

Distinguishing adult-onset asthma from COPD: a review and a new approach

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Abstract: Adult-onset asthma and chronic obstructive pulmonary disease (COPD) are major public health burdens. This review presents a comprehensive synopsis of their epidemiology, pathophysiology, and clinical presentations; describes how they can be distinguished; and considers both established and proposed new approaches to their management. Both adult-onset asthma and COPD are complex diseases arising from gene–environment interactions. Early life exposures such as childhood infections, smoke, obesity, and allergy influence adult-onset asthma. While the established environmental risk factors for COPD are adult tobacco and biomass smoke, there is emerging evidence that some childhood exposures such as maternal smoking and infections may cause COPD. Asthma has been characterized predominantly by Type 2 helper T cell (Th2) cytokine-mediated eosinophilic airway inflammation associated with airway hyperresponsiveness. In established COPD, the inflammatory cell infiltrate in small airways comprises predominantly neutrophils and cytotoxic T cells (CD8 positive lymphocytes). Parenchymal destruction (emphysema) in COPD is associated with loss of lung tissue elasticity, and small airways collapse during exhalation. The precise definition of chronic airflow limitation is affected by age; a fixed cut-off of forced expiratory volume in 1 second/forced vital capacity leads to overdiagnosis of COPD in the elderly. Traditional approaches to distinguishing between asthma and COPD have highlighted age of onset, variability of symptoms, reversibility of airflow limitation, and atopy. Each of these is associated with error due to overlap and convergence of clinical characteristics. The management of chronic stable asthma and COPD is similarly convergent. New approaches to the management of obstructive airway diseases in adults have been proposed based on inflammometry and also multidimensional assessment, which focuses on the four domains of the airways, comorbidity, self-management, and risk factors. Short-acting beta-agonists provide effective symptom relief in airway diseases. Inhalers combining a long-acting beta-agonist and corticosteroid are now widely used for both asthma and COPD. Written action plans are a cornerstone of asthma management although evidence for self-management in COPD is less compelling. The current management of chronic asthma in adults is based on achieving and maintaining control through step-up and step-down approaches, but further trials of back-titration in COPD are required before a similar approach can be endorsed. Long-acting inhaled anticholinergic medications are particularly useful in COPD. Other distinctive features of management include pulmonary rehabilitation, home oxygen, and end of life care.

Keywords: chronic obstructive pulmonary disease, diagnosis, management, adults, inflammometry

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are both chronic inflammatory diseases of the airways that induce airflow limitation. Asthma often starts

in childhood, in such cases being commonly associated with allergies. It may remit and recur in adulthood,¹ or symptoms may continue throughout adolescence into adult life. Asthma may also develop *de novo* at any age, in some cases apparently triggered by a severe respiratory tract infection.² Asthma is characterized by intermittent and variable wheeze, chest tightness, and shortness of breath. COPD becomes apparent in middle to older age, but is now considered to have origins in early life.³ COPD is characterized predominantly by gradually increasing dyspnea. Clinical features common to both include cough, mucus hypersecretion, wheeze, and intermittent exacerbations or “flare-ups”.

Asthma and COPD are usually considered to be distinct diseases and up until recently were associated with distinct approaches to diagnosis and management.^{4–6} However, it has become increasingly evident that differentiating asthma from COPD can be difficult, particularly in older populations. This is because older patients frequently exhibit features of more than one disease.^{7–9} This is commonly referred to as asthma–COPD overlap, and includes the coexistence of asthma, and emphysema or chronic bronchitis.^{10,11}

Distinguishing between adult-onset asthma and COPD is a vigorously debated topic in respiratory medicine. This review compares and contrasts the current evidence on epidemiology, pathophysiology, diagnosis, and management of these two diseases.

Epidemiology of asthma and COPD

Burden of disease related to asthma and COPD

Adult-onset asthma and COPD have become much more common in the recent past and are now major public health problems in many countries.^{12,13} Asthma prevalence has increased in epidemic proportions over the last few decades and continues to rise in most parts of the world.¹³ COPD burden is also set to increase during the next few decades, especially with the aging of the population and continued use of tobacco.

Adult-onset asthma differs from childhood asthma in that it is more often nonatopic and severe and has a lower remission rate.¹⁴ Although asthma has a relatively low mortality in younger adults, in the elderly, it is associated with substantial morbidity, healthcare utilization,¹⁵ and mortality.¹⁶ The prevalence of current asthma in Australian adults is around 10%, which includes both childhood and adult-onset disease.¹⁷ Substantial variation in the prevalence of adult asthma across 25 countries has been reported by the European Community Respiratory Health Survey, the largest international study of

asthma in young adults.¹⁸ This variation has been attributed more to differences in potential environmental risk factors than to genetics, as variation was observed even across countries with similar ethnic populations.

COPD is the fourth leading cause of death worldwide and expected to be the third leading cause by 2030.¹⁹ However a systematic review of the health burden of COPD has shown that mortality has now started to decrease for men in some Western countries, whereas rates have continued to rise or plateau for women.²⁰

There is substantial variation in COPD prevalence across countries, and the use of various diagnostic classifications has been suggested as one reason. However, the findings of the Burden of Obstructive Lung Disease Study (BOLD) that used similar methodology across 12 countries suggest otherwise. BOLD estimated overall 11.8% of middle-aged to elderly men and 8.5% of similarly aged women as having COPD, identified using spirometric criteria,¹² but the prevalence varied significantly across study centers. Perhaps not surprisingly, the variation followed a similar geographical distribution to the variation in the prevalence of smoking.

Both diseases have substantial economic and social costs. These include both direct costs related to medical management and indirect costs related to disability, lost revenue from not attending work, and caring for patients. In Europe, 6% of the health budget is used for direct costs related to respiratory diseases, just over half of which are related to COPD.²¹ A recent study in the UK found the annual per patient cost of COPD management, excluding medications, to be £2,108 for all patients, while this ranged from £1,523 to £3,396 for mild to severe COPD.²² Annual per person costs for an adult with asthma have also been found to vary from \$2,646 to \$12,813 USD for mild to severe asthma in a sample of patients in California.²³

Definitions used in epidemiology

The demarcation between childhood-onset and adult-onset asthma is somewhat arbitrary, but adult-onset has been defined as from as young as 16 years.²⁴ The combination of airway hyperresponsiveness (AHR) and current asthma symptoms is a reliable indicator of clinically important asthma across age groups.²⁵ However, the presence of wheeze alone within the last 12 months has been used by many large epidemiological studies to determine current asthma prevalence regardless of the age of onset.^{26–28}

Post-bronchodilator (BD) airflow obstruction is fundamental to the definition of COPD.²¹ A clinical diagnosis

of COPD also relies on the presence of coexistent symptoms and risk factors.²¹ However, epidemiological studies have mainly adopted only the spirometric criterion.^{12,29,30}

The Global initiative for Obstructive Lung Disease (GOLD) endorses the spirometry criterion of post-BD forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) less than 0.70, with spirometric staging by the BOLD study also including an FEV₁ less than 80% predicted.^{12,29} This fixed cut-off is susceptible to the risk of overdiagnosing a substantial number of older symptomatic individuals as having COPD,³¹ which might contribute to the relative underdiagnosis of asthma in the elderly, particularly females. An alternative approach has been proposed to overcome this problem, whereby the cut-off is based on the lower limit of predicted normal.³² This cut-off assumes the “usual progressive” lung function decline of COPD is greater than the physiological age-related decline of the FEV₁/FVC ratio.

