

Airway obstructive diseases in older adults: From detection to treatment

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Asthma and chronic obstructive pulmonary disease occur commonly and may overlap among older adults. Smoking, air pollution, and bronchial hyperresponsiveness are the main risk factors. The treatment of these diseases in older adults does not differ from the available guidelines but may be complicated by the presence of comorbidities. Smoking cessation is essential for smokers, and pulmonary rehabilitation must be considered regardless of the age of the patient. (J Allergy Clin Immunol 2010;126:702-9.)

Key words: Asthma, COPD, elderly, obstructive lung disease

Abbreviations used

BHR: Bronchial responsiveness
COPD: Chronic obstructive pulmonary disease
FVC: Forced vital capacity
GOLD: Global Initiative for Chronic Obstructive Lung Disease
ICS: Inhaled corticosteroid
LABA: Long-acting β -agonist agent
TORCH: Toward a Revolution in COPD Health
UPLIFT: Understanding Potential Long-Term Impacts on Function with Tiotropium

All diseases run into one, old age.

—Ralph Waldo Emerson

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality worldwide. The World Health Organization estimates that COPD will become the fifth most prevalent disease in the world and the fourth leading cause of worldwide mortality by the year 2020.^{1,2}

Considerable overlap exists between asthma and COPD, and this overlap can be particularly challenging to disentangle in elderly populations. Asthma, traditionally described as an allergic disease that develops in childhood, is characterized by the presence of reversible airflow obstruction. In contrast, COPD, largely related to tobacco smoking, develops later in life and is characterized by the presence of incompletely reversible or irreversible airflow obstruction and accelerated lung function decline. Although the clinical features of these diseases help us to differentiate between them in most patients, the spectrum of obstructive lung diseases seen in clinical practice is more complex, particularly among the elderly, who may have components of both diseases (Table I).

The growing burden of obstructive lung diseases appears to be caused, at least in part, by the aging of the world's population. The World Health Organization estimates that between the years 2000

and 2050, the proportion of persons over 65 years of age is expected to more than double, representing up to 17% of the total world population.³ The definition of “older person” or “elderly” is imprecise, although most developed world countries consider the chronologic age between 60 to 65 years of age to define the lower limit for an “older” adult.

The prevalence estimates of obstructive lung diseases in the elderly is complicated by several sources of bias.⁴ For example, COPD prevalence increases with aging, with an estimated prevalence of 20% to 30% in patients >70 years of age.⁵ In the case of asthma, the prevalence in the elderly is also high, with studies showing asthma affecting >10% of patients >60 years of age.⁶

Our understanding of obstructive pulmonary diseases has evolved in recent years. For example, we now recognize that both asthma and COPD are characterized by lung function changes, and evidence suggests they both share pathophysiologic alterations similar to the natural aging process in the lungs, including mechanisms of inflammation, cellular senescence, and apoptosis (leading into irreversible airway disease).⁷ It is not surprising, then, to note that the morbidity and mortality of both COPD and asthma increase with advancing age.

Despite a high prevalence, COPD remains underdiagnosed. Moreover, the existence of overlap syndromes of asthma, COPD, and other lung diseases in some patients complicates the ascertainment of prevalence in the general population. It is likely that current prevalence estimates largely underestimate the true burden of both diseases, particularly in the elderly population.

This review summarizes the epidemiology and diagnosis of COPD in older adults, with specific emphasis on common features and differences between COPD and asthma, and provides a brief overview of the different treatment strategies used in this population.

DEFINITIONS

The definition COPD has evolved in the last decade. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defined COPD as a preventable disease with extrapulmonary

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TABLE I. Differentiating features of COPD and asthma

	COPD	Asthma (early-onset)	Asthma (late-onset)	Overlap syndrome
Onset	Mid life	Early life	65 y or older	May have history of asthma in early life
Risk factors	Smoking	Atopy, airway hyperresponsiveness	Atopy, irritant exposures	Smoking, aging
Symptoms	Slowly progressive	Intermittent, worse at night/morning	Intermittent, poor perception of symptoms	Slowly progressive
Family history	May be present	Frequently present	May be present	May be present
FEV ₁ /FVC ratio	<70%	≥70%	<70%	<70%
FEV ₁ % predicted	<80%	>80%	<80%	<80%
Bronchodilator response	Absent	Present	Present	Absent

effects characterized by progressive airflow limitation that is not fully reversible associated with an abnormal inflammatory response.⁸ This contrasts with the earlier definition of COPD (American Thoracic Society) that required the presence of chronic bronchitis (determined clinically) or emphysema (determined pathologically) to confirm a diagnosis.

