (LABA) is already recommended for AECOPD treatment if EOS is ≥300 cells/μL. Low EOS was an independent risk factor for noninvasive mechanical ventilation treatment in AECOPD. Infections, especially viral ones, are the most common cause of AECOPD, and the low-eosinophilic group is more predisposed to having a clinical diagnosis of pulmonary infection than the non-low-eosinophilic group. The dyspnoea, eosinopenia, consolidation, acidemia, and atrial fibrillation score, including "eosinopenia," was designed to identify those with a higher risk of hospital mortality in exacerbations of COPD. AECOPD patients could benefit from appropriate antibiotic and systemic corticosteroid therapy. In the first 72 hours of care, corticosteroids significantly improve dyspnea, lung function, and ventilation-perfusion mismatch compared with placebo. However, recent studies reported that patients with low EOS did not respond to systemic corticosteroids as well as patients with non-low EOS. Interleukin-6 levels were lower in patients with low EOS than in patients with non-low EOS.[10,12]

COPD guidelines summarize the evidence supporting the use of inhaled β-agonist and anticholinergic agents and, for patients with severe COPD, inhaled corticosteroids and phosphodiesterase-4 inhibitors. Bronchodilators are essential for the treatment of COPD because they improve bronchial obstruction and airflow limitation, reduce hyperinflation, and improve exercise tolerance. For this reason, they are recommended by current national and international guidelines as the first line of therapy for all degrees of severity. The inhalation route is the first choice (evidence A), with inhaled short- and long-acting β2-agonists (SABA and LABA) and inhaled short- and long-acting muscarinic antagonists (SAMA and LAMA) preferable to bronchodilators with short duration of action in COPD patients presenting with dyspnea (evidence A). Patients presenting with dyspnea with a single bronchodilator should subsequently be treated with 2 bronchodilators that act by different mechanisms (evidence A). COPD-directed treatments are most effective earlier in the course of the disease. In group D (high risk, more symptoms), initial therapy can be a LAMA because it is effective for dyspnea and exacerbations, and patients with consistent symptoms (COPD assessment test ≥20) can be treated with a combination of LABA/LAMA. In some patients, ICS/LABA or ICS therapy may be the first choice; this treatment has the highest probability of reducing exacerbations when the EOS count is ≥300 cells/μL (Figures 1 and 2).[11]

However, among older comorbid patients, it is necessary to have more vigilant monitoring for adverse effects of these agents than what is indicated in the guidelines. While a pooled analysis of several trials reported increased risks for cardiovascular events and mortality with the use of inhaled anticholinergics, a large randomized controlled trial that did not demonstrate this association excluded patients with previous myocardial infarction, heart failure, or preexisting arrhythmias.[13] There are no studies among patients with COPD examining the representativeness of old frail patients in clinical trials. Studies of inhaled b-adrenergics showed increases in urinary retention associated with inhaled anticholinergics and a greater risk for mortality and heart failure exacerbation among COPD and heart failure patients.[14]

Breathlessness is a nearly universal symptom of advanced COPD, occurring in 90-95% of individuals. Other common symptoms include pain (34-77%), fatigue (68-80%), insomnia (55-65%), and anorexia (35-67%). Patients with advanced lung disease require symptom-directed palliative care coordinated with their COPD-directed treatment. The evidence base regarding the treatment of symptoms is more limited than that for COPD-directed pharmacologic treatments. Several treatment approaches for symptom control, including opioids for refractory dyspnea, are generally safe, adequately researched, and increasingly accepted and recommended in COPD patients. Opioids are essential for refractory

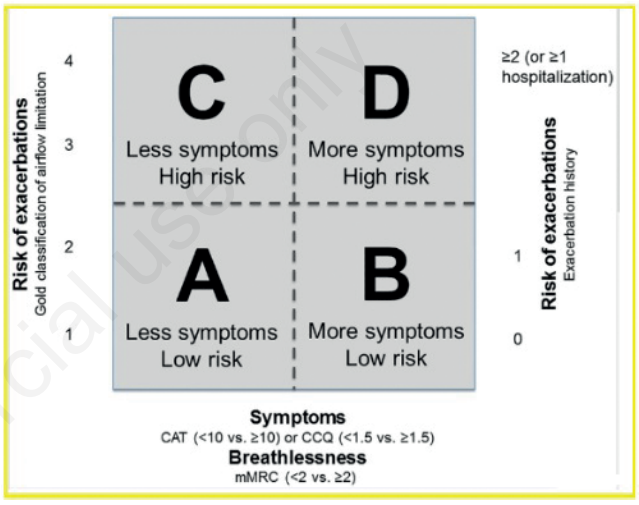

Figure 1. The new global initiative on obstructive lung disease assessment for classification. CAT, chronic obstructive pulmonary disease assessment test; CCQ, clinical chronic obstructive pulmonary disease questionnaire; mMRC, modified medical research council.

