THEMED REVIEW

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Chronic Obstructive Pulmonary Disease

Abstract: *COPD is a common, preventable, and treatable disease characterized by persistent airflow obstruction associated with enhanced inflammation in the airways and the lung in response to noxious particles or gases. Clinical history and pulmonary function testing are necessary for accurate diagnosis. While exposure to tobacco smoke remains a common cause, other etiologies and underlying genetic predisposition play significant roles. Treatment options are numerous and should be individualized based on symptoms and exacerbation frequency.*

Keywords: COPD; exacerbation; GOLD; FEV1

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, resulting in increasing economic and social burdens.[1] COPD affects 5% to 15% of the world's population, and in 2007, it was diagnosed in 12 million Americans, with a substantial amount of unreported cases. In 2010, COPD was projected to result in $29.5 billion in direct health care expenditures, $8.0 billion in indirect morbidity costs and $12.4 billion in indirect mortality costs in the United States.[2] This article will provide a review of the pathophysiology, diagnosis, and management of COPD.

Definition

According to the updated 2013 GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines, COPD is a common, preventable, and treatable disease, characterized by persistent airflow obstruction that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.[3] These new guidelines were updated to reflect an increasing appreciation that the course of COPD in individuals depends on the frequency of exacerbations and comorbid conditions, which do not always correlate with the loss of measured pulmonary function.

Pathophysiology

Lung inflammation after exposure to inhaled particles and gases is thought to be at the root of COPD pathophysiology. Exposure to these inhaled particles in the lung results in the recruitment to and activation of inflammatory cells in the lung. Mucus hypersecretion, small airway remodeling and narrowing, and destruction of lung parenchyma are key features of the disease, which lead to cough, air trapping, and worsening ventilation and perfusion mismatch.[4] While cigarette smoking remains the most closely linked precipitating factor, nonsmokers represent a significant proportion of COPD cases worldwide.[5,6] Exposure to biomass fuels, dusts and fumes, as well as chronic lower respiratory tract infections can also result in COPD. Biomass fuels include wood,

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charcoal, and other organic matter. Estimates show that between 25% and 45% of all cases of COPD are in nonsmokers and that almost half the world's population, 3 billion people, is chronically exposed to biomass fuel smoke.[7] In the United States, about 15% of COPD cases can also be attributed to exposure to workplace air pollutants.[8] Workers involved in coal and hard rock mining, brick and concrete manufacture have a higher risk of COPD and the contribution of these workplace exposures may be even stronger than smoking in those most heavily exposed.[9] Other occupations associated with a higher risk of COPD include plastic, textile, rubber, and leather manufacture, as well as trucking, food production, automotive repair, and even beauty care.[10,11] Previous tuberculosis, maternal smoking, and asthma or respiratory infection during childhood have also been associated with in increased risk of COPD.[12] Genetic predisposition likely plays a role, since only a minority of patients exposed to cigarette smoke develop significant COPD. α-1 Antitrypsin deficiency is the best-known and studied predisposing condition, present in about 1% to 2% of patients with COPD. Specific chromosomal regions involved in predisposition to COPD have been identified using genome-wide association studies.

