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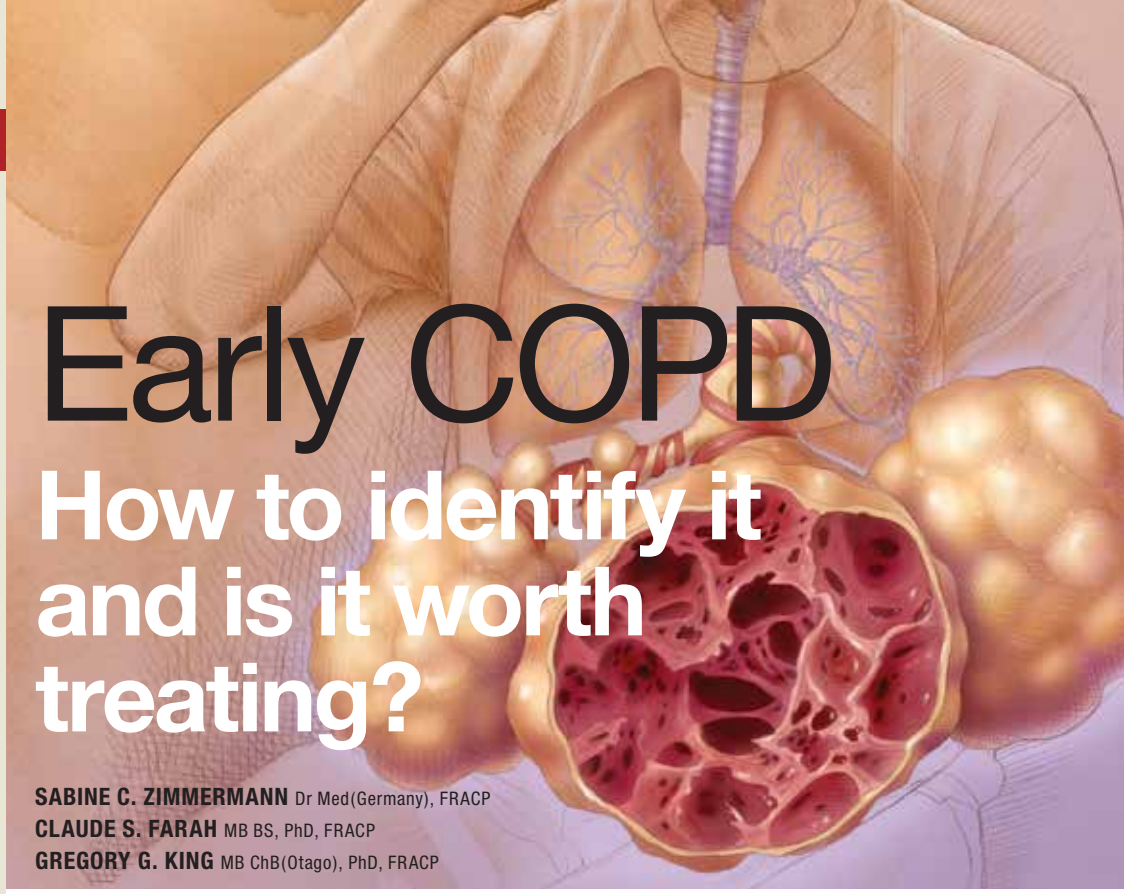

Early COPD

How to identify it and is it worth treating?

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Key points

- **Detecting airflow limitation when the patient has no symptoms and confirming the diagnosis of COPD by spirometry identifies individuals at risk of future symptoms, increased decline in FEV_1 and complications of the condition.**
- **Better stratification of future risk by actively diagnosing COPD (case finding) may alter management in those with additional risk factors for COPD progression and cardiovascular risk.**
- **Performing spirometry in current smokers may increase smoking cessation.**
- **An asymptomatic patient with a new diagnosis of airflow limitation should be monitored for decline in FEV_1, onset of COPD symptoms and occurrence of exacerbations.**
- **Confirmation or exclusion of COPD allows appropriate drug prescription and helps avoid diagnostic confusion.**
- **Management of COPD continues to evolve as understanding of the disease increases, particularly appreciation of its heterogeneity.**

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Case finding of airflow limitation and COPD is an important step to be undertaken by GPs in individuals at risk to help address the increasing burden of this condition in the community.

