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Focus on COPD

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THE PEER REVIEWED JOURNAL OF CLINICAL PRACTICE

FOREWORD FROM THE SUPPLEMENT EDITOR

Focus on COPD

Chronic obstructive pulmonary disease (COPD) affects millions of people worldwide and presents a significant burden to individuals, families and healthcare systems. As well as being burdensome in terms of day-to-day symptoms, this condition is frequently associated with exacerbations or flare-ups and is a leading cause of preventable hospitalisations and mortality. COPD demands our collective attention, and concerted efforts are required to ensure accurate and earlier diagnosis as well as better prevention and management.

In this supplement, titled *Focus on COPD*, our expert contributors offer insights into the latest research as well as their own clinical practice to provide the knowledge and tools necessary to effectively navigate the complexities of COPD management. Highlights include recommendations regarding the key role of spirometry, along with clinical assessment, in reaching a diagnosis; the practicalities involved in obtaining spirometric testing; a vignette-based and management focused discussion of so-called 'asthma-COPD overlap'; recommendations for preventing and managing COPD and its exacerbations, including new options; individualising the choice of inhaler and a consideration of the important role of pulmonary rehabilitation in managing patients with this disorder.

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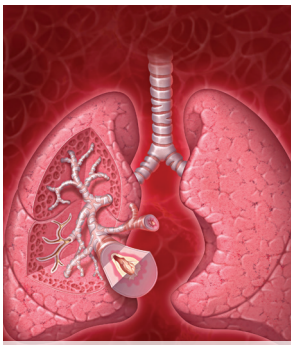
FEATURE ARTICLES PEER REVIEWED



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Early diagnosis of COPD

Recognising the opportunities

MARTIN MACDONALD MRCP, FRACP, PhD

Recognising chronic obstructive pulmonary disease in primary care requires active case finding in symptomatic patients. Spirometry is essential for diagnosis.

Key points

- **A diagnosis of COPD is made in a patient with typical symptoms (dyspnoea, cough, sputum) in whom spirometry demonstrates expiratory airflow obstruction that cannot be fully reversed by a bronchodilator.**
- **Underdiagnosis of COPD likely reflects a multitude of factors related to both patients and doctors.**
- **Screening of asymptomatic patients is not recommended; rather, early diagnosis in primary care relies on active case finding in symptomatic patients.**
- **Early diagnosis allows interventions, such as smoking cessation strategies, that may help to avoid the devastating consequences of advanced COPD.**

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The burden of chronic obstructive pulmonary disease (COPD) is enormous. It is currently the third leading cause of death and the fifth leading cause of disease burden globally, with disease prevalence predicted to further increase.[1] It is estimated that 7.5% of people in Australia aged 40 years or over have symptomatic COPD even though half of them are undiagnosed.[2] COPD accounts for almost 1% of all GP consultations, and acute exacerbations of COPD are the second leading cause of avoidable hospitalisations.[3,4]

A precise, accurate and satisfactory definition of COPD is surprisingly elusive. A diagnosis of COPD is made in a patient with typical symptoms (dyspnoea, cough, sputum) in whom spirometry demonstrates expiratory airflow obstruction that cannot be fully reversed by a bronchodilator. Although described as a distinct entity, in reality COPD encompasses a heterogeneous group of processes including small airways disease (obstructive bronchiolitis), chronic bronchitis and emphysema. Elements of all these processes may be present in an individual patient with COPD.

Who is at risk for COPD?

The major risk factor for COPD is cigarette smoking, although additional risk factors include occupational exposures, exposure to indoor biomass fuel burning, air pollution and childhood asthma.[5-7] Symptoms of COPD may only become clinically evident after lung function has substantially declined.

In healthy people, maximal lung function is generally attained by around 20 to 25 years of age. It then plateaus until around 30 years of age before a gradual slow decline in lung function over the

Table. COPD severity grading according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of airflow limitation (based on postbronchodilator FEV_1)

	FEV_1 (% predicted, in patients with FER <0.7)[1]	Severity
GOLD 1	≥80	Mild
GOLD 2	50 to <80	Moderate
GOLD 3	30 to <50	Severe
GOLD 4	<30	Very severe

Abbreviations: COPD = chronic obstructive pulmonary disease; FER = forced expiratory ratio; FEV_1 = forced expiratory volume in 1 second.

remainder of life. Recently, attention has increasingly focused on the multiple trajectories that can lead to low lung capacity in later life. Smoking is associated with an accelerated loss of lung function, and it is estimated that 50% of persistent smokers will ultimately fulfil criteria for COPD.[8,9] Another important predisposing factor is failure to attain maximal lung capacity in earlier life.[10] Although not yet fully understood, early life factors including feto-maternal health, genetics and childhood exposures may be key determinants of this failure to attain maximal lung capacity, which increases the likelihood of low lung capacity in later life.

Definition and diagnosis of COPD

A diagnosis of COPD requires spirometry demonstrating a reduced forced expiratory ratio (FER; forced expiratory volume in 1 second [FEV_1] : forced vital capacity [FVC]). International guidelines define COPD as a postbronchodilator FER of less than 0.7. In essence, this means that even after bronchodilating medication is administered, of the total air forcibly expelled from the lungs after a maximal inhalation, less than 70% is expelled within the first second. When this is observed in an appropriate clinical context a diagnosis of COPD is made.

This universal threshold definition has the advantage of being simple and practical. However, because FEV_1 tends to decline faster than FVC with ageing, a universal categorisation based on an FER of less than 0.7 may lead to overdiagnosis of COPD in elderly patients and underdiagnosis of COPD in younger patients. As a result, some lung function laboratories may report age-adjusted FER. It should also be noted that a degree of variability in FER measurement within individual patients can be observed, such that in patients with mild to moderate airflow limitation a single spirometry assessment may not be sufficiently reliable. For patients whose spirometry results are around the threshold level, repeat spirometry should be performed to confirm the diagnosis.

Of note, a degree of bronchodilator responsiveness is common in patients with COPD, although a response of greater than 400 mL is unusual and should prompt consideration of an asthma diagnosis. Importantly, lack of reversibility of airflow limitation after a bronchodilator does not necessarily signify lack of clinical benefit from bronchodilator therapy, as long-acting bronchodilators also significantly reduce exacerbation risk.

Spirometry is not only essential to the diagnosis of COPD, but provides a grading of COPD severity. The degree of airflow obstruction relative to a matched population reference (% predicted FEV_1) has important prognostic and therapeutic relevance (Table).

Underdiagnosis and misdiagnosis of COPD

COPD is frequently underdiagnosed and misdiagnosed. It is estimated that, in the US, over 70% of patients with obstructive lung disease may be undiagnosed.[11] Although many of these patients may identify few symptoms, undiagnosed COPD is associated with reduced survival.[11] Conversely, it is estimated that 20 to 30% of patients given a clinical diagnosis of COPD do not demonstrate airflow obstruction on spirometry.

Although classic examination findings of diminished breath sounds and wheeze are often identified in advanced COPD, physical examination is not always reliable in mild and moderate COPD, and spirometry is essential to diagnosis.[12] A study in an Australian primary care setting assessed spirometry results for patients with a clinical diagnosis of COPD and found only 58% of cases had spirometry results consistent with COPD.[13]

Opportunities for diagnosis of COPD are frequently missed. In a retrospective study of 38,859 patients ultimately diagnosed with COPD in UK general practice, missed opportunities for COPD diagnosis in the previous five years were identified in 85% of patients.[14] By the time of COPD diagnosis, 27% were defined using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification as GOLD Stage 2 (FEV_1, 50 to 79%), 15% were GOLD stage 3 (FEV_1, 30 to 49%) and 10% were already GOLD stage 4 (FEV_1 less than 30%). In a study of patients hospitalised for a severe exacerbation, 34% were first diagnosed with COPD at the time of hospitalisation, when they already had established severe disease and sometimes even respiratory failure.[15]

Barriers to diagnosis

Underdiagnosis of COPD likely reflects a multitude of factors related to both patients and doctors.

Patient factors

- COPD is a gradually progressive disease and patients may not identify the insidious onset of progressive exertional dyspnoea.
- Patients may adapt their lifestyle to avoid physical exertion that would provoke symptoms.
- Patients may attribute other key COPD symptoms such as cough and sputum production to current smoking rather than to a disease.
- Symptomatic current smokers may avoid seeking a medical diagnosis due to the stigma associated with smoking-related illness.

Doctor factors

- Doctors may attribute mild respiratory symptoms to normal ageing or effects of current smoking.
- Doctors may not challenge tobacco use.
- Perceived difficulty of access to spirometry may be a barrier to accurate diagnosis.
- GPs may have concerns regarding the accurate performance of spirometry or interpretation of results.

It is therefore important to directly ask about respiratory symptoms in patients at high risk of COPD. Respiratory symptoms in patients with a smoking history should prompt consideration of a COPD diagnosis, which can be evaluated with spirometry. Respiratory symptoms in current or ex-smokers should not be considered normal. Even when lung function is well preserved, symptomatic smokers have significantly increased rates of respiratory exacerbations.[16]

Handheld expiratory flow meters comparing FEV_1 with FEV in 6 seconds (FEV_1 : FEV_6) are simple to use and have shown utility as a screening test for identifying people most likely to benefit from a formal spirometry assessment for COPD (FEV_1 : FVC).[17] Training courses for office spirometry in primary care are available (https://www.nationalasthma.org.au/health-professionals/education-training/spirometry-training). Referral to a pulmonary function laboratory is otherwise required for spirometry.

Should population screening be performed to identify COPD at its earliest stage?

Given the progressive natural history and devastating impact of advanced COPD, it is logical to consider a role for screening to facilitate diagnosis at an early stage of disease. Screening for asymptomatic COPD using questionnaires and simple prebronchodilator spirometry devices has been investigated but is not currently routinely recommended.[18] It is important to consider the difference between screening apparently healthy people for occult disease and case finding, which is the targeted evaluation of high-risk groups to make a diagnosis earlier than would occur by waiting for them to present with symptoms or signs.

The key interventions in COPD management are aimed at alleviation of symptoms and prevention of exacerbations. Patients with very mild COPD may truly be asymptomatic and such patients are generally at relatively low levels of exacerbation risk. As such, population screening of asymptomatic individuals is not indicated for COPD given insufficient evidence of benefit.[19] In contrast, active case finding of COPD in symptomatic patients in primary care is recommended.[20] In this regard, given the tendency of patients with mild COPD to underreport respiratory symptoms, vigilance from their GP is highly valuable.

Case finding for COPD

Active case finding for COPD appears to be more effective than opportunistic case finding. A randomised controlled trial among primary care patients in the UK compared active case finding that identified patients with COPD using a mailed questionnaire with opportunistic case finding using a questionnaire at the time of GP consultation. Active case finding identified more cases that were subsequently confirmed with spirometry (odds ratio, 2.34) and also appeared more cost-effective.[21,22]

Summary of steps for early diagnosis and treatment of patients with COPD

When to consider diagnostic testing for COPD

- Exertional breathlessness, particularly in a patient with a history of smoking
- Episodes of bronchitis in a patient with a history of smoking

What to do if COPD is suspected

- Refer for spirometry to assess expiratory airflow obstruction

What to do when COPD is confirmed

- Smoking cessation – including pharmacological support
- Vaccination – influenza and pneumococcal
- Exercise – consider referral for pulmonary rehabilitation
- Comorbidity screening – particularly for cardiovascular disease, anxiety/depression, osteoporosis
- Pharmacotherapy – stepwise management including inhaler therapies to reduce symptoms and exacerbation risk (https://lungfoundation.com.au/resources/?search=stepwise)

What difference would early diagnosis and intervention make?

Earlier diagnosis and introduction of evidence-based interventions reduce morbidity and mortality in patients with COPD. The steps involved in early diagnosis and treatment of patients with COPD are summarised in the Box.

Smoking cessation

Smoking cessation is the most important intervention in COPD management. The accelerated decline in lung function associated with smoking is significantly reduced after quitting.[23] It is recommended that clinicians ask all adult patients about smoking and offer smoking cessation interventions to current smokers.[24] Evidence supports the impact of smoking cessation interventions from simple clinician advice to pharmacotherapy;[25,26] however, most studies to date have not shown that evidence of COPD from spirometry increases smoking cessation rates.[27] Of note, expressing lung function impairment to patients using the terminology of 'lung age' relative to their chronological age may have more impact on smoking cessation rates.[28,29] Further research into optimising smoking cessation strategies in this context is required.

Exercise and pulmonary rehabilitation

Regular physical activity is of key importance in patients with COPD. It can maintain function and is associated with reduced hospitalisation rates and mortality.[30] Pulmonary rehabilitation is

a tailored exercise and education program that has been shown to improve symptoms and reduce exacerbations in patients with COPD.[31] Local centres offering pulmonary rehabilitation can be found on the Lung Foundation Australia website (https://lungfoundation.com.au/exercise-classes). Patients can be referred directly from primary care.

Vaccination

Vaccination for influenza is recommended annually for patients with COPD. Pneumococcal vaccination and maintaining COVID-19 vaccination in accordance with local guidelines are also recommended.

Pharmacotherapy

In reality, at the time of initial diagnosis many patients with COPD already have established disease with respiratory symptoms and often a history of exacerbations. Pharmacotherapy with long-acting bronchodilators and, for some patients, inhaled corticosteroids will often be indicated. Concise guidelines for comprehensive management of COPD in primary care are available (https://copdx.org.au).