Clinical Features and Diagnosis

Shortness of breath and chronic cough, with or without sputum production, especially in a patient with risk factors for COPD should raise the possibility of disease. Spirometry should be the next diagnostic test, and a postbronchodilator FEV_1/FVC ratio of less than 0.70 is required to make the diagnosis of COPD. This fixed FEV_1/FVC (forced expiratory volume in 1 second/forced vital capacity) ratio is recommended by the GOLD guidelines because of its simplicity and frequent use in studies evaluating therapeutic interventions for COPD, although it may overestimate the prevalence of COPD in older patients without known exposure to noxious gases/fumes.[13] Although not necessary, measuring lung volumes on pulmonary function testing (PFT) can be helpful in confirming obstructive airways disease. Significant increases in residual volume (RV), total lung capacity (TLC), or the RV/TLC ratio can suggest obstructive airways disease by demonstrating lung hyperinflation.[14] A low diffusion capacity on PFT testing, in the presence of obstructive lung disease, can also suggest underlying emphysema.[15] Physical examination findings, such as tachypnea, wheezing, or prolongation of the expiratory phase of respiration, are unusual until the disease is quite advanced.[16] The role of early diagnosis allows for more intensive risk factor modification and evidence is increasing that the loss of pulmonary function may be greatest when the disease is in a mild or moderate stage.[17,18] Asthma, obliterative bronchiolitis, and bronchiectasis can present in a similar manner to COPD. Features favoring asthma include an onset at a younger age or in childhood, associated atopy, more common reversibility with bronchodilators, and the lack of associated tobacco use or occupational exposure. Asthma can, however, be worsened by tobacco use or occupational exposure. Asthma and COPD can overlap in the same patient as well. Obliterative bronchiolitis can be idiopathic, although more commonly is associated with acute infection, inhalation of noxious fumes, connective tissue disease, bone marrow transplantation, and often has a more acute onset. Bronchiectasis shares many features with COPD, including collapsible airways, frequent exacerbations, and chronic cough, but usually can be differentiated by clinical history and lung imaging studies.

Assessment of Disease Severity

Comprehensive evaluation of disease severity in COPD should include an assessment of the patient's symptoms, severity of airflow limitation, exacerbation rate and risk, as well as screening for associated comorbidities. The use of a validated questionnaire can help standardize the impact of dyspnea on daily activities and quality of life. The Modified Medical Research Council (mMRC) is an easy to use questionnaire and measures disability associated with COPD.[19] An mMRC score of 0 means patients only get breathless with strenuous exercise. A score of 1 is breathlessness with hurrying on flat ground or walking up a slight hill. A score of 2 is a slower pace than people of the same age on level ground due to breathlessness, or the need to stop for breath at one's own pace. A score of 3 occurs when stopping for breath while walking 100 yards or so or for a few minutes on flat ground. A score of 4 occurs when breathlessness causes one to not leave the house, or if breathlessness occurs during dressing. Another scoring system for dyspnea in COPD is the COPD Assessment Test, or CAT.[20] This scoring system is composed of 8 questions relating to symptoms and overall scores indicate a low (<10), medium (10-20), high (20-30), or very high (>30) impact of COPD on patients overall functioning. Airflow limitation in COPD is associated with risk of death and prevalence of exacerbations.[21] In patients with an FEV_1/FVC ratio of less than 0.7, FEV_1 at or greater than 80% predicted is considered mild, less than 80% but greater than 50% predicted moderate, less than 50% but greater than 30% predicted severe, and less than 30% predicted very severe airflow obstruction. Apart from the severity of airflow limitation, those patients with more frequent exacerbations should be targeted for more intensive therapy. Hospitalization for an exacerbation of COPD or two or more exacerbations of any kind in the preceding year are indicators of a higher risk population.[22-24] The updated GOLD guidelines separate patients with COPD into 4 groups, group A with mild or moderate airflow obstruction, 1 or less exacerbation per year, and CAT scores of less than 10 or mMRC scores of 0 to 1 (low risk, less

symptoms); group B with mild to moderate airflow obstruction, 2 or more exacerbations per year, and CAT scores of 10 or higher, mMRC scores of 2 or above (low risk, more symptoms); group C with severe or very severe airflow obstruction but 1 or fewer exacerbations per year with a CAT scores of less than 10 or mMRC scores of 0 or 1 (high risk, less symptoms); and group D with severe or very severe airflow obstruction, 2 or more exacerbations per year, with CAT scores greater than 10 or mMRC scores of 2 or higher (high risk, more symptoms).[3] These categories paint a more detailed picture of the COPD population than does a classification based on airflow obstruction alone. The BODE index, which takes into account an assessment of body mass index, severity of airflow obstruction, level of dyspnea, and exercise capacity, and can predict the need for hospitalization and mortality.[25,26] Mortality in patients with high levels of dyspnea, poor functional status, advanced airflow obstruction, and low body mass, approaches 75% at 4 years and should prompt discussions regarding symptom management and end-of-life care.