Chronic obstructive pulmonary disease (COPD) is an important disease globally because of its massive societal, economic and personal burden. It is defined by airflow limitation (measured by spirometry) that does not normalise after administration of a short-acting bronchodilator and by typical symptoms of breathlessness on exertion and cough productive of sputum.[1]

AN OVERVIEW OF COPD

Two important guidelines on COPD are the Australian COPD-X plan and the international Global Initiative for Chronic Obstructive Lung Disease (GOLD)'s strategy document; these contain practical information that is regularly updated.[1,2] Both documents describe the severity of COPD based on impairment of forced expiratory volume in one second (FEV_1). The GOLD document also incorporates symptoms and exacerbations to assign COPD severity.

It is predicted that the burden of COPD will increase due to tobacco-related morbidity so that by 2020 it will be the fifth leading cause of disability worldwide.[3] Therefore, in addition to measures aimed at preventing smoking and helping patients quit smoking, there has been a drive to find strategies to identify people at risk of COPD and to reduce their risk of the condition developing as a result of a sustained excess decline in lung function.[4] Similarly, there is interest in diagnosing COPD in its earlier stages in the hope that the course of the disease can be altered if the pathophysiological changes are not advanced.

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There is also a greater appreciation of the heterogeneity in disease expression and considerable effort is being made to better characterise patients with established COPD, with the long-term goal of targeting treatment.

A deeper understanding of COPD and its underlying processes is therefore needed to enable advances in its management.

SPIROMETRY FOR DIAGNOSIS OF COPD

The prevalence of airflow limitation in the population varies between countries. The most comprehensive study to date on the prevalence of airway obstruction is the Burden of Obstructive Lung Disease (BOLD) study, which involved 12 sites in 12 different countries and 9425 subjects. The investigators reported the presence of moderate or greater airway obstruction (ratio of FEV_1 to forced vital capacity [FVC] less than 0.70 and FEV_1 less than 80% of predicted on post-bronchodilator spirometry testing) in 6 to 20% of the population over 40 years of age.[5] The reported prevalence is a surprisingly large proportion of the population. The study did not include any developing countries where environmental pollutant exposure and tobacco consumption are high and, therefore, where COPD could be even more prevalent. In Australia, the prevalence of COPD in women and men aged 40 years or older was found to be 7.5%.[6]

Other studies have reported that when the largest at-risk population in western societies – current and former smokers of 10 pack-years or more and 40 years of age and older – is screened, between one in seven and one in three people have COPD.[7-9] The proportion varies depending on the prevalence of COPD in the population being tested. Considering the relation between pack-years and severity of airway obstruction, the likelihood of finding airway obstruction will be even higher if individuals who have smoking histories exceeding 20 pack-years are targeted.

Is spirometry really necessary for diagnosis?

The diagnosis of COPD needs confirmation in individuals who have symptoms. As the symptoms associated with COPD are nonspecific, such as productive cough that could be due to bronchitis without COPD, bronchiectasis or postnasal drip, diagnosis by clinical symptoms and signs alone is highly inaccurate. The implications of misdiagnosis are significant: treating a patient with drugs for an erroneous diagnosis is wasteful of resources, needlessly exposes patients to potential drug side effects and may delay the correct diagnosis and appropriate management.

Arguably spirometry is mandatory in any patient who presents with worsening breathlessness or wheeze during a respiratory tract infection because such a scenario constitutes an exacerbation, which in itself has significant clinical connotations. An exacerbation of COPD is commonly defined as worsening symptoms (cough, sputum production or breathlessness) for three or more days. Apart from the short-term consequences, exacerbations are associated with increased rate of decline in lung function, further exacerbations, increased risk of death, reduced quality of life and increased health care utilisation.[10]

AIRFLOW LIMITATION

Although the most common cause of COPD is cigarette smoking, it is not the sole cause. Other causes include domestic and occupational inhalants and asthma. Although long-standing asthma can cause airflow limitation that is incompletely reversible by acute bronchodilator inhalation, the pathology of long-standing asthma is very different from that of COPD and the clinical features frequently differ. In COPD, neutrophilic inflammation in the large and small airways, including the respiratory and terminal bronchioles, is characteristic and leads to tissue destruction that also involves the lung parenchyma, resulting in emphysema.[11] Even after smoking cessation, inflammation persists when COPD is established and severe.[12] In asthma, however, inflammation is commonly eosinophilic, although neutrophilic inflammation becomes more common with more long-standing asthma.[13]

The combination of smoking and asthma results in additive effects on decline in lung function.[14] If asthma is severe and smoking exposure has been heavy, the chances of having incompletely reversible airflow limitation are increased, and all such patients should have spirometry performed. The value of making a diagnosis of asthma versus a diagnosis of COPD or a diagnosis of 'overlap' is open to debate. The criteria on which such diagnostic splitting is based are also a matter of opinion. Whether such diagnostic labelling should alter management or affect outcomes is even more complex and will probably be influenced by greater understanding of different clinical subtypes, or phenotypes, of obstructive airways disease.