Risk factors for adult-onset asthma and COPD

Both asthma and COPD are acknowledged as complex diseases related to both genetic and environmental risk factors, but environment seems to play the stronger role. Although asthma has a high heritability, genetic studies to date have been able to explain only a small proportion of the variability. The evidence for a genetic etiology of adult-onset asthma is even less convincing, with neither family history nor atopy being clearly linked to this phenotype.¹⁴ Homozygous α -1-antitrypsin deficiency (PiZZ) is the most common genetic risk factor for COPD, and the odds are also increased among heterozygous alpha-1-antitrypsin deficient (PiMZ) smokers.³⁰ Very recently, an interaction has been demonstrated between the PiMZ genotype and occupational exposures to vapors, gas, dust, and fumes, on annual decline in lung function.³³

A growing body of evidence suggests that early life and childhood factors are important in both adult-onset asthma and COPD.^{34,35} This concept is based on data that show associations between various adverse perinatal outcomes and harmful environmental stimuli, with slowing of lung function growth for susceptible children and adolescents.^{36–39} This effectively reduces peak lung function and impacts on the corresponding trajectory of lung function decline in adulthood. Such prenatal and postnatal factors include intra-uterine growth restriction, prematurity, second-hand smoke exposure, air pollution, recurrent respiratory infections, and personal smoking.³⁵

Occupational exposures are major preventable risk factors for adult-onset asthma.^{40,41} During an individual’s “productive working years”, occupational asthma can frequently be overlooked, and from middle-age, symptoms may be attributed erroneously to COPD. A systematic inquiry into past and current occupational exposures is often required to confirm the diagnosis, as asthma might be still present after the exposure ceases.⁴ A combined effect of occupational exposure and personal smoking has been shown to further increase the likelihood of airflow obstruction.⁴²

Nonoccupational risk factors for adult-onset asthma are heterogeneous and play a lesser role. These can be either childhood or adult exposures. Longitudinal studies have shown that childhood infections, tobacco smoke exposure, obesity, and allergic phenotypes influence adult-onset asthma.⁴³ In addition, female reproductive history, especially contraception,⁴⁴ menopause,⁴⁵ and hormone replacement therapy⁴⁶ is emerging as a strong risk factor for adult-onset asthma.

The patterns of COPD risk factors differ between geographical areas. In high- and middle-income countries, tobacco smoke is the biggest risk factor. However, in low-income countries, exposure to indoor air pollution, such as through the use of biomass fuels for cooking and heating, and occupational exposures, are more important.^{47,48} Personal tobacco smoking is the principal risk factor for COPD in industrialized countries; however, a meta-analysis has also shown an independent association for second-hand tobacco smoke exposure, which may be causal.⁴⁹ Traffic-related air pollution has been associated with COPD mortality,⁵⁰ as have decrements in lung function among people with asthma.^{51,52}

Introduction to the pathophysiology of asthma and COPD

Asthma pathophysiology

Asthma is predominantly an airway disease, generally without involvement of lung parenchyma. It is viewed as a condition characterized by Type 2 helper T cell (Th2) cytokine-mediated eosinophilic airway inflammation. Bronchial biopsies from subjects with asthma demonstrate infiltration with eosinophils, activated mast cells, and Th2 predominant T cells.⁵³ There is also significant thickening due to collagen deposition in the basement membrane underpinning the bronchial epithelium. The concept of a variety of asthma syndromes is longstanding.² However, recent studies have highlighted the potential for the presence of a variety of different pathological asthma phenotypes, with some studies

demonstrating neutrophilic or paucigranulocytic findings in sputum rather than eosinophilia in patients with a range of asthma severities.²

Asthma is associated with AHR, which may be evident though reversibility to BD on spirometric testing or through responses to a variety of challenge tests. Asthma symptoms classically relapse and remit over time and are responsive to corticosteroids. However, over time, a proportion of individuals with asthma may develop some degree of persistent airflow obstruction, which does not remit with anti-inflammatory therapy.⁵⁴ In this case, differentiation from COPD may be very difficult. As around 30% of people with asthma smoke, a proportion of these will develop chronic airflow limitation, which is likely to be indistinguishable from COPD. Recent studies suggest that 13%–20% of patients with COPD have an overlap phenotype with asthma; this is as high as 50% in patients over 50 years.^{54–57}

COPD pathophysiology

In COPD, repeated exposure to noxious stimuli triggers an inflammatory response, which appears to continue even after removal of the inciting stimulus.⁵⁸ Early inflammation in young smokers is associated with mononuclear cells in the airway wall and macrophages in the small airway lumen. In patients with established COPD, the inflammatory cell infiltrate in small airways comprises predominantly neutrophils, cluster of differentiation (CD)8 positive lymphocytes, and mast cells.⁵⁹ There may be associated “spill-over” of the inflammatory response from the lungs into the systemic circulation, leading to potential downstream effects such as arterial stiffness and its consequences.^{60,61}

Although, as with asthma, there has been a tendency to “lump” patients with COPD into a homogeneous group, clinicians have for decades recognized variations in clinical phenotype of patients with COPD, which is underpinned, to an extent, by variations in the underlying pathology. Pathological features of small airways disease may predominate, with such patients having relatively minimal parenchymal destruction. Other patients may have relative sparing of airways and a more prominent picture of acinar destruction (emphysema). Parenchymal destruction is associated with loss of lung tissue elasticity, and small airways collapse during exhalation, leading to so-called “gas trapping”. Goblet cell metaplasia and impaired mucociliary function contribute to excess mucus accumulation and worsening obstruction.

An approach to grading and treating COPD based on clinical phenotypes aligned to pathology has been described in the recent Spanish COPD guidelines, which propose four

different phenotypes including 1) infrequent exacerbators with either chronic bronchitis or emphysema, 2) asthma–COPD overlap, 3) frequent exacerbators with emphysema predominant, and 4) frequent exacerbators with chronic bronchitis predominant.⁶² It has been proposed that such clinical phenotypes may help clinicians identify patients that respond to specific pharmacological interventions.