Comorbidities

COPD is frequently associated with comorbidities including cardiovascular disease, anxiety, depression and osteoporosis. High vigilance in primary care for coexisting cardiac disease is of key importance. Spirometric evaluation of patients with suspected COPD is one of the steps required to disentangle the respiratory and cardiac contributions in the breathless patient. Cardiac disease is highly prevalent but underdiagnosed and undertreated in COPD populations. Evaluation of cardiac health and cardiac risk factors in primary care is recommended.[32]

Conclusion

COPD is highly prevalent but underdiagnosed. Opportunities for earlier diagnosis of COPD are frequently missed and patients often have advanced disease by the time of diagnosis. Spirometry is the key investigation for diagnosing COPD. **RMT**

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A list of references is included in the online version of this article (www.respiratorymedicinetoday.com.au).

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Early diagnosis of COPD
Recognising the opportunities

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New developments in COPD

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COPD is a heterogeneous disease that presents many management challenges. This review presents an update on promising advances from research.

KEY POINTS

- Patients with chronic obstructive pulmonary disease (COPD) should be encouraged to maintain regular physical exercise, and referral to pulmonary rehabilitation is recommended.
- Inhaled corticosteroids should be reserved for patients with moderate to severe COPD to reduce exacerbations; and patients with a blood eosinophil count of 0.3×10^9/L or greater are most likely to benefit.
- Inhaled corticosteroids may be withdrawn safely in patients with COPD who do not have frequent exacerbations and have a blood eosinophil count of less than 0.3×10^9/L (excluding patients with an asthma overlap syndrome).
- Highly selected patients may be suitable for endobronchial valve placement or lung volume reduction surgery. Referral to a respiratory specialist and an expert centre is recommended.

Chronic obstructive pulmonary disease (COPD) is characterised by fixed airway obstruction on spirometry, persistent respiratory symptoms including dyspnoea, chronic cough, wheeze or sputum production and a history of exposure to noxious stimuli, generally cigarette smoke.[1] COPD was the fifth leading cause of death in 2021 and affects almost 8% of Australians aged over 45 years.[2] Presentations due to COPD have a substantial impact on health service use, contributing to 1% of general practice encounters, and are the second leading cause of avoidable hospital admissions.[3,4]

The COPD-X guidelines are a useful resource for investigation, diagnosis and management of COPD.[5] COPD should be considered in people aged over 35 years with a history of smoking or exposure to dust, gases or fumes. The diagnosis must be confirmed on spirometry with a forced expiratory volume in 1 second (FEV_1) to forced vital capacity ratio of below 0.70.[1] There is no evidence that COPD treatments have

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any benefit in patients without COPD diagnosed on spirometry. Smoking cessation is paramount to prevent further deterioration in lung function and symptoms. Other nonpharmacological interventions including annual influenza vaccination, COVID-19 vaccination and referral to pulmonary rehabilitation are strongly recommended. For COPD patients with persistent symptoms or frequent exacerbations, a stepwise approach to inhaler therapy can be initiated (Figure).[6]

It has been identified that eosinophilic inflammation may play a role in COPD, and therefore may present a potential target for treatment options. Selected patients with severe COPD and persistent breathlessness despite optimal medical treatment may be suitable for advanced therapies including endobronchial valve placement or lung-volume reduction surgery. Frailty has been identified as a clinical syndrome and has significant impacts in patients with COPD. This article examines these three topics in further detail.

The role of eosinophils in COPD

Eosinophils are innate immune cells that are believed to play a role in host defences in allergic disease. Historically, eosinophilic inflammation in airways disease has been considered to be suggestive of asthma, with neutrophilic inflammation predominantly seen in COPD. However, over recent years there has been increasing interest in the role of eosinophilic inflammation in COPD including its impact on morbidity and the potential role for treatment targeting this form of inflammation.

A normal blood eosinophil count is less than 0.5×10^9/L. A blood eosinophil count of 0.3×10^9/L or greater, which may still be within the normal range, is associated with an increased risk of acute exacerbations of COPD.[7,8] In 37 to 68% of people with COPD, blood eosinophil count was shown to be consistently 0.3×10^9/L or greater and to correlate with elevated levels of eosinophils in sputum.[9,10] In a small retrospective cohort study undertaken in Canada involving 167 patients hospitalised with an acute exacerbation of COPD, an elevated blood eosinophil count at initial admission was associated with an increase in readmissions for exacerbations (odds ratio [OR], 3.59; 95% confidence interval [CI], 1.65-7.82; p = 0.01) and an increase in all-cause readmissions over a 12-month period (OR, 2.32; 95% CI, 1.10-4.92; p = 0.03). Patients with blood eosinophilia also had a shorter time to first exacerbation.[11]

Eosinophils have been proposed to be a useful biomarker in COPD for prognostic purposes and to guide treatment with inhaled and oral corticosteroids. It has been suggested that patients with COPD and elevated blood eosinophil counts (defined as $\geq 0.3 \times 10^9$/L) may benefit from inhaled corticosteroid therapy to reduce the risk of exacerbations; however, this has not been assessed prospectively in a randomised controlled trial.[12,13]

Withdrawal of inhaled corticosteroids (ICS) is safe in some patients with COPD, as shown by a randomised, double-blind, multicentre controlled trial involving 1053 patients with COPD who were receiving long-term triple therapy. Withdrawal of ICS to de-escalate to dual bronchodilator therapy with a long-acting muscarinic antagonist (LAMA) and long-acting beta agonist (LABA) in patients without evidence of eosinophilic inflammation was safe, with no difference in exacerbation rate over a six-month period compared with participants who remained on triple therapy.[12] However, in patients with an elevated blood eosinophil count ($\geq 0.3 \times 10^9$/L), ICS withdrawal was associated with an increased risk of exacerbations and a small decrease in lung function.

Data suggest that treatment with oral corticosteroids for acute exacerbations of COPD may also be directed by baseline blood eosinophil count. Retrospective analysis of three randomised controlled trials comparing prednisolone to placebo showed a higher rate of treatment failure in patients with an elevated blood eosinophil count of 0.3×10^9/L or greater who did not receive prednisolone, whereas in patients with a blood eosinophil count of less than 0.3×10^9/L there was no difference in treatment failure in the prednisolone group compared with the placebo group.[14] However, in at least one of these trials, patients with a history of asthma were not specifically excluded. Asthma-COPD overlap is an increasingly recognised condition and corticosteroid treatment for acute exacerbations remains a key management strategy in patients with this condition. A 2024 UK trial randomised 308 patients in primary care presenting with an exacerbation of COPD to eosinophil-guided prednisolone or standard care. Patients in the intervention arm only received prednisolone if their blood eosinophil count was above 2%. This trial found that eosinophil guided prednisolone use was noninferior to standard care.[15]

The current evidence on the role of eosinophils in COPD is intriguing; however, the data are retrospective and mostly based on post-hoc analyses. There are no current clear cut-offs for blood eosinophil count to guide management, and further prospective trials are required to determine the association and guide treatment recommendations.

Biologic therapy in COPD

The introduction of targeted biologic therapy in eosinophilic asthma has had a significant impact among patients with symptomatic severe asthma. Benralizumab and mepolizumab are humanised monoclonal antibodies that are administered subcutaneously and block interleukin-5, thereby reducing peripheral circulating eosinophils in blood and tissue.[16,17] Mepolizumab significantly reduces exacerbation rates and symptoms and improves quality of life in patients with severe eosinophilic asthma.[18]

The data with regard to COPD are still emerging. A systematic review of randomised controlled trials comparing anti-IL5 therapy with placebo (three trials with mepolizumab and three trials

STEPWISE MANAGEMENT OF STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

	MILD	MODERATE	SEVERE
Typical symptoms	◦ few symptoms ◦ breathless on moderate exertion ◦ recurrent chest infections ◦ little or no effect on daily activities	◦ breathless walking on level ground ◦ increasing limitation of daily activities ◦ cough and sputum production ◦ exacerbations requiring oral corticosteroids and/or antibiotics	◦ breathless on minimal exertion ◦ daily activities severely curtailed ◦ experiencing regular sputum production ◦ chronic cough ◦ exacerbations of increasing frequency and severity
Typical lung function	**FEV_1 ≈ 60-80% predicted**	**FEV_1 ≈ 40-59% predicted**	**FEV_1 < 40% predicted**
Non-pharmacological interventions	**RISK REDUCTION** Check smoking status, support smoking cessation, recommend annual influenza vaccine and pneumococcal vaccine according to immunisation handbook		
	OPTIMISE FUNCTION Encourage regular exercise and physical activity, review nutrition, provide education, develop GP management plan and written COPD action plan (and initiate regular review)		
	CONSIDER CO-MORBIDITIES especially cardiovascular disease, anxiety, depression, lung cancer and osteoporosis		
	REFER symptomatic patients to pulmonary rehabilitation		
		Consider oxygen therapy for hypoxaemia, surgery, bronchoscopic interventions, palliative care services and advanced care planning	
Stepwise pharmacological interventions (inhaled medicines)*	**START with short-acting relievers:** (used as needed)		
	SABA (short-acting $beta_2$-agonist) OR **SAMA** (short-acting muscarinic antagonist)		
	ADD long-acting bronchodilators: **LAMA** (long-acting muscarinic antagonist) OR **LABA** (long-acting $beta_2$-agonist) Single inhaler dual therapy (**LAMA/LABA**) may be suitable		
		CONSIDER adding ICS (inhaled corticosteroids) FEV, ≤50% predicted AND ≥two exacerbations in last 12 months AND significant symptoms despite LAMA and LABA therapy*	**ICS/LABA** and **LAMA** Single inhaler triple therapy (**ICS/LAMA/LABA**) may be suitable
	Assess and optimise inhaler device technique at each visit		

REFER PATIENTS TO LUNG FOUNDATION AUSTRALIA FOR INFORMATION AND SUPPORT - FREECALL 1800 654 301

Lung Foundation Australia has a range of resources to promote understanding of COPD and assist with management.

Based on The COPD-X Plan: Australian and New Zealand Guidelines for the Management of COPD and COPD-X Concise Guide for Primary Care

*Refer to PBS criteria: www.pbs.gov.au

Register at www.copdx.org.au to receive an alert when the COPD-X Guidelines are updated

Lung Foundation Australia

1800 654 301 | Lungfoundation.com.au

Figure. Stepwise management of stable chronic obstructive pulmonary disease (COPD). (Information on inhalers is provided on page 2 of this two-page reference guide.)

Reproduced with permission from Lung Foundation Australia.[6]

with benrolizumab) suggested that anti-IL5 therapy was likely to reduce exacerbations in people with COPD and higher eosinophil levels, but did not improve health-related quality life.[19]

Dupilumab, a monoclonal antibody targeting IL-4 and IL-13, is used to prevent exacerbations in moderate to severe asthma. A 2023 randomised controlled trial showed that dupilimab reduced exacerbations in patients with COPD, chronic cough and sputum, and an eosinophil count above 0.3×10^9/L.[20] Although monoclonal antibody therapy may be beneficial in a specific subgroup of patients with COPD and eosinophilia, these therapies are not currently approved for use in COPD in Australia.

Endobronchial valves

Insertion of endobronchial valves may be an option for carefully selected patients with severe COPD with an FEV_1 of less than 50% predicted, hyperinflation with a total lung capacity of more than 100% predicted and residual volume of more than 175%.[21] Valves are inserted via bronchoscopy and occlude emphysematous lobes to block inspiratory airflow while allowing expiratory airflow, with the aim of reducing gas trapping by creating areas of atelectasis and shunting airflow elsewhere.[22]

Retrospective analysis of the large early endobronchial valve trials showed that patients with intact pleural fissures were most likely to benefit.[23] Several subsequent randomised controlled studies only recruited COPD patients with intact pleural fissures and showed a significant improvement in FEV_1, six-minute walk distance (6MWD) and quality of life in carefully selected patients.[24-28] However, it is important to recognise that there are potential major complications with endobronchial valve placement including pneumothorax (in 1.4 to 26% of patients) and COPD exacerbation (in 4 to 20% of patients).[29]

Endobronchial valves are not yet recommended as routine care. However, in highly selected patients with significant breathlessness despite optimised medical care and pulmonary rehabilitation, endobronchial valves may be a potential treatment option and patients should be assessed in a centre of expertise.[30]

Lung volume reduction surgery

Lung volume reduction surgery (LVRS) involves resection of emphysematous lung to decrease hyperinflation with the proposed benefits of improving diaphragmatic function, reducing respiratory muscle fatigue and intrathoracic pressure and improving cardiac ventricular filling.[31-34]

Patients with severe COPD who may benefit from LVRS include those aged under 75 years with persistent dyspnoea despite optimal medical treatment and pulmonary rehabilitation, who have heterogeneous emphysema (with varying emphysema tissue destruction between pulmonary lobes) and a 6MWD of greater than 140 metres.[35]

The National Emphysema Treatment Trial (NETT) was a large multicentre study involving 1218 patients with severe emphysema who were randomly allocated to either lung volume reduction surgery or standard medical care following completion of a pulmonary rehabilitation program.[35] Patients in the surgical group had a significant improvement in exercise capacity, FEV and quality of life scores. There was an increased 90-day mortality in the surgical group (7.9% compared with 1.3%); however, there was no overall difference in mortality at the end of follow up (mean follow up, 29 months). A recent systematic review and meta-analysis – heavily influenced by NETT data – concluded that LVRS reduces gas trapping and significantly improves FEV_1 and quality of life with an early increase in mortality but no difference in overall mortality.[29] Postoperative complications included prolonged air leak.