Patient	First choice	Second choice	Alternative Choices
A	SAMA prn *or* SABA prn	LAMA *or* LABA *or* SABA and SAMA	Theophylline
B	LAMA *or* LABA	LAMA and LABA	SABA *and/or* SAMA Theophylline
C	ICS + LABA *or* LAMA	LAMA and LABA	PDE4-inh. SABA and/*or* SAMA Theophylline
D	ICS + LABA *or* LAMA	ICS and LAMA *or* ICS + LABA and LAMA *or* ICS+LABA and PDE4-inh. *or* LAMA and LABA *or* LAMA and PDE4-inh.	Carbocysteine SABA and/*or* SAMA Theophylline

Figure 2. Therapeutic procedures according to clinical features. SAMA, short-acting muscarinic antagonists; SABA, short-acting β2-agonists; LAMA, long-acting muscarinic antagonists; LABA, long-acting β2-agonists; ICS, inhaled corticosteroids; PDE4-inh, phosphodiesterase-4 inhibitor.

dyspnea but may cause bothersome side effects, including constipation, urinary retention, and confusion. Benzodiazepines are considered third-line (after opioids and oxygen), primarily useful for dyspnea-related anxiety, and carry significant risks for elderly patients.[15]

ICS/LABA is recommended as the first-line treatment choice in patients with asthma-COPD overlap. Adverse effects, including candidiasis, cataract, glaucoma, diabetes, bone fracture, and pneumonia, have been associated with high-dose ICS and have raised concerns, particularly in elderly patients. In addition, an increased risk of lower respiratory tract infection associated with the use of ICS has also been reported in patients with bronchial asthma. Studies have demonstrated a reduced incidence of rehospitalization for COPD exacerbation or death in hospitalized elderly patients with COPD exacerbation following ICS withdrawal, using propensity score analyses. ICS withdrawal was also significantly associated with a decreased frequency of antimicrobial prescriptions in the outpatient setting after discharge, but not with the frequency of systemic corticosteroid prescriptions. Withdrawal of ICSs in elderly patients with COPD did not increase the risk of re-exacerbation requiring hospitalization or corticosteroids in the outpatient setting. ICS increases the risk of lower respiratory tract infection, including pneumonia, in patients with COPD. ICS withdrawal is safe for elderly patients with COPD who are hospitalized for exacerbations. Further studies are needed to specify the patient population among elderly patients with COPD who may benefit from ICS discontinuation.[16]

Triple therapy, combining the 3 inhaler classes, is now prevalent in the management of COPD, including its use as the initial treatment. The triple therapy in obstructive lung disease trials reported significant hazard ratios of all-cause mortality over 1 year of 0.72 [95% confidence interval (CI) 0.53-0.99] and 0.51 (95% CI 0.33-0.80), respectively, comparing triple therapy with its dual bronchodilator formulation.[17]

Budesonide is a steroid with high efficiency and a local anti-inflammatory effect that can enhance the stability of endothelial cells, smooth muscle cells, and lysosomal membrane, reduce the release and activity of allergic active mediators such as histamine, reduce the enzymatic process stimulated by antigen-antibody binding, inhibit the synthesis and release of bronchoconstrictor substances, and reduce the contraction reaction of smooth muscle. Clinically, it is used in patients with glucocorticoid-dependent or independent bronchial asthma and asthmatic chronic bronchitis. Glycopyrronium bromide is a long-acting quaternary ammonium muscarinic receptor antagonist. Its selectivity for the human M3 receptor is more than 4 times that for the human M2 receptor. Its most common adverse reaction is dry mouth, but in most cases, it is mild. Formoterol fumarate is a bronchodilator that can effectively relax the airway smooth muscle, relieve airway obstruction, and quickly improve symptoms such as dyspnea. Relevant studies have pointed out that the combination of formoterol fumarate and tiotropium bromide can further enhance the therapeutic effect of COPD and accelerate the improvement of pulmonary function.[16]