The role of age in both diseases

Age-related features

Asthma of an earlier onset is closely linked to other allergic diseases and to skin test sensitivity.⁶³ Most children with the persistent asthma phenotype have current symptoms as adults; however, around half are in remission by mid-adulthood.⁶⁴ Compared to childhood-onset asthma, asthma of adult onset is more likely among nonatopic females and features a greater fall in lung function despite a shorter duration of disease.^{63,65} A history of allergic rhinitis, and less so, atopic dermatitis, were associated with retrospectively recalled history of physician-diagnosed asthma from age 16 years for young to middle-aged adults in the European Community Respiratory Health Survey.²⁴ However, there was no association between skin test positivity and adult-onset asthma for middle-aged adults followed for 14 years in the Busselton Health Study.⁴⁰

The diagnostic value of atopy in distinguishing adult-onset asthma from COPD decreases with advancing age despite increasing levels of sensitization until mid-adult life, which plateau after the age of 55 years.⁶⁶ The adult-onset asthma phenotype shares similar clinical features with the noneosinophilic asthma phenotype and like COPD is associated with greater corticosteroid resistance when compared with younger individuals with eosinophilic asthma.⁶⁷

For those with childhood asthma who become asymptomatic by mid-adolescence, a recurrence of asthma symptoms in adulthood may be misclassified as “adult-onset asthma” if the past childhood history cannot be recalled.^{68,69} One epidemiological study that prospectively documented childhood asthma and/or wheezy breathing when participants were aged 7 years, identified two-thirds of young adults as being unable to accurately recall their childhood history, and this was mostly for those without severe eczema or allergic rhinitis.⁶⁹

COPD generally manifests clinically from mid-adult life, with increasing prevalence and disease severity with advancing age.¹² The rate of disease progression varies between individuals, with an accelerated FEV₁ decline more common for current smokers and those with BD-reversibility, emphysema, and/or acute exacerbations.⁷⁰ The link between

advanced age and COPD may be weakening for populations of developed countries given that the probability of asthma as the cause for underlying symptoms for an older individual seems to have increased, particularly for countries of high asthma prevalence. This requires validation by prospective cohorts that use consistent asthma and COPD definitions over time.

Apart from respiratory infection, adults with asthma appeared to have less comorbidity than those with COPD.⁷¹ COPD is associated with multiple comorbidities including ischemic heart disease, cardiac failure, osteoporosis and muscle weakness, obesity and the metabolic syndrome, depression and anxiety, lung cancer, pneumonia,⁷¹ and pulmonary embolism.⁷² Although these may be due in part to the common risk factor of smoking, the development of the comorbidities may also be linked by systemic inflammation driven by the elevation of proinflammatory mediators and their receptors, including tumor necrosis factor alpha, interleukin (IL)-6, and IL-1 receptor antagonist IL-1Ra, leading to an increased production of diverse chemokines (RANTES, MIP-1 α , IL-8, MCP-1) and an increase in C-reactive protein.^{61,73-75}

Altered perception of airway obstruction

Some data have suggested that for people over 65 years, those with adult-onset asthma of a longer duration may have more severe airway obstruction than those with a more recent asthma diagnosis, yet they report fewer asthma symptoms.⁷⁶ This might adversely influence the implementation of an asthma action plan, which relies on the accurate interpretation of asthma symptoms.⁷⁷ Older individuals might attribute respiratory symptoms to bronchitis, respiratory tract infection, obesity, poor fitness, or even to the “aging process”⁷⁷ and be more accepting of a progressive decline in mobility and activity.⁴

Differential diagnosis of adult asthma and COPD

Dyspnea due to cardiac failure is a common and important differential diagnosis for adult-onset asthma and COPD in the elderly, including acute exacerbations of COPD.⁷² Bronchiectasis is another important differential diagnosis for non-smoking individuals with post-BD airflow obstruction and a productive cough, particularly for females. Bronchiectasis can complicate severe asthma in the form of allergic bronchopulmonary aspergillosis, where identifying proximal bronchial dilatation on high resolution computed tomography

(HRCT) chest scan may be used to confirm the diagnosis. An accelerated FEV₁ decline has been observed for those with clinically apparent bronchiectasis despite medical therapy, averaging 49 mL per year over an 8 year period.⁷⁸ Around half of older COPD patients with moderate to severe airflow obstruction have been documented to have radiologically-defined bronchiectasis when screened with HRCT chest scans.^{79,80} As bronchiectasis is frequently associated with AHR⁸¹ and/or BD-reversibility, it seems possible that this entity could contribute to the overlap between asthma and COPD. Bronchiectasis in the presence of COPD is also a poor prognostic marker, where its severity has been independently associated with increases in all-cause mortality.⁸⁰

Asthma

Clinical practice guidelines propose diagnostic criteria to assist clinicians in distinguishing between asthma and other obstructive airway diseases.⁴ A diagnosis of asthma is made following a clinical assessment of symptoms and demonstration of variable airflow obstruction. This hallmark feature of asthma can be assessed by performing pre-BD and post-BD spirometry.⁴ An improvement of FEV₁ and/or FVC of greater than 12% or 200 mL is considered a significant BD response, consistent with asthma.⁸² However, such BD responses may also be seen in patients with COPD,⁸³ and a subgroup of patients with long standing asthma do not demonstrate reversible airflow obstruction,⁸⁴ which creates diagnostic challenges for clinicians.

Another diagnostic measure used in the assessment of asthma is AHR, a term that describes the ability of the airways to narrow excessively after exposure to bronchodilator agonists.⁸⁵ AHR plays a crucial role in the pathogenesis of asthma,⁸⁵ and the severity of AHR predicts the response to inhaled corticosteroids.⁸⁶ However, in an older population, AHR is a common and important determinant of accelerated decline in lung function.⁸⁷ This makes AHR a risk factor for the progression of airflow limitation in COPD,⁸⁸ and while AHR is a common physiological component of asthma, it is also frequently present in patients with COPD.

COPD

As previously mentioned, there are disease-specific guidelines and recommendations that propose diagnostic criteria to assist clinicians in the diagnosis of COPD.⁸⁹ The GOLD recommendations define a post-BD FEV₁/FVC of less than 0.7 as diagnostic of COPD.^{5,21} These recommendations also define spirometric indexes for grading severity,

and treatment recommendations are based on this severity grading scale.^{5,21}

A normal gas transfer factor in symptomatic smokers with airflow obstruction is an inexpensive and simple measurement to exclude significant morphological emphysema, whereas variable amounts of emphysema can be present for those with low gas transfer factor levels.⁹⁰ The use of HRCT can identify individuals with a predominant emphysematous phenotype, where the extent of low attenuation areas has been linked to increased respiratory mortality.⁹¹ These data suggest that the identification of COPD-associated emphysema and/or bronchiectasis has some prognostic value, although HRCT scans are not currently recommended in the routine clinical management of COPD.²¹

Differentiating adult asthma and COPD

In differentiating the two diseases a number of factors are often considered (Table 1), including

1. accurate medical history involving assessment of age of symptom onset and variability of symptoms;
2. reversibility of airflow obstruction and BD response;
3. smoking and occupational history;

4. response to treatment trials;
5. and atopic status.

Each of these, however, is associated with error due to the overlap and convergence of symptoms and clinical characteristics. We have outlined the traditional approach to differentiating asthma and COPD and the problems associated with this approach in Table 1.

Recently, airway inflammation has been frequently but erroneously considered in the differential diagnosis of asthma and COPD. While the assessment of airway inflammation can assist in the guidance of treatment decisions, it does not differentiate between diagnoses due to the heterogeneity of inflammation across and within disease groups.