LVRS may be a suitable treatment option for highly selected patients with severe COPD. Patients should undergo pulmonary rehabilitation before considering surgery and should be assessed in an expert centre with a multidisciplinary panel including a respiratory physician, thoracic surgeon, radiologist and interventional pulmonologist.[30] A meta-analysis pooling all modalities of lung volume reduction (surgical and endobronchial) showed benefits in lung function, health related quality of life and 6MWD but reported that the odds ration for a severe adverse event including death was six times higher in the intervention group.[29]

Frailty and COPD

Frailty is a clinical syndrome in which there is a decline in physiological and functional reserve associated with increasing age, resulting in a reduced ability to cope with daily and acute stressors.[36,37] Frailty affects 7 to 13% of the older population aged above 65 years with the prevalence increasing with advancing age.[38-40] The syndrome is characterised by the presence of three or more of the following characteristics: loss of weight, slow walking speed, low physical activity, reduced grip strength and reduced endurance.[38] The phenotype is useful for identifying people at risk of poor health outcomes and is an independent predictor of increased risk of falls, hospitalisation and mortality among the elderly population.[38]

People with COPD are twice as likely to be frail as people without the condition, with the prevalence of frailty ranging between 19 and 57%.[37,40-43] Frailty in people with COPD has significant impacts, including increased risk of acute exacerbations and of readmission due to a new exacerbation episode during the 90 days after hospitalisation for an acute exacerbation of COPD.[40,42] Furthermore, frailty in COPD is associated with worsening impairment of lung function, poorer exercise tolerance (including a reduced 6MWD), increased levels of depression and anxiety and low socioeconomic status.[40,41,43] People with COPD and frailty are more likely to have multiple comorbidities, in particular cardiovascular disease.[40]

Exercise has been shown to improve frailty, and the addition of nutritional intervention is associated with further benefits.[44,45]

Although exercise appears to be an essential component in addressing frailty, the optimal exercise program has not yet been determined. Despite the benefits of pulmonary rehabilitation in patients with COPD being widely known, to date there have been no randomised controlled trials assessing the impact of pulmonary rehabilitation on frailty markers in COPD. A single centre prospective cohort study undertaken in the UK involving 816 patients with COPD and frailty showed that pulmonary rehabilitation improved exercise capacity, dyspnoea, hand grip strength, anxiety and depression. However, patients with frailty were also significantly less likely to complete pulmonary rehabilitation owing to either progression of their frailty or hospitalisation. Among the frail patients who persevered, 60% improved their frailty status to either prefrail or robust after completion of pulmonary rehabilitation.[43]

Increasing recognition of frailty among older adults and the population with COPD has highlighted the complex interplay between physiological, psychological and social factors. Although further data on effective exercise and nutritional interventions are needed, individuals at high risk of frailty may benefit from early identification and prompt referral to pulmonary rehabilitation.

Conclusion

Despite falling smoking rates in Australia, the burden of disease due to COPD remains substantial and has significant impacts on health care resources and utility. Although preventive health measures such as smoking cessation are vital, early identification and diagnosis of COPD is important to maintain lung function and prevent progression of symptoms. Both nonpharmacological and pharmacological interventions are recommended to reduce symptoms, prevent exacerbations and maintain lung function. Smoking cessation (beyond the scope of this article) is vital to prevent disease progression. Maintenance of physical activity and prevention of frailty is imperative in older adults with COPD and may improve their health outcomes. Further prospective studies assessing the impact of eosinophilic inflammation and targeted antieosinophilic treatments may be of benefit. In carefully selected patients with severe and persistent breathlessness in advanced COPD, advanced therapies including endobronchial valves or lung volume reduction surgery may be accessible. We recommend the COPD-X Guidelines as a useful resource to assist in identification, diagnosis and management of patients with COPD. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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New developments in COPD

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Inhaler therapy for COPD

An individualised approach to inhaler selection

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Inhaled therapy for chronic obstructive pulmonary disease can help reduce exacerbation frequency, admission to hospital and risk of death. Appropriate inhaler choice for the patient's capabilities and education and frequent assessment of inhaler technique can help improve adherence to therapy.

Chronic obstructive pulmonary disease (COPD) affects around one in seven adults over the age of 40 years in Australia and rises to 29% among people aged 75 years and older.[1,2] This common respiratory condition is the leading cause of potentially preventable hospital admissions.[3] Optimal management of COPD requires nonpharmacological and pharmacological strategies to optimise function through symptom relief and to reduce the risk of exacerbations. All patients with COPD can benefit from smoking cessation, pulmonary rehabilitation and vaccination.[1] Effective management of COPD should involve a multidisciplinary team including general practitioners, pharmacists, allied health professionals and practice or respiratory nurses.[4] This collaborative approach can help enhance quality of life and reduce disability for patients living with COPD.[1]

Although pharmacological therapy has not been shown to slow decline in lung function over time, inhaled therapy can reduce exacerbation frequency and improve symptoms and exercise tolerance.[1] This article outlines the inhaler devices available in Australia and discusses their benefits and drawbacks with respect to co-ordination of actuation and the patient's capabilities and preferences.

Key points

- **Adherence and inhaler satisfaction copredict improved health outcomes for patients with chronic obstructive pulmonary disease (COPD).**
- **The best inhaler device for a patient with COPD is one they can use; patient- and device-related factors should be considered when choosing an inhaler device.**
- **Assessment of a patient's co-ordination and inspiratory flow patterns should guide selection of inhaler devices.**
- **Adherence and device technique should be assessed regularly and before changing a patient's therapy.**
- **Patients should use only one type of device for all of their inhaled therapies, where possible.**

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Medication management

The mainstay of pharmacological treatment of COPD is inhaled bronchodilators and corticosteroids (Table). The Lung Foundation Australia recommends a stepwise approach to the pharmacological management of patients with stable COPD based on increasing severity of symptoms, lung function and history of exacerbations (Figure 1).[5] Inhaler device technique should be assessed and optimised at every opportunity.[1] Inhaler device polypharmacy should be minimised by using single-inhaler dual and triple therapy, where possible.

Adherence

Adherence to inhaled medication regimens is associated with reduced risk of death and admissions to hospital due to exacerbations in COPD.[6] Inhaler devices vary widely with regard to technique, patient suitability and patient preference; therefore, choosing the right device for the individual patient is crucial to ensuring correct technique and improving the likelihood of good adherence to therapy.[7] A large multinational survey showed that patients' overall satisfaction with their inhaler was significantly associated with treatment adherence, resulting in fewer exacerbations and fewer hospitalisations due to exacerbations.[8] Exploring a patient's concerns and capabilities is important when initiating or switching devices.[7] Pharmacists can play a pivotal role in optimising adherence and persistence, and providing education on safe and effective use of medications for COPD when dispensing and conducting collaborative medication reviews.

Table. PBS-listed pharmacological treatments for COPD

Medication class	Active ingredient	Inhaler device
Short-acting beta-2-agonist (SABA)	Salbutamol	pMDI (with counter)
		Autohaler
	Terbutaline	Turbuhaler
Short-acting muscarinic antagonist (SAMA)	Ipratropium	pMDI
Long-acting muscarinic antagonist (LAMA)	Aclidinium	Genuair
	Glycopyrronium	Breezhaler
	Tiotropium	HandiHaler, Respimat
	Tiotropium	Zonda
	Umeclidinium	Ellipta
Long-acting beta-2-agonist (LABA)	Indacaterol	Breezhaler
LAMA/LABA	Glycopyrronium/indacaterol	Breezhaler
	Aclidinium/formoterol	Genuair
	Umeclidinium/vilanterol	Ellipta
	Tiotropium/olodaterol	Respimat
ICS/LABA	Fluticasone propionate/ salmeterol	pMDI, Accuhaler, Easyhaler
	Budesonide/formoterol	Rapihaler, Turbuhaler, Spiromax, Easyhaler
ICS/LAMA/LABA	Fluticasone furoate/ umeclidinium/vilanterol	Ellipta
	Beclometasone/glycopyrronium/ formoterol	pMDI

Abbreviations: COPD = chronic obstructive pulmonary disease; pMDI = pressurised metered-dose inhaler.

Inhaler selection

Inhaled therapy is the primary route of administration for the treatment of patients with COPD. It comprises bronchodilators, antimuscarinic agents and corticosteroids delivered via various inhaler devices. A growing number of inhaler devices are available in Australia and can be grouped as:

- pressurised metered-dose inhalers (pMDIs)
- breath-actuated (BA)-pMDIs
- soft mist inhalers (SMIs)
- dry powder inhalers (DPIs).

Simultaneous use of different inhaler types, particularly a mixture of pMDI and DPI devices, is predictive of increased errors in inhalation and poor adherence to therapy.[9] Therefore, where possible, patients should use a single inhaler device to deliver multiple pharmacotherapies.

Aerosol science

A number of device-related factors influence aerosol deposition in the airways and include the following.

Particle size

Inhaler devices need to generate drug particles of an appropriate size to penetrate beyond the oropharyngeal area and deposit in the lungs. The aerodynamic diameter is the most important particle-related factor that affects aerosol deposition.[10] Particles greater than 5 micrometre are most likely to deposit by impaction in the oropharynx and be swallowed; particles between 1 and 5 micrometre will deposit in the large and conducting airways; and particles less than 1 micrometre are likely to reach the peripheral airways and alveoli or be exhaled.[10,11]

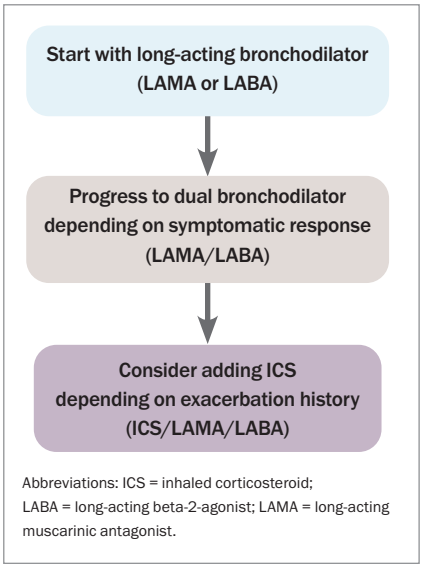


Figure 1. Stepwise management of a patient with stable chronic obstructive pulmonary disease.

Aerosols with high fine particle fraction have a high probability of penetrating beyond the upper airways and depositing in the lungs.[10] In the peripheral airways, particles deposit predominantly by sedimentation, highlighting the importance of breath-hold after inhalation with some inhaler devices.[11]

Aerosol velocity and duration

pMDIs generate a high velocity cloud over a short period of time, creating difficulties in synchronising inhaler actuation with inspiration. High aerosol velocity from pMDIs also increases the probability of deposition by impaction in the oropharynx and large conducting airways.[11] Only about 10 to 20% of the delivered dose from a pMDI is deposited in the lungs.[12] Use of spacers with pMDIs reduces aerosol particle velocity, increasing lung deposition. Aerosol velocity from an SMI (such as Respimat) is three to 10 times slower than for pMDIs.[13] The mean spray duration is 1.5 seconds, compared with 0.15 to 0.36 seconds for pMDIs.[14]

Inspiratory flow rate and volume

The patient's inspiratory volume and flow rate are important patient-related factors influencing aerosol deposition in the airways. Each inhaler device has its own unique optimal peak inspiratory flow rate (PIFR).[15] For pMDIs, BA-pMDIs and SMIs, inspiratory flow rate should be about 30 L/min to minimise deposition in the upper airways and enhance delivery to the lungs.[10]

Exhalation before inhalation

Exhalation to functional residual capacity or residual volume increases PIFR and inhaled volume, which may augment drug dispersion and facilitate fine particle generation from a DPI.[16] This is also a commonly missed step before actuation with pMDIs.[17]

Internal resistance of inhaler

The internal resistance of DPIs varies by device, requiring different inspiratory effort to produce sufficient flow rate.[18] Lower resistance devices require patients to produce a higher PIFR at a given pressure gradient than higher resistance devices.[19]

Simultaneous use of different inhaler types ... is predictive of increased errors in inhalation and poor adherence to therapy. Therefore, where possible, patients should use a single inhaler device to deliver multiple pharmacotherapies

Duration of breath-hold

Breath-holding increases lung deposition through the process of sedimentation.[11] Although the breath-hold capacity of patients with COPD is often limited, it is important that patients are advised to hold their breath for five seconds, or as long as possible, after inhalation.[20] Breath-holding time may be more critical with fine particle pMDIs.[9]

Metered dose and soft mist inhalers

pMDIs are aerosol-based devices that require a slow and steady inhalation over four to five seconds to reduce oropharyngeal deposition and optimise delivery to the lungs.[10] pMDIs come as either a solution or suspension system and all contain propellants. Co-ordination of actuation with inhalation is required with pMDIs.