In clinical practice, the definition of COPD is not straightforward, particularly in older adults. For example, COPD includes a heterogeneous group of clinical manifestations and diverse disease phenotypes (ie, emphysema, chronic bronchitis), sometimes characterized by the presence of partially reversible airflow obstruction, whereas long standing asthma often leads to airway remodeling and partly irreversible airflow obstruction,⁹ making the differentiation between these 2 entities difficult clinically. In addition, there can be overlap with other disease processes such as bronchiectasis, bronchiolitis, interstitial lung disease, and congestive heart failure.

SPIROMETRY IN OLDER ADULTS

Spirometry is necessary to establish the presence of airflow obstruction and to classify the severity of the obstructive defect in COPD. Guidelines for standardization and interpretation of pulmonary function tests are widely available, and in the majority of adult subjects, acceptable and repeatable spirometric maneuvers can be achieved. Nevertheless, several pitfalls must be considered when performing and interpreting spirometry in the elderly.

Interpretative problems

1. Studies have shown that “healthy” elderly subjects develop physiological changes that resemble the presence of airflow obstruction.¹⁰ Aging is associated with a decline of forced vital capacity (FVC) and FEV₁ by 15 to 30 mL/y, and the decline in FEV₁ often exceeds the reduction in FVC, resulting in a decline in the predicted values and lower limit of normal. Using a fixed cutoff value (<70%), as is recommended by GOLD, potentially results in overestimation and misclassification of obstructive lung disease in older adults. The American Thoracic Society/European Respiratory Society pulmonary function test interpretation guidelines recommend that the lower limit of the normal range for FEV₁/FVC ratio, based on the fifth percentile corrected for age, sex, height, and race, be used to detect airflow obstruction.¹¹ Conversely, though, the prevalence and morbidity of obstructive lung diseases increase with aging.

2. Use of inappropriate reference equations may result in misclassification of disease: the majority of reference equations used in older adults have been extrapolated from studies that failed to include subjects >65 years of age.¹⁰

Technical barriers

1. Spirometry requires performance of unusual and athletic-type breathing maneuvers. Older patients may find it difficult to perform these, and submaximal efforts may lead to interpretation misclassification. Nevertheless, reports suggest that 50% to 90% of older adults achieve standard goals for test session quality.^{12,13}
2. Good quality testing from an elderly patient may require 20 to 30 minutes more than the time required for younger subjects.¹³
3. The minimum number of FVC maneuvers needed to achieve consistent results is higher in older adults (up to 5-8 maneuvers required).¹²
4. Older patients have difficulty achieving end-of-test thresholds and are frequently unable to exhale 20 seconds.¹⁴ For this reason, some have advocated using slow vital capacity maneuvers or the measurement of the FEV₁/forced expiratory volume in 6 seconds ratio to detect airflow obstruction.

EPIDEMIOLOGY

Disease burden

The prevalence of COPD in the general population increases with age. The Burden of Obstructive Lung Disease initiative reported the prevalence of COPD in different parts of the world (n = 9245). The prevalence of GOLD-defined COPD stage II (FEV₁/FVC ratio <0.70 and FEV₁ <80% of the predicted value) or higher was 11.8% for male and 8.5% for female subjects. The study also showed an increased risk of COPD that approximately doubled for each 10-year age increment over the age of 40 years.¹⁵ The prevalence was higher in smokers than in nonsmokers and increased with the intensity and duration of smoking. In a subgroup analysis of this study, the highest prevalence of COPD was found in patients >70 years of age, with a prevalence of 22.3% in men and 25% in women.¹⁶ Similarly, a study in Sweden described an increase in prevalence from 17.1% at 61 to 62 years of age to 28.7% at 76 to 77 years of age.¹⁷ In a cohort study of general adult population in Norway, the incidence of COPD was highest in the oldest age cohort: among subjects age 60 to 74 years at baseline, 18.8% developed COPD during the study versus 9.6% for those age 45 to 59 years.¹⁸