Non-medical treatment

Along with therapeutic measures, preventive and behavioral measures are also important. Pulmonary rehabilitation, including exercise, education, breathing techniques (pursed-lipped), and psychological support, may also provide social support important to elderly patients.[18] Supplementation of oxygen is connected with benefits only for patients with hypoxia [partial pressure of oxygen (PaO2)<55 mm Hg].[19] Cigarette cessation has good evidence for symptomatic improvement, but the benefits of reducing dyspnea may be delayed by a number of weeks.[20] Influenza and pneumococcal vaccines may be useful for older patients with COPD by preventing infections and COPD exacerbations. Prophylactic antibiotics have more limited supporting evidence. However, antibiotics to treat infections causing COPD exacerbations are effective.[21]

COPD is associated with a range of extrapulmonary complications, including cardiovascular morbidity, osteoporosis, and muscle weakness, all of which may contribute to frailty. The frailty phenotype, but not the frailty index, was associated with a lower percent-predicted FEV1. Both frailty definitions were associated with higher all-cause mortality, major adverse cardiovascular events, hospitalizations, and both hospitalized and community COPD exacerbations. The relationship with each of these adverse outcomes was independent of the degree of airflow limitation. The severity of COPD is best characterized by a multidimensional assessment reflecting these broad impacts. For example, the body-mass index, airflow obstruction, dyspnea, and exercise index comprise 4 domains (body mass index, FEV1, dyspnea assessed using the modified medical research council scale, and exercise capacity based on the 6-minute walking distance).[22]

Exacerbations of chronic obstructive pulmonary disease

COPD is a progressive disease characterized by exacerbations, which are acute worsening of respiratory symptoms that may lead to hospitalization. Additionally, patients with stable COPD often experience AECOPD due to risk factors, comorbidities, poor treatment adherence, and insufficient treatment. Frequent exacerbations, defined as at least 2 episodes per year, are considered a marker of increased burden and reduced survival in clinical epidemiology studies. Our findings also indicate a significant relationship between age and exacerbation (raw data $p<0.0001$). Among those with exacerbations, 47% are aged 65-75 years, 40% are aged 75-85 years, and approximately 14% are 85 years of age or older. In our study, the age of patients in the exacerbation group was higher than that in the group without exacerbation: 75 years old *versus* 74 years old (raw data $p<0.0001$). Low income in the local area was an important determinant of exacerbations among patients with COPD aged 65+ and can be explained by a number of other cofactors, such as more severe COPD, comorbidities, less inclination to use regular inhalers/medications, less healthy lifestyle, or poor living conditions.[23] Treatment with long-acting bronchodilators is also effective for preventing COPD exacerbations, which represent acute worsening in patients with COPD. Prevention of COPD exacerbations may, in turn, improve the prognosis of patients with COPD.[13]

COPD may lead to gas exchange abnormalities, including hypercapnia. Chronic hypercapnia is an independent risk factor for mortality in COPD, leading to epithelial dysfunction and impaired lung immunity. Moreover, chronic hypercapnia affects cardiovascular physiology, increases the risk of cardiovascular morbidity and mortality, and promotes muscle wasting and musculoskeletal abnormalities. The presence of alveolar hypoventilation, and thus the development of consequential hypercapnia, is more common in severe forms of COPD, although hypercapnia is present even in moderate disease in a proportion of patients. The prevalence of hypercapnia is around 30-50% in patients with very severe COPD (predicted FEV1). Hypercapnia causes alveolar epithelial dysfunction, resulting in alveolar edema formation

and further deterioration in gas exchange. Moreover, the repair mechanisms of the airway epithelial cells are also damaged, as hypercapnia causes mitochondrial dysfunction and impaired cell proliferation. Overall, chronic hypercapnia is an independent risk factor for hospitalizations and mortality in COPD and has thus attracted attention as a possible treatable trait. Correction of hypoventilation and acute respiratory acidosis using noninvasive ventilation (NIV) is a widely used and evidence-based treatment for acute hypercapnic respiratory failure. Alterations in the ventilation-perfusion (V/Q) ratio represent one of the first and main mechanisms that occur during COPD exacerbation and lead to the development of hypercapnic respiratory failure. Many regions of the parenchyma are perfused but not ventilated due to the presence of bronchospasm, edema, and secretions, which increase dead space ventilation. Additionally, there is an increase in respiratory and muscular work, resulting in a consequent rise in oxygen demand. Hypercapnic respiratory failure during COPD exacerbation is mainly linked to alterations in V/Q due to remodeling of the airways, bronchospasm, and hypersecretions. During exacerbations, the resistance of the airways, and therefore the flow restriction, increases due to bronchoconstriction, edema of the walls, and the accumulation of bronchial secretions. This is superimposed on hyperactivation of the respiratory neural drive with a rapid, shallow breathing pattern and consequent lengthening of the time constant and air entrapment. These elements cause a progressive vicious circle underlying dyspnea, a key symptom of COPD exacerbations. NIV is the recommended initial therapy for acute hypercapnic respiratory failure during an acute exacerbation of COPD.[24]

