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A persistent cough is one of the key symptoms of COPD.

Chronic obstructive pulmonary disease (COPD)

Epidemiology and disease characteristics

Chronic obstructive pulmonary disease (COPD) is a serious condition with a significant risk of disability and mortality. The Global Burden of Disease Study estimated that it affected 250 million individuals worldwide in 2016 and the World Health Organization (WHO) estimated that it resulted in 3.04 million deaths (5.4% of the global total) in that year. The overall worldwide age-standardised incidence rate for COPD has decreased in recent years, as well as in most socioeconomic groups. The one exception is in the highest sociodemographic category, where rates have remained relatively constant over the past 25 years. However, the absolute numbers are still the lowest in this latter group.[1-5]

Persistent respiratory symptoms and airflow limitation characterise the illness. It is associated with a variable mixture of airway disease and anatomic destruction of lung tissue. There are several different subtypes of COPD including chronic bronchitis, emphysema and chronic obstructive asthma.[1-3]

A chronic productive cough for three months in two successive years, inflammation in the airways and increased mucin production are the defining characteristics for chronic bronchitis. A requirement for diagnosis is that no other conditions present explain the chronic cough.[2]

Anatomic changes in the lung tissue are the hallmark of emphysema. The key feature is enlargement of the airspaces beyond the terminal bronchioles that results from destruction of the walls of the alveoli or gas exchange air sacs in the lung parenchyma.[2]

Asthma is associated with chronic inflammation and hyper-responsiveness of the airways with resultant obstruction to airflow. In pure asthma this obstruction is reversible, either spontaneously or with treatment. However, if the obstruction persists between distinct attacks, the condition is referred to as chronic obstructive asthma and is considered a variant of COPD.[2]

Diagnosis

According to the Global Initiative for Chronic Lung Disease (GOLD), the diagnosis of COPD depends on three factors:

1. A post-bronchodilator forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) – FEV1/FVC – ratio < 0.7 or 70% on spirometry
2. Presence of symptoms compatible with the diagnosis – dyspnea, chronic cough, excess sputum production or wheezing
3. Significant exposure to causative agents such as cigarettes or other respiratory toxins

The diagnosis does not require imaging studies such as a chest x-ray or CT scan. These tests are used primarily to rule out alternative diagnoses or complicating conditions such as tumours or infections.[6, 7]

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Risk factors

The most important risk factor for the development of COPD is cigarette smoking. The critical threshold for the development of lung disease appears to be at least a 10 pack-year history of smoking. Other significant risk factors include:

1. Occupational exposure (dusts, chemicals, fumes etc.)
2. Air pollution
3. Older age
4. Female sex
5. History of chronic asthma
6. Factors that influence lung development in childhood (low birth weight, severe infections etc.)
7. Genetic factors (alpha-1-antitrypsin deficiency, others)
8. Rates are higher in lower socioeconomic groups [2, 5, 7]

Symptoms

The major symptoms of COPD are dyspnea, cough and sputum production. Other, less common complaints are of wheezing and chest tightness. It is important to make note of the degree of physical exertion when evaluating the severity of dyspnea. Individuals with severe COPD will often limit their activity due to their lung disease and not complain about shortness of breath until late in the course. The presence of dyspnea at rest and weight loss are indicators of more advanced disease.[2, 7]

Prognostic factors

The 2017 GOLD system for classifying the severity of COPD uses a combination of symptoms, number of exacerbations and FEV1 percentage of normal from spirometry. Using symptoms (Table 1) and the number of exacerbations (Table 2), individuals can be placed into 1 of 4 groups labeled A to D. Group A has low symptoms and low exacerbations. Greater symptoms and low exacerbations characterise group B. Group C has low symptoms and more frequent exacerbations. More severe symptoms and frequent exacerbations is indicative of group D.[7]

Table 1: Modified mMRC dyspnea scale[7]

Grade 0	Breathless only with strenuous exercise
Grade 1	Short of breath when hurrying on the level or walking up a slight hill
Grade 2	Walk slower than people of the same age on the level because of breathlessness, or have to stop for breath when walking at own pace on the level
Grade 3	Stop for breath after walking about 100 meters or after a few minutes on the level
Grade 4	Too breathless to leave the house or breathless when dressing

Table 2: Exacerbations in past year[2, 8]

Group 1	0 exacerbations
Group 2	1 exacerbation without hospital admission
Group 3	1 or more exacerbation with a hospital admission
Group 4	2 or more exacerbations