SMIs, for example Respimat, generate an aerosol mist from an aqueous solution and do not contain propellants.[13] Respimat has a significantly slower plume velocity and longer spray duration compared with pMDIs.[13] Therefore, SMIs require less patient co-ordination than pMDIs.[19]

Spacers

Co-ordination errors are the most common error with pMDIs.[10,21,22] Many patients cannot use a pMDI correctly, even with education and training. Spacers can be used to overcome the difficulty of co-ordinating inhalation and actuation while inhaling slowly and deeply.[11] If a slow inhalation over four to five seconds is not achievable, tidal breathing with four breaths in and out normally through the spacer is an alternative method. In addition, spacers reduce oropharyngeal deposition, facilitate vaporisation of particles to an optimal size and increase deposition of the active ingredient in the lungs.[9,23] When using a spacer, it is important for patients to shake the pMDI before use and start inhalation promptly, as aerosolised particles remain suspended in the spacer for less than 10 seconds.[9] It is also important that the pMDI is shaken before a second dose via a spacer.

Dry powder inhalers

DPIs are breath-actuated devices that deliver the medication in powder form from a capsule, reservoir or sealed blister strip. DPIs require exhalation to functional residual capacity before inhalation with a forceful, deep inhalation over two to three seconds.[10]

The European Respiratory Society/International Society for Aerosols in Medicine taskforce recommends choosing an inhaler based on two factors:[10]

- level of inspiratory flow
- co-ordination of inhalation/actuation (Figure 2[24]).

When considering prescribing a DPI, evaluating the patients' PIFR is important. Patients with COPD may have severe airflow limitation, accompanied by decreased inspiratory capacity, hyperinflation and compromised respiratory muscles, which may reduce inspiratory flow rates and diminish lower airway deposition from

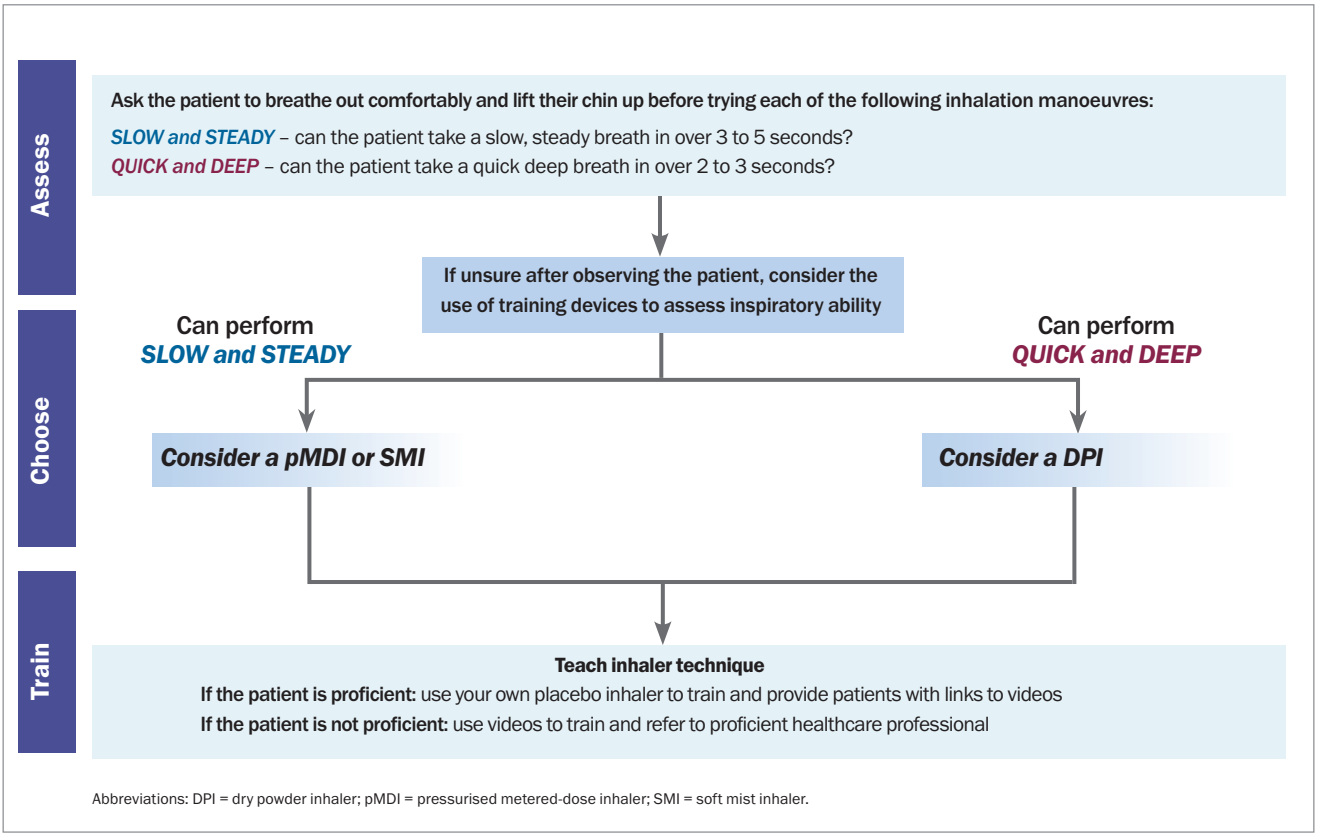


Figure 2. Inhaler choice decision aid.
Adapted with permission from: Usmani OS, et al. Inhaler choice guideline 2017.[24]

DPIs. Suboptimal PIFR in patients with COPD may limit their ability to effectively use DPIs and deliver the medication throughout the lungs, particularly during acute exacerbations.[11,19,24,25] However, most patients with COPD are able to generate inspiratory flows necessary for effective DPI use.[26]

Insufficient inspiratory flow rate is one of the most common errors with DPIs.[10,21,22,27] A PIFR value of 60 L/min is generally accepted to be optimal for most DPIs.[28] PIFR values greater than 60 L/min can be associated with excessively turbulent flow and therefore poor lung deposition.[15] A quick and forceful inhalation is required with DPIs to deagglomerate the active ingredient powder from carrier powder (usually lactose) and aerosolise the particles.[10] Airflow achieved early in the inspiratory profile disaggregates drug from carrier powder and determines particle size distribution of the aerosol.[29]

The minimal inspiratory flow rate required for low resistance DPI devices (e.g. Breezhaler) is above 90 L/min, 50 to 60 L/min for medium-resistance DPI (e.g. Turbuhaler, Genuair, Spiromax) and below 50 L/min for a high-resistance DPI (e.g. Handihaler).[30]

Although the optimal flow rate differs between each DPI device due to differences in inhaler design and internal resistance, the principle remains the same for all – a rapid and forceful inhalation is required. It is important that the inspiratory flow rate at the start of the inhalation is forceful, rather than gradually increasing.[31]

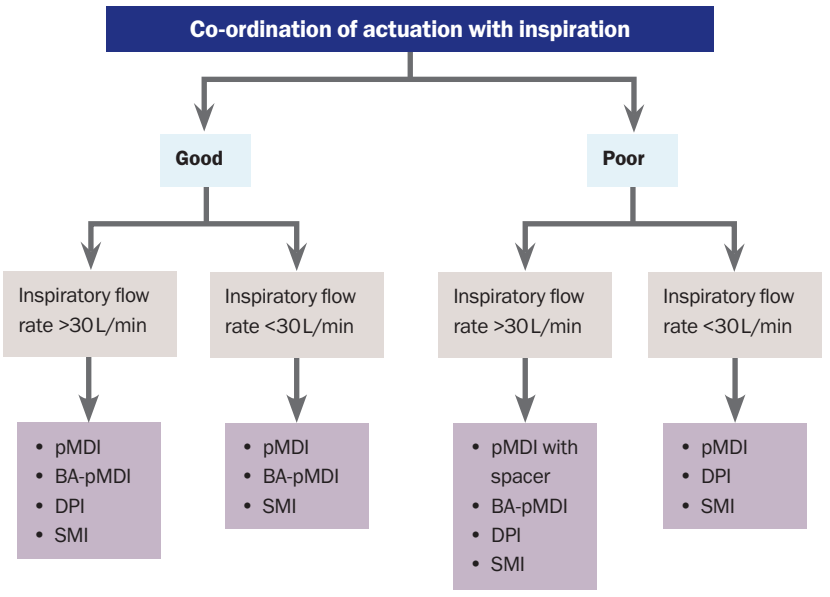
A decision algorithm based on inspiratory flow rate and ability to co-ordinate inhalation actuation is shown in the Flowchart.[32] An In-Check Dial is a handheld device with an adjustable dial to mimic the internal resistance of different inhalers and can be used to measure and identify suboptimal PIFR and optimise inhaler device selection.[15]

Inhaler technique

Optimal inhaler technique is critical to effective COPD management. When used correctly, all inhalers are effective and can achieve the same therapeutic effect, although different doses may be required.[33] Mastering an inhaler device involves correct preparation and handling before inhalation, and optimal inhalation technique. There are seven basics steps to using an inhaler device, pertinent to all devices (Box).[34] Errors in any step may lead to inadequate drug delivery to the lungs.

Up to 94% of patients do not use their inhaler device correctly, resulting in inadequate dosing, suboptimal disease control, worsening of quality of life and increased hospital admissions and mortality.[35] A recent analysis of inhaler technique in 364 patients with COPD showed that two-thirds of patients made one or more crucial errors, particularly among those using several different devices.[36] The most common errors

An approach to inhaler device selection



Abbreviations: BA-pMDI = breath-actuated pressurised metered-dose inhaler; DPI = dry powder inhaler; pMDI = pressurised metered-dose inhaler; SMI = soft mist inhaler.

Seven steps to correct inhaler technique

1. Prepare the inhaler device, check dose counter (when present), shake inhaler if applicable
2. Prepare or load the dose
3. Breathe out, fully and gently, away from the mouthpiece
4. Place inhaler mouthpiece in the mouth, tilt the chin up and seal the lips around the mouthpiece
5. Breathe in
   - pMDI and SMI: slow and steady
   - DPI: quick and deep
6. Remove inhaler from the mouth and hold the breath for up to 10 seconds
7. Close inhaler/replace cap and wait for a few seconds then repeat as necessary

Adapted from Scullion J et al, 2018.[34]

with DPIs include failure to exhale before actuation, failure to breath-hold after inhalation, incorrect positioning of the inhaler, incorrect rotation sequence and failure to execute a forceful and deep inhalation.[35] Common errors with pMDIs include insufficient inspiratory force (not slow and deep enough), failure to actuate before inhalation and breath-hold after inhalation and incorrect second-dose preparation, timing or inhalation.[21] Older age, cognitive impairment, multiple inhaler devices and lack of previous training are all risk factors for poor inhaler use and adherence.[37]

As many as 25% of patients have never received verbal inhaler technique instruction.[35] All health professionals involved in the care of patients with COPD should check a patient's inhaler technique at every opportunity. Numerous studies show that inhaler technique interventions in community pharmacies can be effective.[38-41] Pharmacists conducting comprehensive medication reviews (Home Medicine Review) have an opportunity to check inhaler device technique in the privacy of the patient's home. Providing written instructions highlighting incorrect steps helps patients maintain correct technique for longer.[38] Inhaler technique can decline in as little as one to two months after mastering correct technique; therefore, follow-up over time is essential to maintain correct technique.[42,43] Videos on inhaler device technique are available on the Lung Foundation Australia website (https://lungfoundation.com.au/patients-carers/after-your-diagnosis-title/inhaler-devices/).

Conclusion

Choosing the right inhaler for the right patient is crucial to optimal management for patients living with COPD. Choice of an inhaler can be based on many patient and prescriber factors; two important patient-related factors are the patient's inspiratory flow rate and their ability to co-ordinate inhalation and actuation. The patient's inhaler preferences should also be considered. Inhaler device technique should be diligently reviewed and optimised at each formal review and at other opportune times. Multidisciplinary collaboration can improve the management of patients with COPD in primary care. **RMT**

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A list of references is included in the online version of this article (www.respiratorymedicinetoday.com.au)

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Inhaler therapy for COPD

An individualised approach to inhaler selection

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COPD exacerbations

A pragmatic approach to prevention, diagnosis and management

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Prevention, timely diagnosis and evidence-based management of exacerbations of chronic obstructive pulmonary disease (COPD) are crucial in primary care, to maintain the wellbeing of people living with COPD.

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease that is a leading cause of death globally. Smoking is the most important modifiable contributing risk factor, and smoking cessation can slow decline in lung function.[1,2] COPD exacerbations are defined as an acute worsening of respiratory symptoms that require a change in management. This management can be through self-management by the patient using their COPD action plan, GP care or, for more severe exacerbations, emergency department and hospital care. Prevention, timely diagnosis and effective management of exacerbations of COPD are of the utmost importance in primary care, to maximise the wellbeing of people living with COPD.

This article discusses the steps in diagnosis and the primary care management of patients with an exacerbation of COPD. It also outlines the recommended components of a strategy to prevent further COPD exacerbations.

KEY POINTS

- Exacerbations of COPD can be infective (bacterial or viral) or noninfective.
- Early diagnosis and treatment of exacerbations is crucial to prevent hospital admission and delay decline in lung function.
- Principles of management are to reverse bronchoconstriction (with bronchodilators) and inflammation (with corticosteroids), reduce dyspnoea (through airway clearance, controlled oxygen therapy and ventilatory assistance) and treat or remove triggers (with antibiotic therapy).
- Prevention of exacerbations is important, encompassing both pharmacological and nonpharmacological treatment in a stepwise approach.