The question that must be asked then is, does it matter? One argument is to justify alternative management approaches. However, treatments for asthma and COPD have tended to converge, and there is a large degree of overlap for treatment recommendations in these diseases.¹⁰ This is discussed further in the next section.

As a counter argument, COPD prognosis differs significantly from that of asthma, and this may also apply to asthma–COPD overlap. In a recent longitudinal study,

Table 1 Common symptoms, physiology, and pathology used to distinguish asthma and COPD and the common problems with this approach

| Traditional approach to differentiating disease | | Problems with this approach |
|--|---|---|
| Asthma | COPD | |
| Onset anytime throughout lifespan and often early in life (childhood) | Onset usually after the age of 40 years | Asthma is frequently diagnosed in adults and older people. ¹⁰ |
| Often atopic | Usually not atopic | Atopy also occurs in COPD ⁹² and not in all people with asthma, particularly those with adult-onset disease. ⁹³ |
| Symptoms often worse at night and in the morning Variable symptoms | Dyspnoeic with activity Progressive symptoms over time | A subgroup of patients with long-standing asthma do not demonstrate reversible airflow obstruction. AHR and bronchodilator responsiveness are common features of COPD and asthma. ^{94–96} Symptoms may be specific to the pathophysiological component of the disease rather than aligning with the diagnosis. |
| Reversible airflow obstruction | Only partially reversible airflow obstruction | The presence of inflammatory cells in the airways does not diagnose asthma or COPD, but their measurement is useful for clinical assessment and may guide treatment decisions. Moreover, airway inflammation is heterogeneous, and these inflammatory phenotypes do not define disease states. ^{97,98} |
| Airway inflammation – eosinophilic predominant | Airway inflammation neutrophilic predominant | Data suggests that a high proportion of COPD patients are never smokers, ⁹⁹ and smoking rates among patients with asthma are high. ¹⁰⁰ |
| May or may not have a history of smoking | >10 pack year smoking history | A moderate proportion of patients with COPD have eosinophilic airway inflammation ¹⁰¹ and may have a therapeutic response to corticosteroids. Conversely, patients with noneosinophilic asthma ¹⁰² may be less likely to respond to corticosteroids. |
| Treatment trials of a short course of systemic corticosteroids and 3 month-course of inhaled corticosteroids | | |

Abbreviations: AHR, airway hyper-responsiveness; COPD, chronic obstructive pulmonary disease.

Fu et al evaluated and compared clinical outcomes of patients with asthma, COPD, and asthma–COPD overlap at baseline and 4 years.¹⁰³ The results showed significantly greater decline in 6 minute walk distance at 4 years in the COPD group compared with the asthma and the overlap groups. In another cross sectional study, patients with overlap of asthma and COPD had significantly poorer quality of life and were more likely to have experienced a severe exacerbation (odds ratio 3.55, 95% confidence interval 1.76, 7.15) of their airways disease in the last year, than those with COPD alone.¹⁰⁴

The differentiation of asthma and COPD is particularly difficult in older people, where the common pathophysiological components of airflow obstruction, AHR, and airway inflammation overlap and converge and where, in patients over the age of 55 years, overlap of asthma and COPD occurs in up to 50% of individuals.^{10,55,56}

New approaches using inflammometry

In recognition of this difficulty with traditional approaches, alternative approaches to the assessment and management of obstructive airway diseases in adults have been proposed.^{9–11,97,105} These new approaches challenge the rigid categorization of patients into existing diagnostic labels of either asthma or COPD and suggest the importance of multiple clinical, functional, immunological, and molecular assessments that may be used to tailor and optimize treatments.^{9,105–108}

Central to these approaches is inflammometry: the measurement of inflammation to guide treatment decisions.⁹⁷ Importantly, in this management approach, the presence of inflammatory cells in the airways does not diagnose asthma or COPD, but their measurement can be useful for clinical assessment in guiding treatment decisions and in long-term

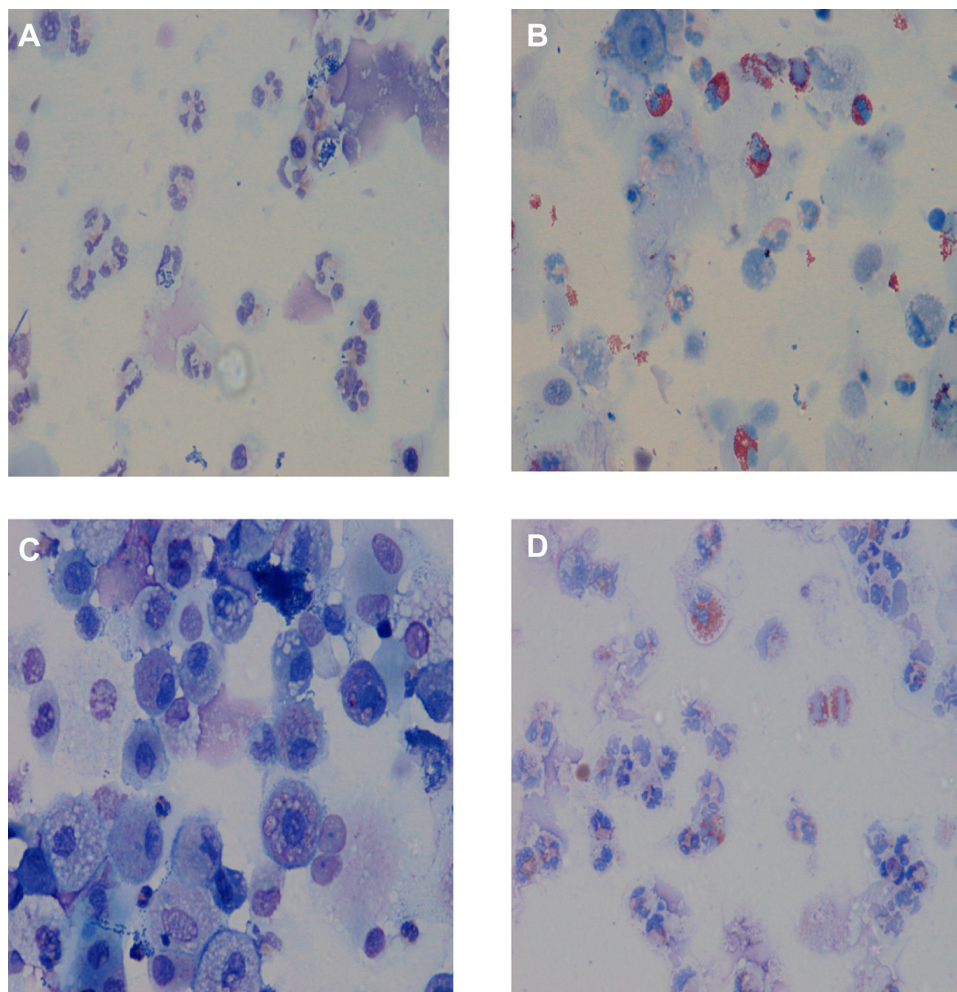


Figure 1 Airway inflammation phenotypes present in sputum from asthma and COPD patients.