CASE FINDING IN COPD

The practical aspects of case finding in COPD have been discussed in the article 'COPD: practical aspects of case finding, diagnosing and monitoring', published in a previous issue of *Medicine Today*.[15] COPD should be actively sought in all current or former smokers, and in particular in those who have respiratory symptoms (typically cough, wheeze or breathlessness) as they may have more severe disease than asymptomatic smokers. The German research team who were part of the BOLD study of COPD prevalence, together with primary care physicians, found that a new COPD case would be identified in one of every two individuals if they screened all smokers older than 40 years of age who also had symptoms of cough or breathlessness.[16]

There is good evidence that screening with spirometry is helpful for successful smoking cessation. In a study performed in a primary care setting in the UK, smoking cessation rates in those aged over

TARGET POPULATION FOR COPD CASE FINDING[2]

Case finding should be considered in individuals aged at least 35 years who meet at least one of the following risk factor or symptom criteria:

- current or ex-smoker
- current or previous occupational dust, gas or fume exposure
- coughs several times on most days, with or without mucous production
- gets more easily short of breath than other people of the same age
- feels wheezy or tight in the chest
- suffers from frequent chest infections

35 years were increased by telling individuals their estimated lung age (the age of the average healthy individual who would have similar spirometry to them), independently of whether the results were normal or abnormal.[17] Such evidence may be sufficient justification for mass screening with spirometry in all smokers for some healthcare givers. However, the US Preventive Services Task Force in 2009 stated that there was no net benefit in mass screening for COPD with spirometry in terms of the overall cost–benefit ratio.[18] Nevertheless, we believe there is sufficient evidence to support case finding of COPD with spirometry in high-risk populations, including current and ex-smokers older than 35 years of age. The Box lists the target population for COPD case finding.[2]

Successful smoking cessation before there is loss of lung function will have larger potential benefits in preserving lung function. In early COPD, lifestyle changes (optimisation of weight, exercise, dietary changes) should be instituted as early as possible, with or without pharmacological treatment, depending on the presence of symptoms and exacerbations. The diagnosis of COPD should also alert GPs and other physicians to the increased risk of mortality from any cause, importantly cardiovascular disease, respiratory failure, cerebrovascular disease and cancer, which may have implications for patient management in relation to risk modification.[19]

POTENTIAL TO IMPROVE CLINICAL OUTCOMES

The aim of early detection of airflow limitation is to allow early intervention and, as a result, to improve outcomes. The benefits of early diagnosis of COPD and airflow limitation are poorly studied but the natural history of COPD strongly suggests that intervention should be as early as possible. The earlier the intervention, the greater the potential benefits in terms of improved life expectancy and health outcomes; therefore, the earlier patients can quit smoking, the greater the benefits in terms of preserving lung function.[20] Furthermore, as symptoms usually do not occur until there has been about a 50% loss of FEV_1,[4] then early diagnosis of COPD clearly mandates case-finding: that is, performing spirometry in smokers.

All smokers should be strongly encouraged to quit smoking and, therefore, the presence of COPD should not influence management in terms of smoking cessation. However, there is evidence that smoking cessation is more likely if the subject has airway obstruction. In a smoking cessation program in Poland involving 100,000 people, about 4500 individuals with a history of at least 10 pack-years of smoking were invited to attend a smoking cessation session.[21] More than two-thirds of subjects attended the sessions where spirometry was used as a tool to help quitting. The presence of airway obstruction was associated with higher quit rates at one year (verified by exhaled carbon monoxide level), with the difference being highest in those with severe airflow limitation (16.3% versus 12% in those with normal spirometry results).

After airflow limitation is detected with spirometry, it should be interpreted in the context of the individual patient, as for any test result. Patients are concerned about the consequences to them, in terms of current or future impairment and disability, and possible treatment requirements. Although there is a sound evidence base to inform treatment in some instances, given the heterogeneity of COPD, there are many instances where there is little evidence to inform treatment strategy. Examples include people with asthma who have smoked and those with asthma who have not smoked but have fixed airway obstruction. These people are usually excluded from both asthma studies and COPD studies, so the evidence from studies may not be generalisable to these populations. However, management that is based on identifying and treating clinical problems such as frequent exacerbations, breathlessness, obesity and anxiety in patients who have airways disease may result in greater clinical benefits than the more narrow approach of prescribing an inhaler as specific treatment for the airways.[22] This approach seems logical as the quality of life in patients with airways disease is impaired in proportion to the number of identifiable comorbidities.[23]

The management of patients with COPD, symptomatic and asymptomatic, is summarised in the Figure.[24]

CAN WE ALTER PROGRESSION OF THE DISEASE?