Epidemiology of COPD exacerbations

Exacerbations of COPD are the major cause of morbidity and mortality in patients with COPD and contribute significantly to healthcare costs in Australia. In 2018, 7113 people (3783 men and 3330 women) died from COPD, making it the fifth leading cause of death.[3] In 2015-16, COPD cost the Australian health system an

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Figure 1. Algorithm for managing exacerbations in primary care (https://lungfoundation.com.au/resources/managing-exacerbations-algorithm/).

estimated $977 million: $536 million for hospital care, $189 million for nonhospital medical services and $252 million for pharmaceuticals.[3] An 18-fold variation in hospitalisation rates for COPD is seen across jurisdictions nationally, emphasising the need to achieve better equity of healthcare access for all Australians with COPD.[4]

Causes of COPD exacerbations

A range of factors can trigger COPD exacerbations, most commonly bacterial or viral infections and ambient pollution.[5] Nearly half of COPD exacerbations are caused by bacterial infection.[6] Respiratory viral infections may become more serious, with bacterial coinfections worsening the exacerbation. The most frequent bacterial causes of COPD exacerbations are *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa*.

Conventional culture-based methods have confirmed the role of bacteria in the progression of lung disease. Further, investigations into the lung microbiome, which includes bacterial, fungal and viral elements, have found that complex microbial communities interact with the host immune system to influence clinical outcomes.[7,8] Exacerbations and respiratory infections are significant clinical features in progression of COPD.[9] The composition of the lung microbiome changes with smoking and stage of COPD severity, during exacerbations and with treatment of COPD during stability and acute episodes.[10]

Air pollutants, including fine particle matter, ozone, nitrogen dioxide and sulfur dioxide, have been associated with increased exacerbations and increasing mortality.[11] Extremes of temperature, both hot and cold, have also been implicated.[12] Other causes of acute respiratory distress, including heart failure, pulmonary embolism and pneumothorax, should also be considered in the differential diagnosis of COPD exacerbations.

Pathology and pathophysiology

Respiratory infections and inhaled irritants increase inflammation (especially infiltration by inflammatory cells) and excess respiratory secretions in the airway lumen. These pathological features in the airway during an exacerbation lead to the pathophysiological changes of worsened airflow obstruction, dynamic hyperinflation and sputum production. The end result is a cascade of increasing symptoms, fatigue and respiratory failure, particularly in more severe exacerbations.

Diagnosis of COPD exacerbations

A COPD exacerbation should be suspected in patients with an acute change in breathlessness, with or without a change in sputum production or colour or fever.

Early diagnosis and treatment of exacerbations is crucial as it can prevent hospital admission and delay decline in lung function.[13,14]

In a mild exacerbation, physical examination at rest may have unremarkable results; however, exertional dyspnoea or wheeze may be unmasked after walking a short distance. In moderate to severe exacerbations, observation may show an increased respiratory rate, hypoxia, tachycardia and fever. On chest auscultation, a wheeze or crackles may be present. The patient should be thoroughly examined, and other potential causes of acute breathlessness should be considered, including congestive cardiac failure, cardiac arrhythmia and, less commonly, pulmonary embolism.[15] Further diagnostic testing with an ECG, basic blood tests and chest x-ray is often warranted to guide further treatment.

Patients with a severe exacerbation presenting with significant hypoxia, respiratory distress or altered mental status require additional supports and should be referred to the local emergency department for review.[16]

Management of COPD exacerbations

Early identification and treatment of a COPD exacerbation are important, as each exacerbation can contribute to progressive loss of lung function and reduction in quality of life.[17] Treatment usually begins with a patient self-management plan (https://lungfoundation.com.au/resources/copd-action-plan/) and may require medical review in primary care (Figure 1) or hospitalisation (Figure 2).

Principles of management of a COPD exacerbation are to:

- reverse bronchoconstriction (with bronchodilators)
- reverse inflammation (with corticosteroids)
- reduce dyspnoea (through airway clearance, controlled oxygen therapy and ventilatory assistance) and
- treat or eliminate triggers (with antibiotic therapy).

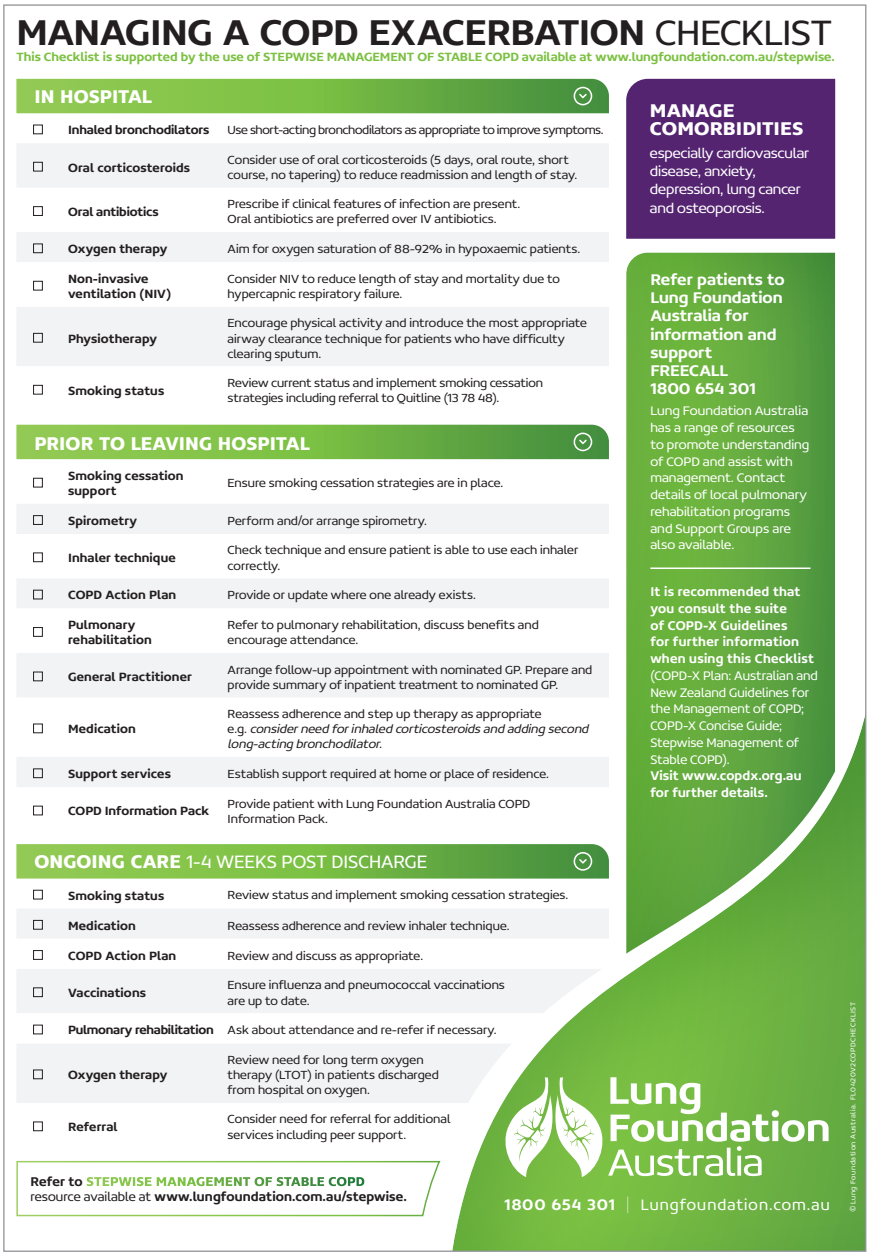

Figure 2. Checklist for managing a COPD exacerbation (https://lungfoundation.com.au/resources/managing-copd-exacerbation-checklist/).

Bronchodilators

The initiation of a regular short-acting beta-agonist (e.g. salbutamol) is recommended for all patients with a COPD exacerbation as it provides immediate relief of dyspnoea, although high-quality supporting evidence is limited.[2] A long-acting bronchodilator in the form of a long-acting muscarinic antagonist (LAMA) can be either continued during the exacerbation or temporarily replaced by a short-acting muscarinic antagonist (ipratropium).

Bronchodilators can be delivered via either a metered-dose inhaler with spacer or a nebuliser. A Cochrane review found

no significant difference in outcomes of patients in a nonintensive care setting between these two methods of delivery.[18] Thus, the method of delivery should be determined by infectious risk, cost and the patient's ability to co-ordinate an inhaler with spacer. The dose and frequency can be titrated to symptom severity.

Corticosteroids

Systemic corticosteroids (e.g. prednisolone) suppress airway inflammation to improve airflow, reduce the risk of treatment failure by over half compared with placebo, shorten the duration of hospitalisation and lower the rate of relapse at one month.[19,20] Oral administration is usually preferred, as there is no significant difference in outcome compared with parenteral administration.[21] A five-day course of prednisolone is recommended (e.g. 30 to 50 mg daily, not tapered), with a Cochrane meta-analysis showing no difference in treatment efficacy compared with longer courses, which are associated with an increased risk of sepsis and corticosteroid-related complications.[22] Evidence is also emerging supporting individualised treatment according to blood eosinophilia count, as eosinophilic inflammation is more likely to be corticosteroid-responsive.[23]

Antibiotics

Infective exacerbations of COPD should be suspected in patients presenting with increased sputum production and a change in sputum colour, with or without fever. Therapeutic guidelines recommend treatment with oral amoxicillin or doxycycline for five days for patients whose clinical presentation suggests a bacterial exercerbation.[24]

Noninfective and viral exacerbations of COPD are common and can be challenging to distinguish from bacterial infection. Inflammatory markers, including C-reactive protein, can be measured to guide antibiotic therapy.[25] PCR testing of swabs for respiratory viruses including SARS-CoV-2 can be considered, as viral coinfection is detected in 25% of infective exacerbations.[25] Sputum culture is not routinely recommended for exacerbations because persistent colonisation of the lower airways in many patients means that positive culture results do not always indicate active infection.[1]

Airway clearance

Airway clearance techniques (ACTs) may be considered for patients with an

exacerbation or with daily sputum production.[2] ACTs help optimise sputum clearance to reduce coughing, slow decline in lung function and reduce the frequency of exacerbations. ACTs that utilise positive expiratory pressure resistance may be of greater benefit than other therapies.[26] Referral to a chest physiotherapist is recommended for patient education and training in ACTs.

Respiratory support

In people with COPD, the oxygen saturation target should be in the range 88 to 92%. Overoxygenation increases mortality and the risk of hypercapnia.[27] If an acute exacerbation leads to hypercapnic respiratory failure ($PaCO_2$ >45 mmHg and pH less than 7.35 on arterial blood gas assessment) then hospital admission is required for noninvasive ventilation, as this reduces mortality.[28]

Care after an exacerbation

Medical review is recommended within seven days of hospital discharge. Following the patient's discharge from hospital or acute management in primary care, COPD management should be reassessed, including the level of physical activity, spirometry and referral for pulmonary rehabilitation (Figure 2). Pulmonary rehabilitation reduces breathlessness, improves exercise capacity and wellbeing and reduces exacerbations.[29] All medicines should be reviewed, as well as inhaler technique (useful video resources are available at www.lungfoundation.com.au). Pneumococcal, influenza and COVID-19 vaccination status should be checked, smoking cessation encouraged and the COPD written action plan updated. Any chest x-ray abnormalities should be reviewed for resolution, with repeat chest x-ray in four to six weeks.[2]

Prevention of exacerbations

Preventing further exacerbations is crucial as exacerbations contribute to disease progression and mortality. Exacerbations are a strong predictor of future exacerbations.[30] Prevention of exacerbations encompasses both pharmacological and nonpharmacological components.

Smoking cessation is essential. Recommended strategies include combination long and short-acting nicotine replacement therapy, medications, such as varenicline, and Quitline referrals for counselling.

Long-acting inhaled medicines should be optimised using a stepwise approach, along with regular patient education on inhaler technique to ensure appropriate delivery of medication.[2] Vaccinations should be kept up to date according to *Australian Immunisation Handbook* recommendations, to reduce the chance and severity of infective exacerbations.[31]

All patients with dyspnoea on exertion, especially after hospitalisation for an exacerbation, should be offered referral to pulmonary rehabilitation (https://lungfoundation.com.au/patients-carers/support-services/lung-disease-and-exercise/pulmonary-rehabilitation/). This has been shown to reduce patient symptoms and hospitalisations, as well as to improve mental health.[17]

Areas of uncertainty

The current definition of a COPD exacerbation is subjective, defined as the worsening of respiratory symptoms requiring a change in management.[17] Diagnosis can be difficult, with many comorbidities both mimicking and causing exacerbations. These include asthma, pneumonia, pulmonary embolism and cardiovascular events. Predictive factors for short-term hospital readmission have been proposed.[32,33] Risk factors include comorbidities, frailty, low lung function, socioeconomic disadvantage and hypercapnic respiratory failure.[34] Emerging evidence suggests that, in the future, artificial intelligence may be able to assist with accurate diagnosis, phenotype characterisation and prognosis prediction through access to databases of electronic medical records on patients with COPD.[35]

Conclusion

A pragmatic, collaborative approach to diagnosis and treatment of COPD exacerbations can enhance the partnership between clinicians in primary care and tertiary care, to achieve better lives for people with COPD. By effectively managing exacerbations and, importantly, implementing systematic approaches to preventing exacerbations, our multidisciplinary care will keep people with COPD as well as possible in the community. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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COPD exacerbations

A pragmatic approach to prevention, diagnosis and management

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Asthma-COPD overlap

Implications for patient management

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Asthma-COPD overlap (ACO) is characterised by persistent airflow limitation with features typically associated with both asthma and chronic obstructive pulmonary disease (COPD). Because there is no universally accepted definition of ACO, reliable data on managing patients exhibiting ACO are lacking. An approach to treating chronic airways disease that targets identifiable clinical traits rather than the disease label is increasingly recommended.