Notes: (A) Neutrophilic airway inflammation. (B) Eosinophilic airway inflammation. (C) Paucigranulocytic airway inflammation. (D) Mixed neutrophilic/eosinophilic inflammation.

monitoring. High quality evidence from many well-designed clinical trials^{109–111} and a systematic review¹¹² report the superior effects of targeting airway eosinophilic inflammation on exacerbation reduction in both asthma and COPD. Airway inflammation in both asthma and COPD is heterogeneous, with four different airway inflammatory phenotypes having been described (Figure 1):

1. Eosinophilic
2. Neutrophilic
3. Paucigranulocytic
4. Mixed eosinophilic and neutrophilic.

Although traditionally asthma is considered an eosinophilic disease and COPD is associated with airway neutrophilia, the heterogeneity of sputum cellularity in these diseases is now increasingly recognized, with many studies reporting airway eosinophilia in COPD and airway neutrophilia in asthma.^{96,102,107,113,114}

In a large cross sectional study of patients with airways disease, D'Silva et al reported the cellular profile of over 4,000 induced or spontaneous sputum samples.¹⁰¹ In the group with asthma–COPD overlap, eosinophilic bronchitis was seen in 35%, neutrophilic bronchitis in 19%, and a mixed inflammatory pattern in 10%. In COPD, the phenotypes were respectively 18%, 34%, and 7%, and in asthma alone 26%,

14%, and 6%. These data demonstrate the heterogeneous nature of airway inflammation in asthma and COPD. The assessment of airway inflammation in airways disease may be important in order to tailor treatment more effectively.

Gonem et al proposed an approach that tailors treatment using a classification system that takes into account a number of pathophysiological components rather than disease labels.¹⁰⁵ The A to E system includes assessment and management of *AHR*, *Bronchitis* (airway inflammatory phenotype), *Cough* reflex sensitivity, *Damage* (relating to BD and corticosteroid-resistant airflow obstruction resulting from airway and parenchymal damage), and *Extra pulmonary* factors. This system remains an important current research area.

Gibson et al,¹⁰ McDonald et al,¹¹ and McDonald and Gibson¹¹⁵ propose an approach targeted at older patients and those with difficult airways disease. They suggest a model of multidimensional assessment and individualized management focusing on the four domains: airways, comorbidity, self-management, and risk factors (Figure 2). In a pilot study comparing management using this approach to usual care, the intervention achieved significant improvements in health status as well as in both airway and systemic inflammation. This study suggested that a personalized approach was feasible and could result in superior outcomes, but larger studies are required.¹⁰⁷

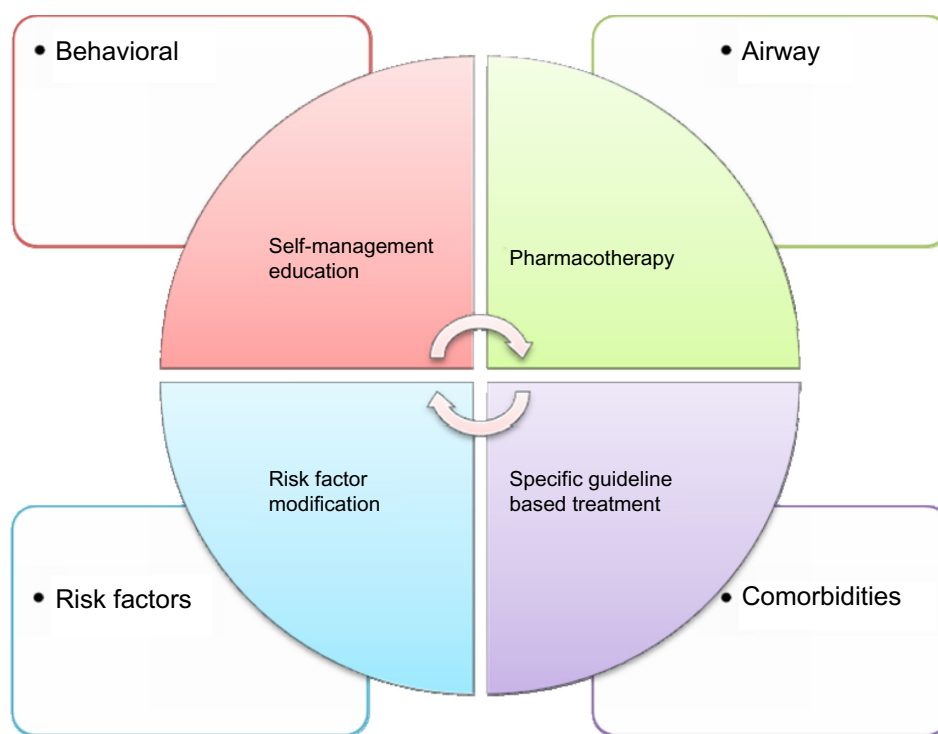


Figure 2 Model of disease components and individualized treatment approach.

Note: Reprinted from *The Lancet*, 376, Gibson PG, McDonald VM, Marks GB, Asthma in older adults, 803-813, Copyright 2010, with permission from Elsevier.¹⁰

Differential management of adult asthma and COPD

Guidance for clinicians around the world is provided by the Global Initiative for Asthma⁴ and GOLD.²¹ However, clinical practice guidelines need to be adapted to national and local conditions.^{89,116} The detailed management of acute exacerbations is beyond the scope of this review.

There are features common to the management of both adult-onset asthma and COPD. Both conditions require the development of a partnership between patients and their health care providers. Both conditions also require the identification and reduction of exposure to risk factors.⁴ A short-acting beta-agonist such as salbutamol or terbutaline provides effective symptom relief in both asthma and COPD and may be the only medication that is required in mild intermittent asthma.

Optimal inhaler technique involving accurate coordination of device actuation and inhalation are necessary for appropriate delivery of any inhaled drug. These require adequate cognitive function, manual dexterity, and strength of the intrinsic muscles of the hand. Elderly individuals can have poor device technique although competence can improve through the use of education as well as breath-actuated devices¹¹⁷ or large volume spacers.¹¹⁸ Given that device selection can also be driven by convenience, cost, and patient preference, regular objective monitoring of inhaler technique and adherence is essential.^{117,119}

Combination inhalers containing a long-acting beta-agonist (LABA) and corticosteroid are widely used both in asthma and COPD. Preventer (or controller) medication is recommended for adults who report asthma symptoms twice or more during the past month, waking due to asthma symptoms once or more during the past month, or an asthma flare-up in the previous 12 months.¹¹⁶ A single fixed dose combination inhaler may enhance adherence to inhaled corticosteroids in asthma,¹²⁰ and several randomized controlled trials suggest that single inhaler therapy reduces asthma exacerbations requiring oral corticosteroids, hospitalization, or emergency visits.¹²¹ The TOWARDS a Revolution in COPD Health (TORCH) trial found a modest reduction in mortality among COPD patients who were randomized to the combination of salmeterol and fluticasone compared to placebo.¹²² However, those who received the inhaled corticosteroid appeared to have an increased risk of pneumonia, although this was not radiologically confirmed. A meta-analysis of 24 randomized controlled trials suggested that the increased risk of pneumonia might be a class effect of inhaled corticosteroids.¹²³