Smoking cessation is the only intervention that can alter the progression of COPD. Although the rate of decline in FEV_1 was shown to be reduced in patients with moderate COPD by treatment with a high-dose, combination inhaled corticosteroid/long-acting β_2-agonist or a long-acting antimuscarinic agent, the effects were small and of uncertain clinical significance.[18,25] Treatment with short-acting antimuscarinic drugs has no effect on the rate of decline in FEV_1.[26] Nevertheless, there is great heterogeneity in the rate of decline in FEV_1, presence of symptoms, systemic disease and exacerbation rates between patients, with some progressing quickly in terms of COPD severity while others remain stable for many years.

Currently, there are no clinically useful markers to identify patients with COPD who will decline rapidly or to predict those in whom drug treatment reduces the rate of decline. Although it is known that airway hyperresponsiveness, acute bronchodilator reversibility, respiratory symptoms, reduced FEV_1/FVC ratio, low baseline FEV_1, emphysema, mucus hypersecretion and episodes of lower respiratory tract illness are associated with increased rate of loss of FEV_1, their predictive ability in an individual is likely to be poor and they are not routinely used for this purpose.[27-34]

It is recognised that for a given impairment in FEV_1, there is a wide range of symptom severity and exacerbation risk in COPD. This heterogeneity is reflected in the updated international GOLD strategy document, in which symptoms are included in the severity assessment.[1] The presence of symptoms as defined by the revised GOLD severity classification is associated with an increased risk of exacerbation as well as of mortality for the same degree of airflow limitation defined by spirometry.[35] Following publication of the new GOLD classification, a study involving a large population of COPD patients showed that the presence of symptoms did indeed signify an increased risk of exacerbations and also mortality.[35]

Drug treatment with either single or combination inhaled corticosteroids, long-acting β-agonists or long-acting anti-muscarinic agents improves symptoms and exacerbation risk in patients with moderate COPD (FEV_1, 50 to 80% of predicted), as well as in patients with more severe COPD.[36,37] Although such individuals in the general population are less likely to report any symptoms than those with lower FEV_1, there is great variability. Overall, such patients benefit from pharmacological treatment in terms of improved quality of life and reduced exacerbation risk, with the decision ideally based on a risk–benefit assessment in each individual. It is worthwhile noting that patients entering clinical studies are more likely to be symptomatic because their symptoms identified them as having COPD prior to enrolment. The absence of symptoms or previous exacerbations after thorough history-taking in a patient with moderate airflow limitation (moderate COPD) is associated with a very low risk of exacerbations in the following year – around 2%.[36] Mortality risk is also low at 0.6%.[36] Therefore, asymptomatic individuals who have COPD do not necessarily warrant drug treatment, particularly if they have only mild to moderate FEV_1 impairment.

Thus, the most important treatment in a patient newly diagnosed with airflow limitation whose FEV_1 is greater than 50% of predicted and who is asymptomatic is smoking cessation. Other considerations in such a patient are dealing with cardiovascular risk factors, maintaining ideal weight, considering bone health and maintaining exercise. However, there is no or little justification for pharmacological treatment for COPD because there is little known of the benefits of such treatment in patients with asymptomatic, mild to moderate COPD. This is an area that requires further research.