Asthma and chronic obstructive pulmonary disease (COPD) are the most prevalent chronic lung diseases and are responsible for considerable morbidity, mortality and the use of healthcare resources globally.[1,2] In Australia, up to 11% of the population report a diagnosis of asthma.[3] The prevalence of COPD is estimated at 7.5% of Australians over 40 years of age, and this increases to 30% for those over 75 years.[4] Once managed as distinct diagnoses, it is now increasingly acknowledged that asthma and COPD have

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Key points

- **The term asthma-COPD overlap (ACO) was proposed to reflect the overlapping aetiologies and clinical features of asthma and chronic obstructive pulmonary disease (COPD) and the large population of patients who demonstrate features of both.**
- **Clinical features and underlying inflammatory and physiological mechanisms of asthma and COPD are highly variable and affect the utility of the ACO umbrella in clinical practice. This heterogeneity limits both high-quality research on the subject and treatment recommendations specific to ACO.**
- **Initiation of inhaled corticosteroids is recommended in patients who clearly demonstrate features of both asthma and COPD, as this is a critical component of asthma control.**
- **An individualised approach to treatment, with a focus on identifying and treating disease traits is more important than managing disease labels, and will lead to better overall care of the patient with chronic airway disease.**

overlapping aetiologies and clinical features that translate to a high likelihood that patients will demonstrate features of both conditions.[5] Despite this reality, guidelines for both conditions have evolved separately and differ significantly in recommendations for treatment.[1,2] The term asthma-COPD overlap (ACO) was proposed to assist clinicians resolve this dilemma and provide an approach to treatment; however, there is controversy over whether ACO should be regarded as a separate entity in itself. The alternative is for clinicians to move away from the confinement of disease labels and instead take a 'treatable traits' approach to chronic airways disease and identify important clinical phenotypes and target treatment towards these.[6] This article discusses ACO its implications for patient treatment.

What is asthma-COPD overlap (ACO)?

Although proposed definitions of ACO differ between respiratory societies, ACO is generally characterised by persistent airflow limitation with features typically associated with both asthma and COPD, such as a history of smoking, a documented history of asthma before the age of 40, a history of atopy and elevated eosinophils on full blood count (FBC; more than 0.3×10^9/L).[7,8] This definition is based on expert opinion and does not define ACO as an independent entity based on either pathophysiology or disease outcomes.

In clinical practice, the relative contribution from features of asthma or COPD will differ substantially between patients, resulting in a cohort of patients with the label of ACO who display highly variable disease mechanisms and clinical outcomes A patient who fits the above definition of ACO may indeed have asthma and COPD concurrently, though they may instead have an atypical manifestation of one of these conditions alone, such as COPD with eosinophilic inflammation, or asthma with irreversible airflow obstruction due to airway remodelling.

The alternative is for clinicians to move away from the confinement of disease labels and instead take a 'treatable traits' approach to chronic airways disease

Pathophysiology and clinical features

Asthma and COPD are conditions that feature airflow limitation and chronic airway inflammation,[1,2] although each of these chronic airway diseases are themselves heterogenous conditions with various contributing disease mechanisms and inflammatory processes. This highlights the complexity and lack of utility of the ACO umbrella.

Asthma is defined as an inflammatory airways disease that often, but not exclusively, begins in childhood. Asthma involves the large and small airways, but not the terminal bronchioles or alveoli, and is characterised by airway hyper-responsiveness and reversible airway obstruction.[2] COPD is also an inflammatory airways disorder associated with inhaled noxious agents such as tobacco smoke, which usually manifests in people over 40 years of age. COPD predominantly affects the small airways and is associated with varying amounts of alveolar tissue breakdown and mucous hypersecretion. The condition is characterised by progressive and irreversible airway obstruction, loss of lung elastic recoil and hyperinflation, and symptoms of breathlessness, productive cough and wheeze.[1]

The inflammatory cells and mediators that drive COPD and asthma broadly differ but there is no pathognomonic inflammatory endotype that defines ACO. COPD is typically characterised by inflammation, referred to as a type 1 (T1) immune response, featuring a predominance of neutrophils, CD8+ T cells, macrophages and inflammatory mediators such as interleukin (IL)-8 and tumour necrosis factor (TNF) alpha-1. Asthma is usually a type 2 immune process characterised by elevated eosinophils, mast cells, CD4+ T cells and cytokines IL-4, IL-5 and IL-13.[2,9] Type 2 (T2) inflammation refers to a pattern of inflammation driven by T helper 2 cells and other components of the innate immune system, with increased activity of eosinophils and the allergic inflammatory cascade. Active T2 inflammation has been demonstrated to correspond with asthma symptoms, increased exacerbation frequency and lung function decline. T2 inflammation is generally responsive to inhaled corticosteroid (ICS) or oral corticosteroid (OCS) therapy. Neither of these inflammatory processes are specific for either disease. Asthma driven by neutrophilic inflammation is a recognised phenotype in 15 to 20% of people with asthma,[10] and eosinophilic inflammation is recognised in up to 20% of people with COPD.[2,11] The differences between and similarities in airway inflammation and airway remodelling in asthma, COPD and ACO are complex and require further investigation.[12]

Similarly, spirometry does not always distinguish between asthma and COPD. Bronchodilator reversibility (BDR) is a defining feature of asthma; however, patients with COPD often and variably demonstrate a significant improvement in forced expiratory volume in one second (FEV_1) with bronchodilators.[13] Conversely, airflow obstruction that is not fully reversible is a defining feature of COPD, but can occur as a result of airway remodelling in cases of asthma alone, particularly in patients with longstanding disease.[2] Patients with either COPD or asthma can also demonstrate hyper-responsiveness on bronchial provocation testing.[14]

Diagnosing patients with ACO

Box 1 outlines three case studies of patients with aetiologies that fit the description of ACO based on current consensus statements. However, it could be argued these patients have different diseases that will affect their prognosis and response to treatment.

Patient 1 has a history of early-onset asthma with typical symptoms, a history of atopy and elevated biomarkers to suggest active type 2 inflammation. Elevated levels of eosinophils on FBC (particularly when higher than 0.3×10^9/L) correlate with active T2 inflammation and are a readily available way to assess this. Eosinophils can be elevated due to other causes, such as potential atopy in the case of Patient 1. Although not routinely available in general practice, fractional exhalation of nitric oxide (FeNO) is a more

specific and noninvasive method of detecting eosinophilic airway inflammation, with readings over 50 ppb consistent with this. Despite the patient's features of allergic asthma, his heavy smoking history and CT evidence of emphysema are typically associated with COPD.

Patient 2 has a diagnosis of early-onset asthma and significant airflow obstruction. The incompletely reversible airflow obstruction suggests a diagnosis of COPD, although her smoking history is relatively mild and there is no CT evidence of emphysema. It is likely that the patient's fixed airflow obstruction is a direct result of her longstanding asthma and subsequent airway remodelling, rather than loss of elastic recoil and increased airway resistance as that occurs with COPD associated with an emphysema predominant phenotype. The absence of biomarkers of T2 inflammation suggests a poor response to typical ICS and OCS therapy. A poor response to corticosteroid therapy has been well described in people with neutrophilic asthma.

Patient 3 has a heavy smoking history and clear radiological evidence of emphysema. BDR can exist in COPD alone; however, the magnitude of BDR in this case increases the likelihood that this is true evidence of concurrent asthma. Although eosinophilic inflammation is recognised in COPD, the elevated T2 biomarkers in Patient 3 may suggest a diagnosis of asthma as described above.

The patients described in these case studies will be recognisable to all clinicians and will raise questions including: What treatment paradigm should be followed? Do you treat a disease label, such as asthma, COPD, or ACO, or do you treat the individual treatable traits?

Quality of research on ACO

Prospective intervention trials of patients who meet a definition of ACO are lacking, with most research limited to cohort and case-controlled studies.[15] Data from these studies yield varying and sometimes conflicting results because of the lack of an accepted definition of ACO and inconsistent inclusion criteria.[7,15] Treatment recommendations for ACO are extrapolated from trials of asthma and COPD alone; however, the inclusion criteria for these same trials would have excluded most patients with ACO.[7,16-19] For example, asthma trials will often exclude patients with even a minor smoking history or with a past diagnosis of COPD,[20-22] and most COPD studies will exclude never-smokers or those with a history of asthma.[17,23]

Epidemiology and natural history

The reported global prevalence of ACO varies between 15 and 55% but is critically dependent on the inclusion criteria in the individual studies.[8] Patients who meet the definition of ACO are generally younger, have a higher body mass index, are less likely to have a smoking history, have a higher FEV_1 and more healthcare utilisation than patients with COPD alone.[15] Patients with ACO are at increased risk of exacerbations, hospitalisations and a greater number of chronic respiratory symptoms; therefore, outcomes may be worse with ACO compared with asthma or COPD alone.[5,15] Observations are often inconsistent between studies, which makes it difficult to draw valid conclusions.

1. Case studies. Typical aetiologies for patients with asthma-COPD overlap

Patient 1

Greg is a 68-year-old man who was diagnosed with asthma in childhood. He exhibits typical episodic symptoms, including wheeze and chest tightness, which supports the diagnosis of asthma, and a productive cough consistent with chronic mucous hypersecretion (also known as chronic bronchitis). He has frequent exacerbations of these symptoms – three episodes per year – and a history of atopy.

Greg was a pack-a-day smoker for 30 years (i.e. has a 30 pack year smoking history), but successfully quit 10 years ago.

Spirometry testing reveals that Greg has moderate airflow obstruction (forced expiratory volume in one second [FEV_1] 68% predicted) and significant bronchodilator reversibility (BDR) (200 mL and 15% response to salbutamol). Greg's blood eosinophils level is 0.4×10^9/L and fractional exhaled nitric oxide (FeNO) is 67 ppb. He does not have evidence of lower respiratory tract infections, and there are no organisms isolated on sputum culture. A chest CT scan reveals he has bilateral upper lobe emphysema.

What are the alternative disease labels for Patient 1?

Allergic asthma and emphysema.

Patient 2

Susan is 54 years old with a longstanding history of asthma since childhood that has been poorly controlled. She experiences regular cough and purulent sputum. She is often breathless on exertion, such as walking up one flight of stairs.

Her exacerbations are increasing in frequency, with three in the past 12 months, all requiring treatment with antibiotics. She has no history of atopy.

She has a 10 pack year smoking history, but has recently quit.

Susan has severe airflow obstruction (FEV_1 48% predicted) but no significant BDR (100 mL and 5% response to salbutamol). Her blood eosinophils level is 0.1×10^9/L and FeNO is 13 ppb. Sputum microbiology reveals infection with *Haemophilus influenzae*. Her chest CT scan is clear, with no emphysema or bronchiectasis.

What are the alternative disease labels for Patient 2?

Asthma with non-T2 inflammation.

Patient 3

John, 73 years old, has declining exercise tolerance in the last 12 months, which is now limited to 100 m on the flat. He is an active smoker of 40 pack years. He has no previous history of asthma or atopy.

John has frequent exacerbations, with four in the past year, all requiring oral prednisone. He has moderate airflow obstruction (FEV_1 62% predicted) and significant BDR (400 mL and 20% response to salbutamol). John's blood eosinophils level is at 0.3×10^9/L and FeNO at 55 ppb. He has no lower respiratory tract infection. A chest CT scan reveals widespread centrilobular emphysema.

What are the alternative disease labels for Patient 3?

COPD with eosinophilic inflammation or COPD with bronchodilator reversibility.