Ventilation management

Mechanical ventilation is an effective means of treating respiratory failure and has a significant effect on the treatment of patients with COPD and respiratory failure. Elderly patients undergoing mechanical ventilation may experience a series of psychological reactions, leading to changes in cognitive function and delirium in the intensive care unit. Once delirium occurs, patients may experience prolonged hospital stays, difficulty in weaning off mechanical ventilation, cognitive dysfunction, increased mortality, and other complications. The prevention and early nursing care of delirium are vital to the prognosis of respiratory failure patients undergoing mechanical ventilation. Currently, the risk factors for delirium in elderly patients with COPD combined with respiratory failure undergoing mechanical ventilation remain unclear. In this setting, a recent retrospective study analyzing 231 old patients admitted with acute respiratory failure underlined the importance of frailty measured by the multidimensional prognostic index (MPI) to early detect patients more at risk of in-hospital death and NIV failure.[25] Furthermore, a recent European paper observing 502 older patients hospitalized for COVID-19 infection demonstrated the utility of MPI for individualizing older people hospitalized with COVID-19 benefiting from mechanical ventilation.[26] For patients aged 75 years or older, with COPD, undergoing mechanical ventilation for respiratory failure, the presence of BMI ≤19 kg/m2, hypertension, APACHE II score ≥15, Critical-Care Pain Observation Tool (CPOT) score ≥5, sedation, and PaO2 ≤75 mmHg, increases the risk of delirium. Under the stimulation of mechanical ventilation, a stronger and longer-lasting inflammatory response can occur, leading to abnormalities in neurotransmitters in the brain and damage to the blood-brain barrier, thereby contributing to the occurrence of delirium.

High-flow oxygen therapy *versus* noninvasive ventilation

Definition of high-flow nasal cannula

High-flow nasal cannula (HFNC) is used during early noninvasive management of acute respiratory failure (ARF), alongside conventional oxygen therapy (COT), and NIV. Its benefits are both clinical (*e.g.*, better patient comfort and ease of use compared to COT and NIV) and physiological (*e.g.*, high oxygenation, alveolar recruitment, humidification and heating, increased secretion clearance, reduction of dead space). So, it can prevent lung function deterioration and endotracheal intubation. Conversely, its ability to unload respiratory muscles in ARF is lower than that in NIV. However, there is limited evidence on the most appropriate instrument in the different scenarios. Moreover, prolonging noninvasive respiratory support in patients failing with either HFNC and NIV may result in delayed intubation and worsen hospital mortality.[27]

High-flow nasal cannula for hypoxemic acute respiratory failure

Acute hypoxemic respiratory failure (AHRF) is caused by a wide range of etiologies, including pulmonary infection, inflammation, or exacerbation of chronic heart or lung disease. The clinical spectrum of AHRF ranges from mild hypoxemia to full-blown acute respiratory distress syndrome. Noninvasive respiratory support aims to improve hypoxemia, reduce the work of breathing, enhance comfort, avoid intubation, and provide time to effectively treat the underlying condition, thereby reducing mortality. Unfortunately, many patients with AHRF require escalation to invasive mechanical ventilation (IMV). The most common noninvasive respiratory treatment in AHRF is COT, which increases the fraction of inspired oxygen (FiO2) using simple interfaces such as nasal prongs, face masks with reservoirs, or Venturi mask. Potential mechanisms of COT failure include ineffective support that does not match the patient's ventilatory needs due to altered respiratory mechanics, unreliable FiO2 delivery, lack of humidification, and patient self-inflicted lung injury. HFNC is a noninvasive, high-concentration oxygen delivery interface that addresses some of the limitations of COT. By providing airflows as high as 50-60 L/min, HFNC closely matches the inspiratory demands of dyspneic patients with AHRF and reliably achieves an FiO2 as high as 100%, while also providing a low level of positive end-expiratory pressure in the upper airways, facilitating alveolar recruitment. Other potential benefits of HFNC over COT include a decreased risk of patient self-inflicted lung injury, avoiding harmful changes in transpulmonary pressure, carbon dioxide washout from the upper airways, improved ventilation, and reliable humidification, which may result in increased patient comfort and enhanced secretion clearance. The flow was set in a range between 35 and 60 L/min and titrated as tolerated by the patients. The temperature was set at 34°C or 37°C according to the patient's preference, while FiO2 was adjusted to achieve arterial oxygen saturation measured by pulse oximetry between 88 and 92%.[28]