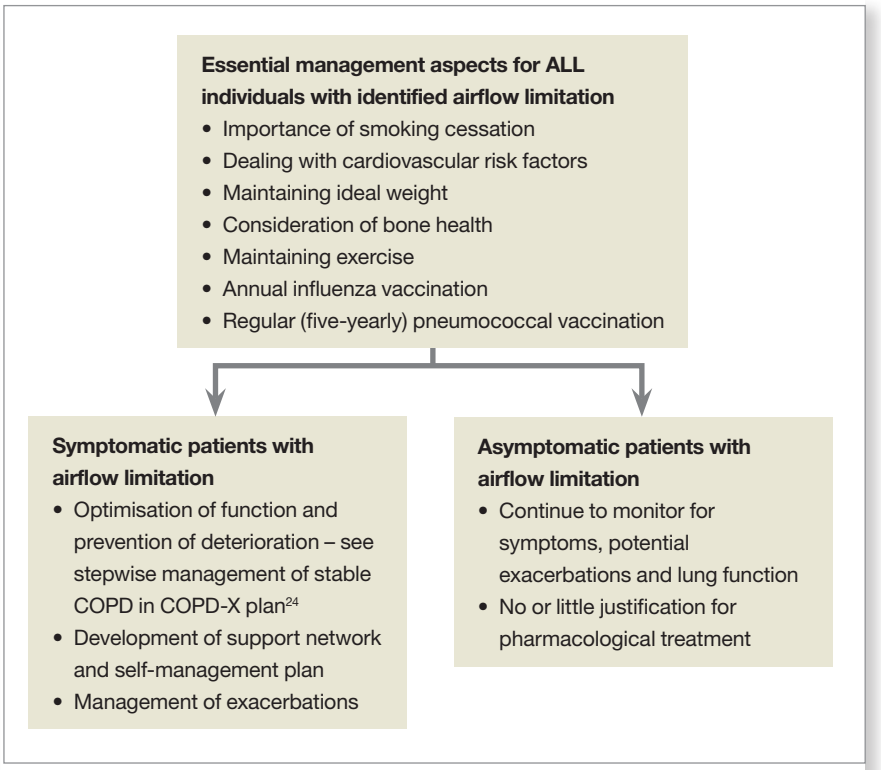

Figure. Management after case finding for COPD in symptomatic and asymptomatic individuals.[24]

FUTURE DEVELOPMENTS IN COPD

There is widespread agreement about the need for more research into COPD phenotyping (i.e. clinical, biochemical and inflammatory characterisation) because of the potential for clinic benefit.[38-40] COPD represents a spectrum of disorders that share airflow limitation as their common underlying pathophysiological process but behave differently in many aspects between individuals. Understanding the heterogeneity of COPD better might allow earlier detection as well as development of treatment methods that are targeted specifically at certain phenotypic subgroups.

Current methods in practice to phenotype COPD include CT imaging to establish, for example, the presence of underlying emphysema. Although there is firm evidence to support a correlation between the extent of emphysema determined by CT and by histological examination,[41-46] using CT imaging for this purpose has the disadvantages of cost and radiation exposure. New methods being used in research, such as the multiple breath nitrogen washout technique as a measure of small airway function, might potentially allow such phenotypic classification.[47-49]

Disease phenotyping is a current area of research because of the potential to help improve COPD outcomes. Certain COPD phenotypes might respond differently to different treatments (e.g. differing bronchodilator responsiveness), which raises the possibility of individualised management regimens. The tools used to phenotype disease could also identify markers of COPD susceptibility (because only about 20% of smokers develop COPD), allowing very early detection of disease, even before spirometry results have become abnormal.[49]

Ultimately, being able to identify the clinical links between phenotypes and the complex relation with genetic, molecular, cellular and environmental components may translate into the ability to practise individualised medicine rather than a generalised 'one-fits-all' approach to COPD. This could lead to better patient outcomes in terms of morbidity and mortality by delaying progression of disease and improving overall survival.[39,40] Such an approach would be of particular relevance for patients with mild COPD.

SUMMARY

It is worthwhile identifying patients with mild COPD and early disease, but this is possible only if case finding occurs in primary care. Detection of airflow limitation when the patient is asymptomatic and confirmation by spirometry of a diagnosis of COPD identifies individuals at risk of future symptoms and complications of the condition. Better stratification of future risk by actively diagnosing COPD may alter the management in individuals who have additional risk factors for COPD progression and a cardiovascular risk. Performing spirometry in current smokers may increase their chances of smoking cessation.

It is important to recognise that when a previously asymptomatic patient with newly diagnosed airflow limitation develops respiratory symptoms, this represents an exacerbation of COPD. This exacerbation needs to be managed accordingly, and not be misdiagnosed as a simple lower respiratory tract infection. Confirmation or exclusion of COPD allows appropriate drug prescription and helps avoid diagnostic confusion.

Management of COPD, including its pharmacotherapy, continues to evolve as understanding of the condition increases, particularly the appreciation of the heterogeneity of the disease. Case finding of COPD raises complex arguments about cost effectiveness, clinical benefit and appropriate treatment. There are a great number of clinical questions that still need answering by well-designed clinical studies to provide a stronger evidence base to guide management in early COPD. MT

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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