Systemic corticosteroids are generally recommended in patients with moderate or severe exacerbations of asthma. Oral corticosteroids are as effective as injected corticosteroids, provided they can be swallowed and retained.¹¹⁶ Prednisolone 40–50 mg daily (or parenteral hydrocortisone 400 mg daily) is as effective as higher doses in hospitalized patients with severe exacerbations of asthma.¹²⁴ Similarly, systemic corticosteroids reduce the risk of treatment failure and the need for additional treatment for an exacerbation of COPD, as well as shortening hospital stay.¹²⁵ A short course of 40 mg prednisone daily for 5 days was recently shown to have non-inferior outcomes to a 2-week course at the same dosage.¹²⁶ Because of the risk of adverse effects, long-term use of oral corticosteroids is not recommended in either asthma or COPD. Specific complications include osteoporosis, weight gain, immobility, insomnia, emotional lability, glucose intolerance and diabetes mellitus, susceptibility to infection, skin atrophy, impaired wound healing, fluid retention, and increased cardiovascular risk.¹²⁷

Distinctive features of asthma management

Written asthma action plans are a cornerstone of asthma management in adults. A systematic review found that optimal self-management allowing for optimization of asthma control by adjustment of medications may be conducted by either self-adjustment with the aid of a written action plan or by regular medical review.¹²⁸ Having a written action plan was also associated with a reduced risk of death from asthma.¹²⁹ Although widely recommended in guidelines, the evidence for self-management in COPD is less compelling. A systematic review of 29 randomized controlled trials of self-management education (SME) compared to usual care found that SME in COPD led to a significant reduction in respiratory related hospital admission and improved health related quality of life and dyspnea. While the authors concluded that SME improves these outcomes, due to the heterogeneity of the interventions, study populations, follow-up time, and outcome measures data are still insufficient to formulate clear recommendations regarding the form and contents of SME programs in COPD.¹³⁰ Another systematic review concluded that giving patients an action plan and limited SME for the management of COPD exacerbations could not be recommended as the standard of care.¹³¹

The stepwise approach

The current management of asthma in adults is based on achieving asthma control and involves a stepwise approach,⁴ titrating

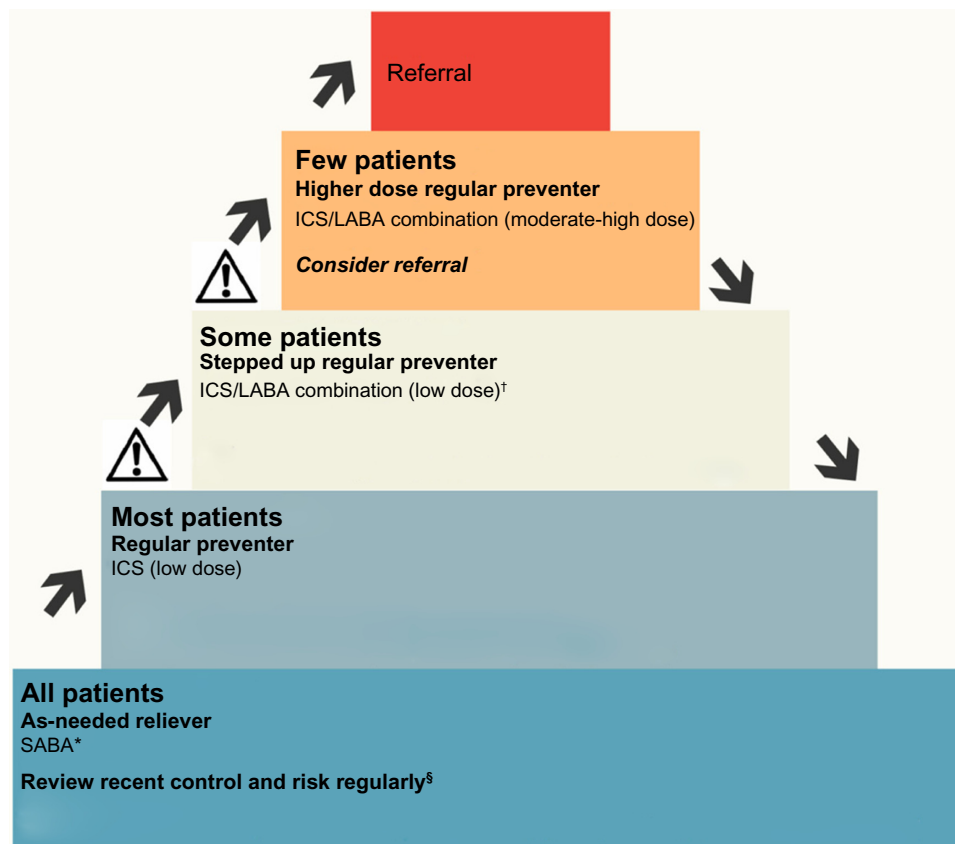


Figure 3 Stepped approach to adjusting asthma medication in adults.

Notes: Copyright © 2014 National Asthma Council Australia. Adapted from: Figure: Stepped approach to adjusting asthma medication in adults (Asset ID 31); National Asthma Council Australia. Australian Asthma Handbook, Version 1.0. National Asthma Council Australia, Melbourne, 2014. Available from: <http://www.astmahandbook.org.au>.¹¹⁶ † Montelukast can be added to inhaled corticosteroid as an alternative to switching to ICS/LABA, but is less effective. *, Reliever: Short-acting beta2 agonist (or low-dose budesonide/eformoterol combination for patients using this combination as both maintenance and reliever). §, in addition, manage flare-ups with extra treatment when they occur, and manage exercise-related asthma symptoms as indicated.

Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; SABA, short-acting beta-agonist.

the inhaled corticosteroid dose, and adding other medications such as LABA, leukotriene modifier, oral corticosteroid, and monoclonal antibody therapy as necessary. When control improves, the dose of inhaled corticosteroid can be reduced and/or other medications ceased (Figure 3). However, there are currently few published trials of back-titration in COPD, so once commenced, many patients with COPD typically remain on high doses of inhaled corticosteroids. Back-titration studies are difficult given the challenges of reconciling the numerous COPD phenotypes that reflect the marked heterogeneity of the disease.^{132,133} A systematic review of three adequate quality trials of back-titration in COPD found that patients who had medication withdrawn were 1.11 (95% confidence interval 0.84, 1.46) times more likely to have an exacerbation in the following year.¹³⁴ The results of the Withdrawal of Inhaled Steroids During Optimised bronchodilator Management (WISDOM) Trial¹³⁵ are awaited with interest.

Leukotriene receptor antagonists such as montelukast are an alternative oral preventer in mild to moderate asthma.