Comorbidities

Lung Cancer

Comorbidities are common and contribute to a decreased quality of life, increased use of medical resources, and higher mortality.[27] COPD is an independent risk factor for lung cancer and the risk increases with more advanced disease.[28] Lung cancer is the most frequent cause of death in patients with mild to moderate COPD.[29] The recent National Lung Screen Trial randomized 53 454 high-risk patients, current or previous smokers (quit within 15 years) with at least 30 pack-years, aged 55 to 74 years to annual screening with reduced-dose chest computed tomography (CT) scanning versus chest radiograph over 3 years. The trial was stopped early after CT scanning showed a significant reduction in mortality of 20%. The high rate of false-positive findings (95%), which require further evaluation and possibly invasive procedures need to be weighed against the benefits, but the practice is becoming more accepted and widespread.

Cardiovascular Disease

Cardiovascular disease is a common comorbidity in patients with COPD. Use of cardioselective beta-blockers is safe in patients with COPD, having been shown in placebo controlled studies to have no adverse effect on FEV1 or increase respiratory symptoms, even with advanced disease.[30,31] They may even reduce the risk of death, when continued, in patients admitted for an exacerbation of COPD.[32]

Sleep-Related Breathing Disorders

Sleep-disordered breathing is also common in COPD. Nocturnal hypoxemia and hypoventilation result from decreased ventilatory responses to hypoxia and hypercarbia during sleep along with reduced lung volume and functional residual capacity (FRC) which increases airway closure and V/Q mismatch. Respiratory muscle tone is also decreased during non–rapid eye movement (NREM) and rapid eye movement (REM) sleep, with active inhibition of compensatory skeletal muscles, such as the intercostal, scalene, and sternocleidomastoids during REM sleep. These muscles play an important role in maintenance of adequate tidal volume during wakefulness in patients with COPD whose diaphragmatic function is impaired by hyperinflation. Coexistent obstructive sleep apnea (OSA) is found in at least 15% of patients with mild COPD, an incidence not much different from those without COPD.[33] However, some evidence indicates that treatment of the overlap syndrome, the combination of OSA and COPD, with continuous positive airway pressure (CPAP) can reduce mortality, an effect that was seen with any consistent CPAP use but increased with longer nightly periods on CPAP.[34]

While cardiovascular disease and lung cancer are the most closely associated comorbidities with COPD, an increased risk of type 2 diabetes mellitus, osteoporosis, depression, and metabolic syndrome is seen in patients with COPD.[35] Although the exact role of these comorbidities in the mortality rates of patients with COPD is difficult to discern from that caused by the disease itself, clearly patients must be managed as those with multisystem involvement.[36]

Management of Stable Disease

Once COPD has been diagnosed, the goals of management are to reduce the progression of the disease and relieve symptoms. Tobacco cessation and reduced exposure to occupational or environmental dusts, fumes, and pollution are critical. Tobacco cessation decreases the rate of FEV_1 decline and decreases mortality.[37,38] The US Public Health Service recommends a plan consisting of asking about tobacco use, advising patients to quit in clear, strong, and personalized manner, assessing their willingness to quit in the next 30 days, assisting in the plan to quit with pharmacologic or more intensive counseling referral, and arranging close follow-up.[39] Nicotine formulations, bupropion, and varenicline, can increase the likelihood of cessation and are recommended unless a contraindication is present. Influenza and pneumococcal vaccinations are recommended and in the case of the influenza vaccine, has been shown to decrease mortality in COPD.[40] Pulmonary rehabilitation, an underutilized intervention, should be encouraged in patients with poor quality of life due to dyspnea or muscle weakness. Rehabilitation has been shown to increase exercise capacity and improve quality of life.[41] Since many patients with advanced COPD lose muscle mass and weight, nutritional supplementation can be useful in increasing weight, lean body mass, and can improve quality of life.[42] Long-term oxygen therapy is used when patients develop exertional or resting hypoxemia, and improves mortality and reduces exacerbation frequency but only when

used for at least 15 hours a day.[43,44] Lung transplantation or lung volume reduction surgery should be considered for appropriate patients with advanced disease and disabling dyspnea.