Table. A treatable traits approach to managing patients with asthma, COPD or asthma-COPD overlap[4]

Treatable trait	Assessment and management in the primary care setting		Advanced options in specialist centre	
	Assessment	Treatment	Assessment	Treatment
Airway smooth muscle hyper-reactivity	• Bronchodilator reversibility test	• LABA or LAMA • ICS	• Bronchial provocation challenge	• LABA or LAMA • ICS
Airflow obstruction	• Spirometry testing	• Short-acting bronchodilators • LABA or LAMA • Theophylline	• Further assessment with lung plethysmography, forced oscillometry	• Short-acting bronchodilators • LABA or LAMA • Theophylline
Eosinophilic airway inflammation	• Blood eosinophils	• ICS • OCS	• Blood eosinophils • FeNO • Sputum eosinophils	• ICS • OCS • Monoclonal antibodies directed against IL-5
Emphysema and loss of elastic recoil	• High-resolution chest CT scan	• Smoking cessation	• High-resolution chest CT scan • Lung plethysmography • Transpulmonary (oesophageal) pressure monitoring	• Smoking cessation • Lung volume reduction surgery • Endoscopic lung volume reduction
Chronic bronchitis	• History • Sputum colour	• Smoking cessation	• History • Sputum total and differential cell count	• Smoking cessation • Sputum clearance
Deconditioning/exercise intolerance	• History • COPD activity questionnaires (e.g. COPD assessment test)	• Rehabilitation, exercise program	• Tests including six-minute walk, shuttle walk, cardiopulmonary exercise, sit to stand	• Rehabilitation, exercise program
Chronic hypoxaemia	• Pulse oximetry, arterial blood gases	• Long-term oxygen therapy	• Pulse oximetry • Arterial blood gas test	• Long-term oxygen therapy
Chronic hypercapnoea	• Arterial blood gases • Sleep studies	• Refer patient for specialist management	• Arterial blood gas test • In-lab sleep study with CO_2 monitoring	• Noninvasive ventilation
Obesity or sarcopenia	• Weight • Height • Body mass index	• Dietary modification • Physical activity	n/a	n/a
Upper airway inflammation (chronic rhinosinusitis or nasal polyposis)	• Screening questionnaires • CT nose and paranasal sinuses	• Intranasal steroids, nasal irrigation	n/a	n/a
Vocal cord dysfunction (paradoxical closure of vocal folds during inspiration, commonly coexists with asthma and can mimic its clinical features)	• Screening questionnaires	• Refer patient for specialist management	• Screening questionnaires • Direct laryngoscopy	• Speech pathology
Dysfunctional breathing (chronic change in breathing pattern with associated dyspnoea, often accompanies severe asthma and COPD, though is not specifically driven by organic pathology)	• Screening questionnaires • History	• Anxiety management	n/a	• Anxiety management • Breathing retraining • Cognitive behavioural therapy
Nonadherence to therapy, poor inhaler technique	• History • Script refills	• Education • Self-management support	• History • Script refills • Electronic monitoring devices	• Education • Self-management support

Abbreviations: COPD = chronic obstructive pulmonary disease; FeNO = fractional exhalation of nitric oxide; ICS = inhaled corticosteroid; IL-5 = interleukin 5; LABA = long-acting beta-agonists; LAMA = long-acting muscarinic antagonist; OCS = oral corticosteroid.

Treatment of ACO – negotiating the contrasting inhaler therapies for asthma and COPD

The most common dilemma for the clinician treating a patient with ACO is which inhaler therapy to initiate and when.[1,2] ICS therapy is the cornerstone of asthma management, and the addition of long-acting bronchodilators is indicated only if insufficient control is achieved with ICS. Bronchodilators – both short- and long-acting – represent a major part of the management of COPD, and ICS is only added in certain circumstances of advanced disease. The recommended management of asthma and COPD, with a focus on inhaler therapy, is briefly outlined below to highlight their sometimes contrasting management.

For adolescents and adults with asthma, including mild asthma, ICS therapy is recommended to decrease the risk of exacerbations and improve control of asthma symptoms.[2,24,25] Long-acting beta-agonists (LABAs) reduce the frequency of severe asthma exacerbations when combined with ICS therapy and are recommended in combination with ICS therapy if inadequate control is achieved with ICS alone.[2,21] LABA monotherapy has been linked with increased rates of asthma-related death and is contraindicated in the absence of ICS therapy.[2,26,27] The long acting muscarinic antagonist (LAMA) tiotropium improves lung function, exacerbation rates and asthma control when added to ICS/LABA combinations, and is recommended only for those with inadequate control and persistent exacerbations despite (high-dose) ICS/LABA combinations.[2,22]

[A treatable traits] approach emphasises a shift from intensifying treatment targeted towards disease labels, to targeting the treatments to the clinical phenotypes present in the individual patient

Treatment of COPD is similarly based on the management of symptoms and to reduce the risk of exacerbations, but in contrast to asthma, bronchodilator therapy is the preferred first-line therapy, rather than ICS.[1] Long-acting bronchodilator therapy (LAMA alone or in combination with LABA) has been shown to improve lung function and COPD symptoms, and reduce the frequency of exacerbations and hospitalisations.[17,18,23] The addition of ICS therapy should be considered in the setting of persistent exacerbations despite long-acting bronchodilator therapy, although this recommendation is strongest for patients with elevated blood eosinophil counts ($>0.3\times10^9$/L), and may offer no benefit to those with persistently low blood eosinophil counts ($<0.15\times10^9$/L).[1,28,29] As described above, the inflammation in COPD is usually driven by neutrophilic (T1) inflammation, which is less responsive to corticosteroids than the eosinophilic (T2) inflammation associated with asthma. With the increased appreciation of an overlap between our traditional understanding of asthma and COPD inflammatory patterns, there will be a cohort of patients with COPD who demonstrate evidence of eosinophilic airway inflammation, with elevated blood eosinophils (above 0.3×10^9/L) and elevated FeNO (above 50 ppb) (although FeNO measurement is not necessary to diagnose eosinophilic inflammation in the primary care setting), and are more likely to respond to ICS therapy. It is therefore important to check for evidence of eosinophilic airway inflammation in patients with COPD, as this will influence treatment options, although it should be noted that the addition of ICS to COPD in the absence of frequent exacerbations or a concurrent diagnosis of asthma constitutes off-label use. The use of ICS in COPD has been linked to an increased risk of pneumonia and tempers enthusiasm for its use in COPD that can be adequately managed with bronchodilator therapy alone, particularly in the majority of patients with COPD who do not demonstrate evidence of eosinophilic inflammation.[13,30]

In people with COPD and moderate to severe exacerbations, mepolizumab (an anti-IL5 monoclonal antibody) reduced exacerbations, with the effect dependent on the degree of peripheral blood eosinophilia.[31] The reduction in exacerbations was more pronounced in patients with persistently higher blood eosinophil counts ($>0.3\times10^9$/L) treated with dupilumab (an anti-IL-4/IL-13 monoclonal antibody).[32] These studies reinforce the importance of targeting T2 inflammatory pathways as a disease trait, specifically in the context of COPD.

Consensus treatment of ACO with inhaled therapy

Evidence to support specific treatment recommendations for ACO as a single disease is limited. Most experts support the initiation of ICS therapy early in the disease course of patients who fit the definition of ACO, as this is an important part of asthma control.[2,5,8] If a patient with an established diagnosis and treatment regimen for COPD demonstrates features of asthma such as bronchodilator reversibility or eosinophilic inflammation (blood or sputum), the addition of an ICS is supported by expert consensus, although data only supports the use of ICS in those with evidence of eosinophilic inflammation.[8,33] Evidence is emerging to support the use of mepolizumab and dupilumad in those with persistent exacerbations despite ICS use and persistently high blood eosinophil counts.[31,32]

Overall care of the patient with ACO: the treatable traits approach

Asthma and COPD are both heterogenous conditions with multiple contributing pathophysiological processes. The classification of patients who display features of both conditions under the umbrella of ACO only risks compounding the complexity of their condition without providing any meaningful value to the individual patient. In 2016, a consortium of physicians proposed that, rather than relying on disease labels for asthma and COPD, they should be viewed as 'a continuum of different diseases that may share biological mechanisms (i.e. endotypes), and present similar clinical, functional, imaging and/or biological features that can be observed (i.e. phenotypes) which require individualised treatment'.[6] In this treatable traits approach, the focus is on identifying disease traits or clinical phenotypes with treatments that specifically target them. Such clinical phenotypes then are not limited to just asthma or COPD. The Table lists some of the traits or phenotypes that may manifest in a patient with asthma, COPD or ACO, and associated management strategies to consider for each.

2. Applying the treatable traits approach to patient case studies from Box 1

All patient management should include a disease care plan including patient education, a review of inhaler technique and a written action plan in the event of exacerbations.

Patient 1 (ACO or possible allergic asthma and emphysema)

Management approach in primary care

Elevated blood eosinophils suggests type 2 airway inflammation
- treat with ICS
- titrate ICS dose based on symptom response

Airflow obstruction
- treat with long acting bronchodilators (LABA or LAMA alone or in combination)

Screen for comorbidities
- allergic rhinosinusitis as a manifestation of atopy
- treat with nasal steroids and nasal irrigation

Further management options in specialist centres
- Titrate ICS dose based on symptoms, with support from biomarkers (i.e. measured reduction in blood eosinophils or FeNO)
- Consider a macrolide antibiotic for persistent exacerbations
- If the patient has persistent exacerbations or symptoms and persistently elevated biomarkers of T2 inflammation, consider monoclonal antibodies directed against allergic/eosinophilic inflammation – targeting this patient's allergic asthma traits*

Patient 2 (ACO or possible asthma with non-T2 inflammation)

Management approach in primary care

Inclusion of an ICS is currently the consensus-based recommended treatment for patients with COPD with a childhood history of asthma
- aim for low-dose ICS

Fixed airflow obstruction (associated with future risk of exacerbations)
- step up to long-acting bronchodilator therapy
- use of an ICS/LABA combination
- addition of a LAMA if ongoing frequent exacerbations (more than two per year)

Evaluate for bronchiectasis
- chest CT scan

If chronic mucus hypersecretion
- physiotherapy review for chest clearance

Include antibiotic therapy targeted against *Haemophilus influenzae* during exacerbations

Impaired exercise capacity and breathlessness
- assess for deconditioning. Refer for pulmonary rehabilitation

Further management options in specialist centres
- Further down-titration of ICS is recommended if FeNO confirms the ongoing absence of eosinophilic airway inflammation
- Consider the use of mucolytics if difficult to clear secretions
- Consider a macrolide antibiotic for persistent exacerbations

Patient 3 (ACO or possible COPD with eosinophilic inflammation or bronchodilator reversibility)

Management approach in primary care

Airflow obstruction
- treat with long-acting bronchodilators
- given severe airflow obstruction, begin treatment with LABA/LAMA combination (no role for stepped introduction)

Eosinophilic airway inflammation
- add ICS

Impaired exercise capacity and breathlessness
- assess for deconditioning
- refer for pulmonary rehabilitation

Recommend smoking cessation to
- improve response to ICS
- reduce mucus hypersecretion
- decrease exacerbation frequency
- slow decline in lung function

Further management options in specialist centres
- Titrate ICS dose based on response to FeNO and blood eosinophils
- If the patient has persistent exacerbations and refractory eosinophilic airway inflammation, add monoclonal antibodies directed against anti-IL-5 – targeting this patient's asthma traits and inflammatory phenotype*
- Evaluate for extrathoracic causes of frequent exacerbations, including chronic rhinosinusitis, vocal cord dysfunction, anxiety or depression, dysfunctional breathing

* This recommendation had not been not specifically studied in ACO and is formed by extrapolating evidence for efficacy in patients with asthma.
Abbreviations: ACO = asthma-chronic obstructive pulmonary disease overlap; ICS = inhaled corticosteroid; IL-5 = interleukin 5; FeNO = fractional exhalation of nitric oxide; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist.

Adopting a treatable traits approach to the management of the patients in the three case studies (Box 1) is outlined in Box 2. Such an approach emphasises a shift from intensifying treatment targeted towards disease labels, to targeting the treatments to the clinical phenotypes present in the individual patient.

Conclusion

Asthma-COPD overlap describes an important cohort of patients who demonstrate features typically associated with both asthma and COPD. This description is useful on a population level to highlight the complexity of chronic airways disease and the heterogeneity of the individual diagnoses of asthma and COPD. However, ACO is clearly not a disease entity in its own right and attempts to fit a label to patients who demonstrate symptoms of both asthma and COPD, and illustrates the limitations with the current approach to chronic airways disease. As we develop a greater understanding of the mechanisms underlying both asthma and COPD, a focus on treating identifiable clinical traits may offer a more targeted approach to therapies to improve symptoms and disease outcomes with fewer side effects. The management of the individual patient who fits the description of ACO should focus on the traits of chronic airways disease that the patient manifests rather than the disease label. **RMT**

References

A list of references is included in the online version of this article (www.respiratorymedicinetoday.com.au).

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Pulmonary rehabilitation for COPD

'Breathe easy, walk easy'

JENNIFER ALISON PhD, MSc, DipPhty

Referring patients with chronic obstructive pulmonary disease to a pulmonary rehabilitation program can have significant benefits on important patient outcomes.

GPs play a pivotal role in the management of people with chronic obstructive pulmonary disease (COPD) and are often the first point of contact for such patients. The prevalence of COPD in Australia is about 7.5% in people aged 40 years or older, which increases to 29% in those aged 75 years or older.[1] As COPD is the second leading cause of avoidable hospital admissions (and in some rural and remote regions, COPD is the leading cause) it places a significant burden on the health system.[2] If well managed in primary care, hospital admissions for COPD may be avoided.

Although the role of pharmacology in the management of COPD is well recognised, physical management is often neglected. This is despite high-level evidence for the positive impact of pulmonary rehabilitation on the outcomes of the disease and recommendations of both national and international guidelines that strongly endorse referral of patients with COPD to pulmonary rehabilitation programs.[3-6]

Key points

- **Pulmonary rehabilitation is an effective nonpharmacological therapy for chronic obstructive pulmonary disease (COPD).**
- **Pulmonary rehabilitation improves symptoms of breathlessness and fatigue, exercise capacity and quality of life, and reduces hospital admissions.**
- **Spirometry is essential to confirm the diagnosis of COPD. Spirometry should be performed on all patients presenting with symptoms of breathlessness and suspected COPD.**
- **All people with COPD should be offered pulmonary rehabilitation.**

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1. Benefits of pulmonary rehabilitation in patients with COPD[10-12]

- Reduces symptoms of breathlessness and fatigue
- Increases exercise tolerance
- Reduces anxiety and depression
- Improves quality of life
- Reduces hospitalisations

This article emphasises the importance of early identification of patients with COPD and GP referral to pulmonary rehabilitation programs, which will lead to improved patient outcomes.