They probably only have a limited role in adult patients, particularly those with aspirin or exercise-induced asthma.¹³⁶ A systematic review of 56 randomized controlled trials found that monotherapy with inhaled corticosteroids was superior to leukotriene antagonists in reducing the requirement for rescue systemic corticosteroids or hospital admission, especially in adult patients with moderate airflow obstruction.¹³⁷

As asthma is primarily an allergic disease, even in adults, new biological agents are being trialed targeting key molecules in the inflammatory pathways. Omalizumab is a monoclonal antibody directed against immunoglobulin E. A recent systematic review of 25 randomized controlled trials found that compared to placebo, subcutaneous omalizumab reduced the risk of exacerbations and permitted many patients to reduce or withdraw from inhaled corticosteroids.¹³⁸ Mepolizumab is another monoclonal antibody directed against the cytokine IL-5. There are clinical trials showing that mepolizumab reduces exacerbations and improves quality of life in patients with refractory eosinophilic asthma.¹³⁹ However, the high cost

of these biological agents means that they can only be considered for patients with difficult to control asthma managed in specialist facilities, where patient selection and management is based on targeted phenotypes.¹⁴⁰

Distinctive features of COPD management

Stable COPD requires both nonpharmacological and pharmacological management. Figure 4 illustrates a stepwise approach to guide treatment decisions.

Smoking cessation

The major risk factor for COPD is active tobacco smoking,²¹ so particular emphasis needs to be given to smoking cessation and maintenance of abstinence. There are now a wide range of interventions including telephone counseling,¹⁴¹ nicotine replacement therapies,¹⁴² and newer pharmacological agents such as bupropion/nortriptyline¹⁴³ and varenicline,¹⁴⁴ which are effective particularly when combined with behavioral support.¹⁴⁵ New methods of delivery such as pharmacist-led interventions are being trialed in hospitalized patients.¹⁴⁶ Of course, smoking cessation is also important in asthma

as continued smoking can lead to fixed airflow limitation in susceptible patients.

Antimuscarinic agents

Long-acting inhaled antimuscarinic medications such as tiotropium, aclidinium, and glycopyrronium are particularly useful in COPD. Randomized controlled trials have demonstrated improvements in dyspnea, lung function, and quality of life compared to placebo or LABA.¹⁴⁷ Tiotropium is also associated with a reduction in and prolongation of time to exacerbations.¹⁴⁸ However, there does not appear to be any reduction in the rate of decline in lung function.¹⁴⁹ The benefits come with an increase in adverse effects such as dry mouth and urinary retention.¹⁵⁰ Some evidence is now emerging regarding the benefit of tiotropium in asthma.^{151,152}

Pulmonary rehabilitation

Pulmonary rehabilitation programs involve patient assessment, exercise training, education, nutritional intervention, and psychosocial support. Systematic reviews have shown that in patients with COPD, these programs reduce dyspnea, fatigue, anxiety and depression; improve exercise capacity,

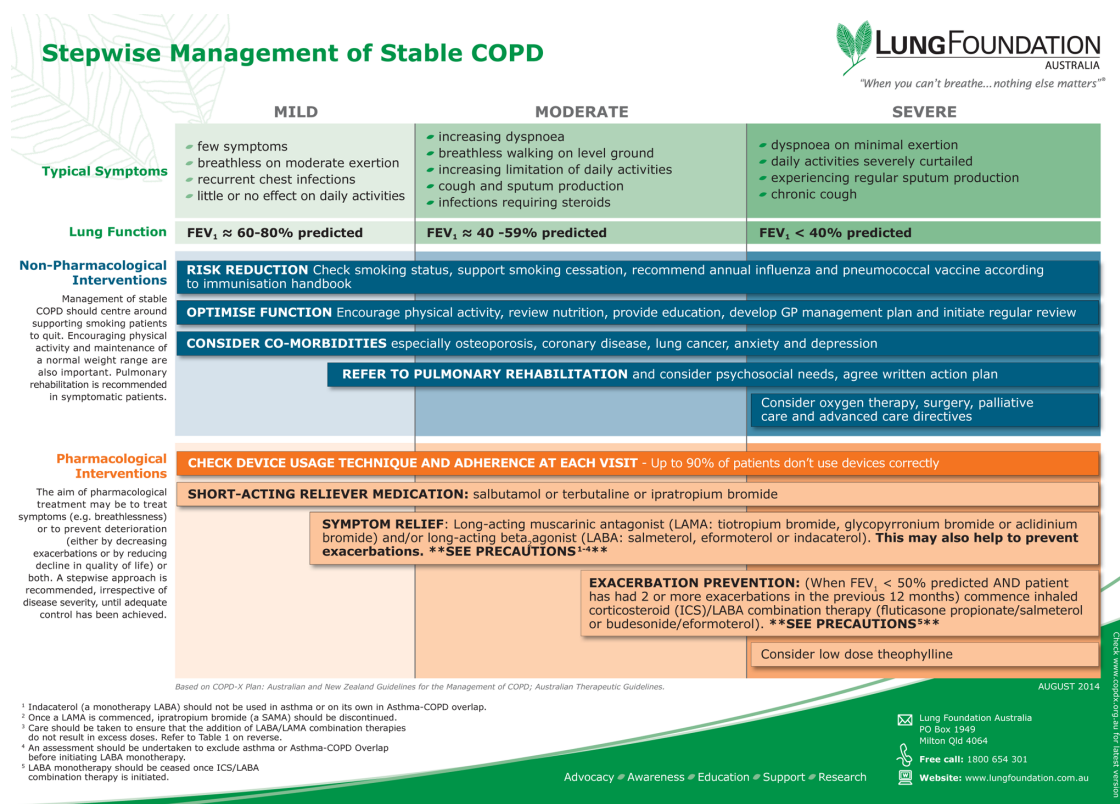


Figure 4 Stepwise management of Stable COPD.

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Abbreviations: COPD, chronic obstructive pulmonary disease; COPD-X, Confirm diagnosis, Optimise function, Prevent deterioration, Develop support, manage eXacerbations; FEV₁, forced expiratory volume in 1 second; GP, general practitioner; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist.

emotional function, and health-related quality of life; and enhance patients' sense of control over their condition.¹⁵³ Pulmonary rehabilitation also reduces the length of hospitalization in COPD patients¹⁵⁴ and is cost effective.¹⁵⁵ In patients with asthma–COPD overlap, exercise training can improve symptoms and health status.¹⁵⁶

Although access to comprehensive pulmonary rehabilitation varies with location, exercise training is an effective option in the management of patients with COPD if multidisciplinary education cannot be offered.¹⁵⁷

Action plans and self-management

Action plans for exacerbations are effective in asthma,¹⁵⁸ allowing patients to develop coping skills, anticipate early exacerbation symptoms, self-initiate appropriate treatment, and seek medical advice prior to significant deterioration. Trials assessing the effects of action plans in COPD management have shown conflicting results, with variable adjuncts to patient care likely contributors. Those with positive results, such as expedited exacerbation recovery and reduced hospital admissions, have included additional supports, such as intensive education and case management.^{159–161} In contrast, action plans with limited or no SME and no case management have little beneficial effect.¹³¹

A recent randomized controlled trial that suggested an unexpected increase in all-cause and COPD-specific mortality with a comprehensive care management program including a COPD action plan for US veterans,¹⁶² highlighted the value of identifying those with adult-onset asthma for whom the benefits are well-documented. Putting this disturbing finding into the context of the COPD literature is important, and identifying factors predisposing to a poor outcome will be a challenge for those involved in developing clinical practice guidelines. While the association did not appear related to increasing age or COPD severity,¹⁶² these findings suggest that self-management programs may not be appropriate for all patients with COPD.