Pharmacologic therapy is aimed at relieving symptoms as well as reducing the risk of exacerbations. Short-acting bronchodilators can be used for patients with mild and infrequent symptoms but GOLD guidelines recommend long acting bronchodilator formulations over short acting for more significant symptoms.[45-47] For patients at higher risk of exacerbations (GOLD groups C and D), regardless of severity of airflow obstruction, combination therapy with an inhaled corticosteroid/long-acting beta-2 agonist (ICS/LABA) or long-acting anticholinergic agonist (LAMA). Both the combination of salmeterol and fluticasone and tiotropium have been studied in chronic stable COPD and have been shown to improve FEV_1, improve symptoms, and reduce the risk of exacerbations by up to 25%.[48-50] For patients with severe symptoms and a high risk of exacerbations, therapy combining an ICS/LABA combination with a LAMA has been evaluated and shown to improve FEV_1 and to decrease exacerbations of COPD requiring hospitalization or emergency room treatment.[51] Theophylline has been shown to improve FEV_1 and FVC, improve PaO_2 and $PaCO_2$ levels on arterial blood gas analysis, but has unclear effects on symptoms of dyspnea or exercise tolerance.[52] It has a narrow therapeutic index and potential for toxicity and is only recommended in the GOLD guidelines if other bronchodilators are not available or too expensive. Roflumilast, a PDE4 inhibitor, is thought to reduce airway inflammation, and has been shown to improve FEV_1, mildly improve quality-of-life measures, and reduce the risk of exacerbations in COPD. It is associated with weight loss, gastrointestinal side effects, and a concern of adverse psychiatric effects, which should be considered in individual patients.[53] Mucolytics, such as *N*-acetyl cysteine (NAC), have in a systemic review been shown small decreases in both exacerbation frequency and the number of exacerbations requiring hospitalization.[54] Previous studies had not shown improvements in pulmonary function or exacerbation frequency using lower doses, whereas a more recent study in Chinese patients with moderate to severe COPD did improve exacerbation frequency by 22%.[55,56] The role of mucolytics in the treatment of COPD remains unclear. 3-HMG Co-A reductase inhibitors, or statins, are commonly prescribed for hypercholesterolemia and cardiovascular disease but also have immunomodulatory and anti-inflammatory properties. Statins in COPD have been linked to a reduced rate of lung function decline and lower rates of COPD exacerbations, hospitalizations, and mortality.[57] Methodological problems plague most of these studies and further study is indicated before their use can be recommended for all patients with COPD.

Management of Acute Exacerbations

Acute exacerbations of COPD (AE-COPD) are marked by an acute increase in symptoms beyond normal day to day variation, lead to an acceleration of lung function decline, decreased physical activity, and reduced quality of life.[3,58-60] They account for between 35% and 84% of COPD-related health care expenses and the mortality associated with them at 2 years is 26%, and at 5 years is 55%.[61-64] Early treatment of AE-COPD leads to reduced time to resolution, improved quality of life, and reduced need for emergent hospitalization.[65] While some patients will report early symptoms of an AE-COPD, others do not. Interest is growing in newer methods of detecting exacerbations early. Daily step count, now easily measurable with wearable accelerometers, has been linked to the risk of AE-COPD, regardless of FEV_1.[66] These measurements can help to encourage increased physical activity in patients with COPD.