Acute exacerbations of COPD are the most common indication of NIV, as COPD patients hospitalized due to acute exacerbations frequently develop ARF and acidosis.

NIV decreased the length of hospital stay and improved pH and blood gas parameters. Besides benefits in mortality and prevention of intubation, NIV shortens the length of intensive care unit stay, decreases the rate of infectious complications, and improves dyspnea. NIV provided a better ventilation/perfusion match and thus improved the arterial blood gas and lung function parameters.[29]

Noninvasive ventilation versus high-flow nasal cannula

In the case of severe exacerbations, COPD patients may develop ARF of varying types, sometimes requiring hospital admission due to the deterioration of gas exchange. While sole hypoxemia may only require COT, in 20% of patients, respiratory acidosis and carbon dioxide (CO_2) retention may occur due to an excessive respiratory workload exceeding the capacity of the respiratory muscles. In these cases, NIV plays a significant role. NIV has been shown to improve gas exchange, reduce breathing difficulty and the need for intubation, and decrease hospital length of stay and mortality. NIV is recommended for patients with ARF leading to acute or acute-on-chronic respiratory acidosis (pH≤7.35), but there is no indication for its use in patients experiencing an AECOPD with hypercapnia but without acidosis. It is important to note that up to 64% of AECOPD patients may fail NIV, mainly due to worsened respiratory function, intolerance of the interface, cardiovascular instability, and neurological deterioration. In such cases, intubation is required, and IMV is initiated. The HFNC has been introduced in clinical practice and is gaining increasing importance. Several studies have investigated its application in AECOPD patients for the treatment of hypercapnic ARF.[29]

Non-invasive positive pressure ventilation (NPPV) can significantly reduce the need for intubation and the in-hospital mortality rate among patients with AECOPD with respiratory acidosis. However, it is currently not recommended for use in mildly hypercapnic acute COPD exacerbations without acute respiratory acidosis (pH≤7.35). Several previous studies have reported that 7-15% of COPD patients experiencing acute exacerbations with COT require escalation to invasive mechanical ventilation, indicating an increased mortality risk. Recent meta-analyses have found that HFNC can reduce the risk of endotracheal intubation in patients with acute hypoxic respiratory failure compared to COT. Physiological studies of small samples of acute exacerbations and stable COPD patients have shown that short-term (within 2 hours) application of HFNC can effectively decrease arterial partial pressure of carbon dioxide ($PaCO_2$) by 4-12%, reduce physiological dead space, attenuate the work of breathing, and improve airway clearance. HFNC therapy can further improve the quality of life and reduce the risk of readmission due to acute exacerbations among patients with stable COPD. HFNC and NPPV can equally reduce $PaCO_2$ levels in patients with mild-to-moderate COPD exacerbations (pH 7.25-7.35; $PaCO_2$≥55 mmHg) after 2 hours of treatment. Another potential advantage of HFNC is its potential to reduce the patient's need for NPPV. Li *et al*. found that HFNC can significantly reduce the demand for NPPV compared to nasal prongs in milder acute COPD exacerbation patients.

For COPD patients with type II respiratory failure and a pH between 7.25 and 7.35, HFNC was statistically non-inferior to NIV as initial ventilatory support in decreasing $PaCO_2$ after 2 hours of treatment in patients with mild-to-moderate AECOPD (Table 1).[30]

Table 1. Potential advantages of high-flow nasal cannula in acute exacerbations chronic obstructive pulmonary disease patients.

Heated and humidified gas delivery
Anatomical dead space washout
"PEEP" effect: reduction in the expiratory flow limitation
Provision of stable inspired oxygen fraction (FiO2)
Delivery of stable inspired oxygen fraction (FiO2)
Treatment comfort

PEEP, positive end-expiratory pressure.

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