Home oxygen

The use of domiciliary oxygen is common at the more severe end of the COPD spectrum. Indications to consider referral for assessment of need for long-term continuous oxygen therapy include severe airflow obstruction ($FEV_1 < 30\%$ predicted), presence of cyanosis, polycythemia, signs of right heart failure, saturation of $\leq 92\%$ breathing room air.¹⁶³ Long-term continuous oxygen therapy has been proven to offer survival benefits and improved quality of life in patients with COPD and severe hypoxemia (arterial blood partial

pressure of $O_2 \leq 55$ mmHg or 55–59 mmHg with evidence of end-organ damage).

However, the role of oxygen therapy in patients with exertional desaturation, nocturnal hypoxemia, or resting mild-moderate hypoxemia is less clear. Recent studies suggest an absence of long-term effects on dyspnea or quality of life from the use of ambulatory oxygen therapy in normoxic or mildly hypoxic patients with COPD who desaturate with exertion, even though they may demonstrate small acute benefits during laboratory-based exercise tests.^{164,165} Occasional so-called “n-of-1 trials” may be of use in some individuals.¹⁶⁵

Isolated nocturnal hypoxemia is not uncommon in COPD patients, particularly during rapid eye movement sleep. However, it has not been shown to lead to worse quality of life, daytime hypoxemia, or pulmonary hypertension. Limited studies have not consistently shown beneficial effects in sleep quality, pulmonary hemodynamics, or survival over 2 years with nocturnal supplemental oxygen.^{166–168} Similarly, patients with COPD and resting mild-moderate hypoxemia have not shown a survival benefit with domiciliary oxygen therapy. The currently recruiting US Long-term Oxygen Treatment Trial (NCT00692198) may provide more data regarding the effects of domiciliary oxygen in the latter patient subgroup.

End of life care

The disease trajectory for COPD is one of deteriorating health status and increasing morbidity, usually over a period of time. This differs from the more predictable trajectory of most cancers and as such, the most appropriate timing for discussions around end of life issues in COPD and referral time for palliative care are not clear.¹⁶⁹ Despite this difficulty, primary care providers and specialist COPD teams have an integral role in developing partnerships with patients and carers to provide information about prognosis, and over time, should introduce topics regarding intubation, admission to intensive care unit, and patients' views on “not for resuscitation” or medical treatment orders. This involves a discussion regarding quality of life and choices they wish to consider.⁸⁹ A useful resource to guide patients in making these choices is the Advance Care Planning website (<http://www.respectingpatientchoices.org.au>). Opioids may have a role in patients with severe intractable dyspnea.¹⁷⁰

Qualitative data suggest that there is a need for clinicians to improve their approach to end of life care in COPD. In one study, participants discussed their expectations about the future; this may have been fear about their future outcome or an idealistic expectation that they would not get any worse.

These data suggest that participants did not have a clear understanding of their disease or of how it would progress.¹⁷¹ This is in accord with a study that interviewed 16 COPD patients within the last year of life. Even at this late stage, half of the participants expressed a desire for more information about their disease and its prognosis.¹⁷²

Areas for further research

Although the importance and management of asthma–COPD overlap remains a strongly debated topic, there are few data to inform practice and policy. This is because large scale randomized trials have largely excluded patients with asthma from COPD trials and those with COPD from asthma studies.^{173,177} Furthermore, epidemiological research to date has mainly treated these as two distinct groups of diseases and, therefore, not much evidence is available on the overlapping or distinctly separate groups. A number of clinical and epidemiological research questions remain outstanding.

An area that needs research is the current classifications for obstructive lung diseases. These classifications are complex, with asthma regarded as multiple overlapping syndromes,¹⁷⁴ and the heterogeneity of both stable COPD and its acute exacerbations being increasingly recognized.¹³³ The GOLD strategy document has progressively acknowledged the overlap between asthma and COPD, and progress is being made on a joint Global Initiative for Asthma/GOLD asthma–COPD overlap document. Other factors besides current or past smoking which may contribute to persistent airflow obstruction in asthma include severe symptoms, long-standing disease, old age at onset, frequent exacerbations, ongoing exposures to allergens and occupational irritants, aspirin sensitivity, elevated serum immunoglobulin E, and ongoing airway inflammation and hyperresponsiveness.¹⁷⁵ With increasing recognition of this overlap phenotype, further revisions of the current taxonomy are likely to be developed.¹⁷⁵ Given the limited data available for this subgroup,^{173,176} developing targeted management-specific guidelines poses challenges.

Clinical questions that need research include whether the unopposed use of LABA in asthma–COPD overlap is problematic, as it is in asthma without COPD.¹⁷⁷ Likewise, does inhaled corticosteroid therapy in asthma–COPD overlap cause the same pneumonia risk as in COPD alone? Furthermore, back-titration of therapy is recommended in asthma as disease control improves. The approach to management involving back-titration in asthma–COPD overlap warrants further investigation. Finally, further clinical studies recruiting the population with asthma–COPD overlap and

testing novel and personalized approaches are needed. The newly proposed system of the tailored treatment approach, which uses a classification system based on a number of pathophysiological components, remains an important current research area.¹⁰⁵ A pilot study has shown that a personalized approach improved health status as well as both systemic and airway inflammation, but larger studies are required to confirm these findings.¹⁰⁷

There has been increasing interest in understanding how long-standing asthma can lead to irreversible airflow limitation.^{34,49,65,84} In this context, distinguishing between adult-onset asthma and COPD can be especially difficult for the high proportion of adults with asthma who have smoked. It has been suggested that risk factors for the multiple phenotypes related to overlaps between asthma and COPD⁵⁷ could vary.⁷ Understanding risk factors for these multiple phenotypes is critical to advancing knowledge of causal mechanisms and modifiable risk factors for both conditions.

Conclusion

Current clinical practice is based upon distinguishing between adult-onset asthma and COPD. There are separate guidelines for each condition. However, it is not always possible to clearly differentiate between these obstructive lung diseases because of common risk factors, such as tobacco smoking, and the convergence of symptoms and other clinical features. Studies based on newer approaches, for example, inflammation, may result in better clinical outcomes. Further randomized controlled trials of these and other novel approaches, for example, a multidimensional approach targeting individualized management, should provide important data to inform future guidelines. The management of asthma and COPD is increasingly converging. This has already occurred for pharmacological therapies such as combination inhalers. Written action plans and self-management currently seem to be more useful in asthma than COPD. Further research is needed to examine back-titration of inhaled corticosteroids in COPD and to determine the best management of the common asthma–COPD overlap syndrome.

Disclosure

The authors report no conflicts of interest in this work.

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