Increased dyspnea, sputum production, and sputum purulence define an exacerbation of COPD.[67] Treatment consists of short acting bronchodilators, corticosteroids, and antibiotics. Alternative etiologies of the symptoms should be pursued as indicated. These include congestive heart failure exacerbations, pulmonary embolism, pneumonia, and pneumothorax. Corticosteroids improve outcomes by reducing treatment failure, hospital length of stay, and time to recovery of FEV_1.[68] Oral steroids have high bioavailability and appear to be as effective for AE-COPD as higher dose intravenous corticosteroids.[69-71] Shorter course regimens also appear to be equally effective with reduced exposure to the adverse effects of corticosteroids, with as few as 5 days of therapy proven to be adequate.[72,73] Viral or bacterial infection is the most common cause of AE-COPD. Infectious agents have been identified in as many as 78% of patients experiencing an exacerbation of COPD.[74] Antibiotic use in AE-COPD reduces treatment failure but the effect on mortality is controversial, with only a clearly reduced mortality rate in those patients with AE-COPD admitted to an intensive care unit (ICU).[75] Antibiotics may also prolong the time to a patient's next exacerbation.[76] Given the concern for increasing bacterial resistance to antibiotics, patients who do not have purulent sputum and whose symptoms are mild seem to be able to recover without antibiotics.[77] C-reactive protein and procalcitonin are serum biomarkers associated with infection and inflammation, although shown in small studies to help guide treatment of AE-COPD, their specific roles remain in evolution. Hypoxemia should be corrected by titrating oxygen saturation levels to 88% to 92%, which appears to reduce complications and mortality. Venturi masks provide more easily controlled levels of supplemental oxygen to achieve this goal. Respiratory acidosis caused by acute increases in carbon dioxide should be ruled out with arterial blood gas analysis. Noninvasive ventilation should be considered early for severe exacerbations and is clearly associated with reduced mortality and need for intubation.[78-80] Noninvasive ventilation reduces dyspnea, improves respiratory acidosis, decreases risk of ventilator associated pneumonia, hospital length of stay, and decreases

respiratory rate. When applied, bilevel positive airway pressure (BiPAP) should be titrated to a difference between inspiratory and expiratory pressures of at least 10 cm H_2O to allow relief of work of breathing.[81] When patients are unable to tolerate noninvasive ventilation due to significantly altered level of consciousness or agitation or if respiratory failure is associated with life-threatening acid-base abnormalities and/or hemodynamic instability, invasive mechanical ventilation is indicated. Although the risk of weaning from mechanical ventilation and overall health status should be considered in the decision to intubate, mortality in patients with COPD who suffer acute respiratory failure is actually lower than those with other etiologies.[82] However, among patients with AE-COPD admitted to an ICU, the 1-year mortality for patients younger than 65 years was 30% and for those older than 65 years was 59%. ICU admission is a late but appropriate opportunity to discuss goals of care.[83] Avoiding hospitalization is appropriate in selected patients and can lead to a reduced risk for rehospitalization and a trend toward a reduced mortality rate, although a recent study cast doubt after it was ended early for an increased risk of mortality in those patients treated at home.[84,85] These "hospital at home" programs consist of more frequent outpatient follow-up, educational interventions, and a trained staff member to assist in monitoring the response to outpatient therapy. These programs are not yet widespread but will garner more attention as reimbursement is further tied to hospital readmission rate and more emphasis is placed on reducing health care costs.

Conclusion

Chronic obstructive pulmonary disease is a common cause of morbidity and mortality worldwide which places a high burden on society. Advanced airflow obstruction and frequency of exacerbations mark a high-risk population who should be aggressively treated. Early diagnosis, modification of risk factors, and treatment are important in altering the progression of disease, relieving symptoms, improving quality of life, and reducing exacerbations. Diagnosis and treatment of common cormorbid conditions is important and can also improve survival and quality of life. Numerous pharmacologic and nonpharmacologic interventions exist and should be utilized to modify the course of the disease. Tobacco cessation assistance remains of paramount importance.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. AJLM

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