Presentation of COPD

Patients with COPD may present with symptoms such as shortness of breath, fatigue and/or cough and sputum, as well as difficulty with daily activities due to general exercise intolerance. Such symptoms can come on gradually over years and some patients may dismiss their symptoms as 'normal' signs of ageing or due to a lack of fitness or they modify their lifestyle to adapt to breathing difficulties.

Common causes of COPD

The most common cause of COPD is cigarette smoking; however, COPD can occur in nonsmokers due to passive smoking or a high exposure to environmental or occupational dust, gas or fumes.[7] Alpha-1 antitrypsin deficiency, which results in early-onset emphysema, is a less common cause of COPD.[6]

Initial investigations for COPD

Spirometry should be performed on all patients presenting with symptoms of breathlessness and suspected COPD – that is, those who are older than 40 years who have a smoking history of 10 or more pack years or have had high environmental or occupational exposure to dust, gas or fumes. Spirometry testing is important to ascertain the degree of airflow limitation. A postbronchodilator forced expiratory volume in one second (FEV_1)/ forced vital capacity (FVC) ratio of less than 0.7 is required to confirm the diagnosis of COPD. Case finding of COPD may be improved by using handheld spirometers as screening devices, such as COPD-6,[8] PiKo-6 or the AirSmart Spirometer.

Importance of an early COPD diagnosis

Although it is not possible to reverse the lung damage caused by COPD, much can be done to improve patient outcomes and give patients the best chance to live their lives fully.[9] Earlier diagnosis provides an opportunity for GPs to initiate management strategies that have been shown to enhance patients' lives, such as avoiding risk factors for disease progression (e.g. smoking cessation), optimising medication use, ensuring regular influenza, pneumococcal and COVID-19 vaccinations to reduce the risk of exacerbations and referral to pulmonary rehabilitation programs.

Pulmonary rehabilitation

Pulmonary rehabilitation is an evidence-based intervention for patients with chronic lung disease. It includes patient assessment, exercise training and patient education on disease management. It is an effective form of nonpharmacological management for people with COPD.[10-12] The benefits of pulmonary rehabilitation in patients with COPD are shown in Box 1.[10-12]

What is involved for the patient?

Patients who are referred to pulmonary rehabilitation programs are asked to attend twice a week for eight weeks.[13] At the initial visit, patients undergo the following assessments:

- a full patient history, including current medications and any comorbid conditions
- spirometry, if a recent result is not provided in the referral letter
- assessment of breathlessness via the modified Medical Research Council Breathlessness questionnaire
- measure of functional exercise capacity with a six-minute walk test
- assessment of health-related quality of life; the most commonly used quality of life questionnaire for COPD in Australia is the St George's Respiratory Questionnaire. Many programs also use the COPD Assessment Test (CAT) to monitor the impact of COPD on a patient's life.

Patients are asked to set the goals they would like to achieve from the program and they are reassessed at the end of the program (using the same measures as above) to evaluate their response to rehabilitation. The online Pulmonary Rehabilitation Toolkit (www.pulmonaryrehab.com.au) provides full details of the assessments conducted throughout a pulmonary rehabilitation program.[14]

At subsequent sessions, patients undertake a program of exercise training. An exercise prescription is developed for a walking and/or stationary cycling program (aerobic training) and is based on the results of the six-minute walk test. Resistance exercises for both the upper and lower limbs are also provided to improve muscle strength. The therapist works with the patient to tailor the exercise program, ensuring that the exercises are appropriate and achievable for the individual and adjusted for any pre-existing musculoskeletal or other comorbid conditions. Within Australia, physiotherapists are responsible for exercise prescription and training in more than 90% of programs, with nurses or exercise physiologists trained in pulmonary rehabilitation providing supervision in the remaining programs.[13]

The exercise sessions last between 60 and 90 minutes (allowing for rests). A group of patients attend each session, although each patient will follow their individual program. Exercising in a group environment can be beneficial as it provides support and motivation from others.

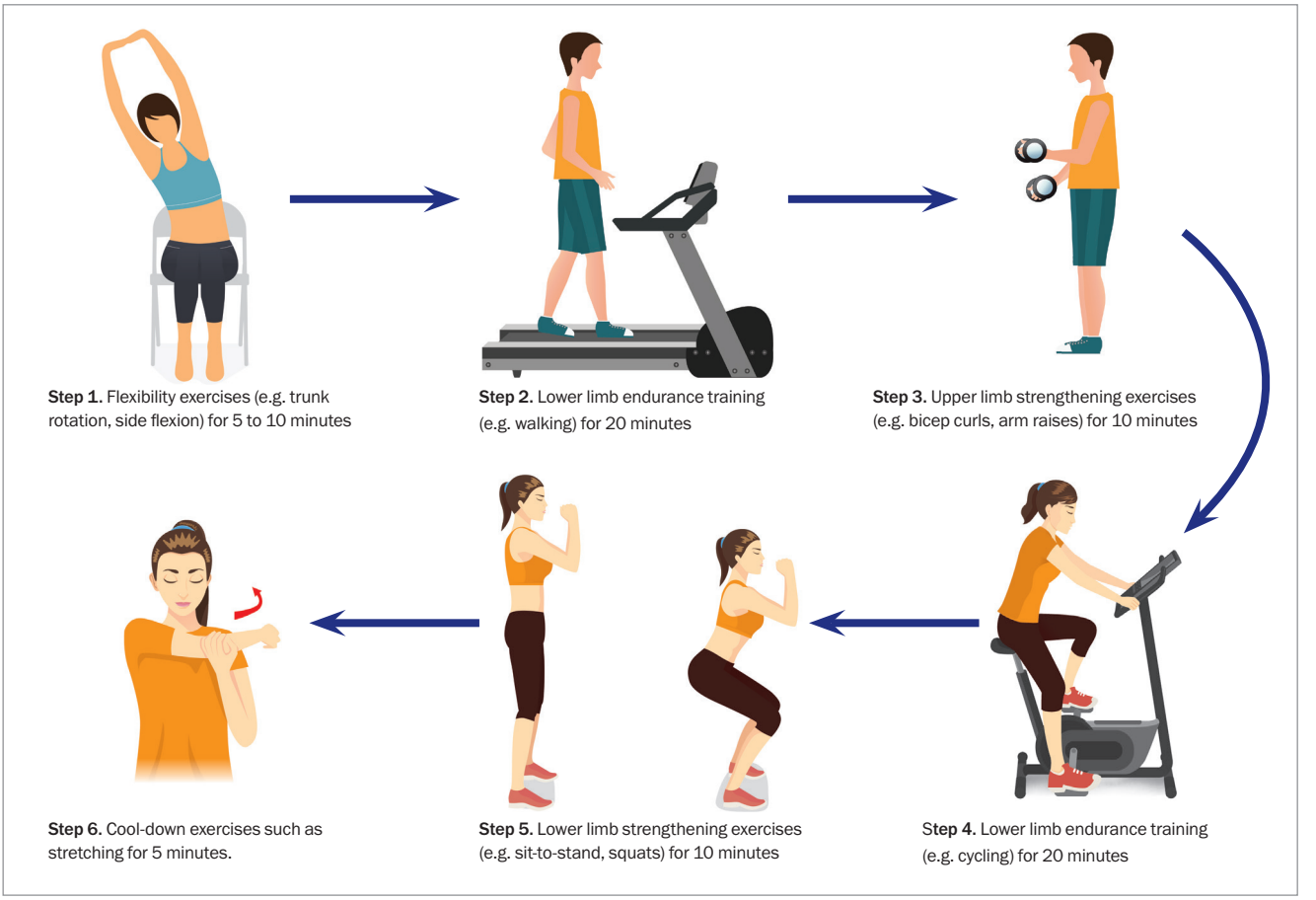

Figure. An example of an exercise session in a pulmonary rehabilitation program.

In addition to the supervised exercise sessions patients are encouraged to exercise at home, on at least two to three other days in the week. Therapists work with the patient to develop a home program that is feasible for the patient. Establishing a home exercise routine is important so the benefits gained during the pulmonary rehabilitation program can be maintained after completion.

Patient education is also included as part of the pulmonary rehabilitation program. Common education topics are: how the lungs work; how and why to use inhaled medications; how to manage breathlessness; why it is important to exercise and stay physically active; and a review of action plans in case of an exacerbation. A pulmonary rehabilitation program also provides the opportunity for referral to smoking cessation programs, psychological support and nutritional advice, if required.

Most pulmonary rehabilitation programs are provided in hospital outpatient departments or community settings. However, there is growing evidence that home-based programs and tele-rehabilitation programs are also effective for patients who have difficulty with transport or live in remote regions.[3,15,16]

What types of exercise are important?

Lower limb endurance training using a walking or cycling program is the most important component of a pulmonary rehabilitation program. Most programs emphasise walking as the mode of lower limb endurance exercise because walking is an essential component of everyday life. To achieve benefits, patients need to walk or cycle for at least 30 minutes per session two to three days each week.[17] If necessary, patients can take short rests to limit the degree of breathlessness or muscle fatigue. Patients need reassurance that breathlessness during activity is not harmful and are taught strategies for managing breathlessness.

Exercises to improve the strength and endurance of the arm and leg muscles are also included so that the patient can more easily perform activities of daily living. In addition, exercises to improve balance in those patients who have had a fall or a 'near miss' fall may be included. An example of a pulmonary rehabilitation program session is provided in the Figure.

As it is important that exercise is continued long term, most programs will use simple equipment to allow replication of the exercises in the home setting.

2. Criteria for referral to a pulmonary rehabilitation program

Inclusions
- Clinical diagnosis of chronic obstructive pulmonary disease confirmed by spirometry
- Optimised medical management
- Breathlessness on physical activity, especially if the patient walks slower than people of the same age on the level because of shortness of breath
- Current smokers (pulmonary rehabilitation programs can assist with smoking cessation as part of lifestyle modifications)

Exclusions
- Comorbidities that compromise a patient's safety or ability to participate in exercise testing or training (e.g. unstable cardiovascular disease, uncontrolled diabetes, recent exertional syncope, severe neurological impairment, severe cognitive impairment)
- No motivation to attend

Why does pulmonary rehabilitation work?

Breathlessness and/or fatigue on exertion are common symptoms in people with COPD, and leads to avoidance of daily activities that elicit these symptoms. This results in a downward spiral of progressive inactivity with adverse consequences that include muscle deconditioning, depression, social isolation and poor quality of life.

Endurance training involving the large muscle groups in the legs induces physiological changes in the exercising muscles. This, in turn, improves the oxidative capacity of the muscles, reduces lactate build up during exercise and leads to a decrease in ventilation and breathlessness.[18] Significant psychological benefits occur as the patient becomes more confident to undertake physical activities. This helps to reduce anxiety, depression and social isolation, and improve the patient's quality of life.[18]

Who should be referred to a pulmonary rehabilitation program?

Any patient with lung disease whose lifestyle is affected by breathlessness may gain benefits from a pulmonary rehabilitation program. Improvements following rehabilitation have been demonstrated in patients with mild, moderate and severe COPD. Often, symptoms of breathlessness when walking up inclines or climbing stairs are ignored and attributed to ageing, weight gain or lack of exercise and not the underlying lung problem. As a result, many patients who potentially would benefit are not identified as candidates for rehabilitation. GPs may find it useful to use the CAT to measure the impact of COPD on the patient's life and help determine whether referral to a pulmonary rehabilitation program may be beneficial. A CAT score of 10 or higher indicates that referral to a pulmonary rehabilitation program would be beneficial.[19,20] The criteria for referral of patients with COPD to a pulmonary rehabilitation program is provided in Box 2.

Although there is high-level evidence for the benefits of pulmonary rehabilitation for people with COPD, there is growing evidence of similar benefits for patients with bronchiectasis, interstitial lung diseases and pulmonary hypertension.[3] GPs should consider referring patients with these conditions to pulmonary rehabilitation programs that have experience in managing such patients and are able to provide airway clearance techniques for patients with bronchiectasis and oxygen (if necessary) for patients with interstitial lung diseases.

Where can a pulmonary rehabilitation program be found?

Lung Foundation Australia has a list of pulmonary rehabilitation programs offered throughout Australia (https://lungfoundation.com.au/exercise-classes/?event_category=127).[21] Most programs take place in hospitals although some take place in community centres. More pulmonary rehabilitation programs are required to meet the need for this effective intervention.

Important role of GPs

GPs play a crucial role in referring patients to pulmonary rehabilitation programs and can increase the likelihood of a patient participating in such a program by being enthusiastic and advocating the benefits.[22-24] GPs can reassure patients that, although pulmonary rehabilitation includes an exercise program, the therapists running the programs will work with each patient to ensure the exercise program is safe and manageable for them.

The pulmonary rehabilitation program co-ordinator will send a letter to the referring GP. This reassures the GP that their patient is attending the program and informs them of the key findings from the assessment. At program completion, another letter is sent to the GP to provide the results of the end of program assessment and highlight improvements and any ongoing needs. Patients are referred back to the GP at any stage throughout the program if the therapist has any concerns.

Conclusion

Pulmonary rehabilitation can have a significant positive impact on the physical and psychological consequences of COPD, as well as reducing healthcare costs. GPs have an important role in identifying patients with COPD and referring them to a pulmonary rehabilitation program so that improved patient outcomes can be achieved. **RMT**

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A list of references is included in the online version of this article (www.respiratorymedicinetoday.com.au).

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