These groups are further divided by using the FEV1 percentage of normal as recorded on spirometry (Table 3). The groupings are designated stages 1 to 4 respectively. Combining these two systems leads to 16 possible combinations or categories of severity labelled A1, A2, A3…D2, D3, D4. Outcomes, including the number of future exacerbations, morbidity and mortality, vary with these categories. [8-13]

Table 3: GOLD stage by FEV1% of normal[7]

GOLD 1	≥ 80%
GOLD 2	50–79%
GOLD 3	30–49%
GOLD 4	< 30%

A number of other factors influence the prognosis with COPD. These include continued smoking, a low body mass

index (BMI < 21), airway hyper-responsiveness, decreased exercise capacity, CT scan evidence of emphysema and greater inflammation as represented by an elevated C-reactive protein level. Individuals with COPD who contract COVID-19 are more likely to get severely ill or die from the infection. [3, 17]

Treatment

All individuals with COPD are encouraged to stop smoking and remove any exposures that might aggravate the condition. Vaccination for influenza, pneumonia and COVID-19 are recommended to reduce the risk of pulmonary infection, which may worsen outcomes with the disease. [1, 6, 18]

Pharmacologic treatment varies by the A-D group and is driven largely by the symptoms and frequency of exacerbations. Therapies for COPD include short- and long-acting inhaled bronchodilators, short- and long-acting inhaled anticholinergic drugs and inhaled corticosteroids. [1, 6, 18]

The use of oral steroids is limited to significant acute exacerbations. Chronic, ongoing treatment with these drugs suggests a more serious or refractory condition. Administration of antibiotics for acute exacerbations is common but use on an ongoing basis is not. Several therapies are indicators of severe or complicated, high-risk COPD. These treatments include home oxygen therapy, lung reduction surgery and lung transplantation. Some newer therapies that are currently under investigation include interleukin-5 (IL-5) inhibitor drugs that reduce eosinophil counts (mepolizumab, reslizumab, benralizumab) and stem cell transplantation. The former may be beneficial in the relatively small subset of individuals with chronic obstructive asthma. The latter is still investigational. Neither treatment is likely to substantially influence the underwriting of most COPD cases in the short term. [1, 6, 18-21]

Prognosis

Progressive lung disease can lead to respiratory failure with reduced blood oxygen levels, carbon dioxide retention and cyanosis. In addition, severe chronic lung disease can put extra strain on the right ventricle leading to cor pulmonale and heart failure.

There is a significant risk of mortality associated with COPD. As documented in the paper by Gedebjerg et al., the risk varies by the severity categories noted above with the lowest risk associated with group A1 and the highest with D4. Using A1 as a referent, Table 4 summarises the hazard ratios for mortality after adjustment for age, gender, marital status, presence of comorbidities, BMI, smoking status, statin administration and use of antihypertensive, antithrombotic and lipid lowering drugs.

Causes of death in COPD include respiratory failure, lung cancer, other cancers related to smoking, coronary artery disease and heart failure. [8] The risk for exacerbation of symptoms and disability parallels the hazard ratios summarised in Table 4. [9] The mortality risk is greater if the decline in pulmonary function is accelerated, and greater than usual, over time. [15]

Table 4: Hazard ratios by symptoms, exacerbations and spirometry [8]

A1 1.00	**B1** 2.35	**C1** 1.53	**D1** 3.23
A2 1.26	**B2** 2.07	**C2** 1.86	**D2** 3.23
A3 1.91	**B3** 3.03	**C3** 2.63	**D3** 4.04
A4 3.06	**B4** 4.32	**C4** 3.63	**D4** 5.90

For example, an individual that has to stop and rest after walking 100 meters, one exacerbation without requiring hospitalisation in the past year and an FEV1 of 30-49% of expected, would fit into category B3 and would have a relative risk of mortality of approximately 3 times the expected value. The risk for morbid events is similarly increased. [8]

In conclusion, COPD is a serious illness that carries a significant risk for morbidity and mortality worldwide.

Three main subtypes exist including chronic bronchitis, emphysema and chronic obstructive asthma. Its primary cause is cigarette smoking but other factors may be involved. Therapy can help manage clinical findings but is not curative. Prognosis depends on the combination of

severity of symptoms, frequency of exacerbations and assessment of lung function as manifested in the FEV1. The more abnormal the combination of these factors is, the higher the risk for disability and death. Evidence-based underwriting actions should reflect this risk pattern as summarised in Table 4.

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