Studies have also investigated the prevalence of concurrent asthma and COPD in the elderly. For example, a study that analyzed 9131 patients age 40 to 64 from administrative Medicaid databases showed that up to 16% of patients between 50 and 64 years of age had concurrent diagnosis of asthma and COPD.¹⁹ An analysis of data from the Third National Health and Nutrition Examination Survey showed combinations of 2 of 3 obstructive lung diseases (COPD, chronic bronchitis, and asthma) occurred among 21.2%, 31.4%, and 14.4% in subjects in the age groups 60 to 69 years, 70 to 79 years, and ≥ 80 years, respectively.²⁰ A similar study of data in the United Kingdom General Practice Research Database reported combinations of 2 of the 3 conditions present among 41.5%, 58.8%, and 65.5% of patients in the age groups 60 to 69 years, 70 to 79 years, and ≥ 80 years, respectively.²¹

Risk factors

Smoking. Exposure to tobacco smoke is the single most important risk factor for COPD. In addition, smoking is a key contributor to development of asthma. Active tobacco use is associated with an accelerated lung function decline, increase incidence of obstructive lung disease, and increases in morbidity and mortality.²² Similarly, passive smoking has been associated with airway hyperresponsiveness, allergic sensitization, and development and exacerbation of asthma.²³

In the elderly, a high proportion of patients with asthma smoke despite a history of respiratory problems. For example, 1 study of elderly (>65 years of age) patients with asthma in France found that 56% of men and 10% of women described themselves as smokers or exsmokers. Compared with younger patients with asthma (18–34 years), older adults with asthma were more likely to report a history of smoking (54% vs 34%).²⁴

Air pollution. Chronic exposure to elevated air pollution levels is considered an important risk factor for an increase incidence and prevalence of respiratory symptoms and is associated with exacerbations of obstructive lung diseases. Although outdoor air pollution has not been directly linked to development of COPD, studies have shown that outdoor air particles have adverse effects on lung function and result in an increase rate of COPD exacerbations, hospital admissions, and sick days as a result of respiratory symptoms, particularly in the elderly.^{25–27} Similarly, air pollutants are involved in promoting and exacerbating asthma. Studies have shown that exposure to ozone, sulfur dioxide, and particulate matter is associated with increased use of asthma medication and hospital admissions for asthma.^{28,29} Although few epidemiologic studies have evaluated the role of air pollution and asthma in the elderly, it is reasonable to assume that elderly individuals with a history of exposure to air pollutants may have an increased sensitivity to environmental triggers. For example, a study in Hong Kong conducted questionnaire surveys in subjects age >70 years over 2 time points (12 years apart). The study found an increase in prevalence of self-reported or physician-diagnosed emphysema for COPD attributed to environmental factors and increasing air pollution.³⁰

Indoor air pollution may play a more important role in the older population, because many older adults spend most of their time at home. Biomass fuels and wood burning have been described as causes of COPD in developing countries.³¹ A study in Italy showed that the amount of indoor exposure to suspended particles was associated to the occurrence of acute respiratory symptoms in a group of older (>65 years) adults.³²

Bronchial hyperresponsiveness. Asthma has been proposed as a risk factor for development of COPD. A longitudinal cohort study that included >3000 patients found that asthma was associated with a 10-fold increased risk for developing COPD, regardless of smoking history.³³ On the other hand, bronchial responsiveness (BHR) to methacholine and histamine has been linked to accelerated lung decline and asthma.

Some studies have shown that BHR is associated with development of COPD and predicts COPD mortality.^{34,35} The role of BHR in the development of COPD is a matter of strong debate because it is unclear whether geometric airway narrowing associated with COPD is a cause or a consequence of BHR. Similarly, the role of BHR as a risk factor for obstructive lung diseases in the elderly has not been well studied, although reports have shown that airway hyperresponsiveness may be more common than previously thought among older adults, with prevalence rates ranging from 29% to 43%.³⁶ It is unknown whether airway narrowing and physiologic changes associated with normal lung aging may explain the higher prevalence of BHR in the elderly.

CLINICAL MANIFESTATIONS AND DIAGNOSTIC CHALLENGES

In clinical practice, differentiation of asthma and COPD is based on the patient's history and pulmonary function testing (Table I). Nevertheless, many factors complicate establishing the diagnosis among older adults. For example, it is known that longstanding asthma can lead to airway remodeling and partly irreversible airflow obstruction⁹; therefore, older adults with a history of asthma may develop clinical features suggestive of COPD. A longitudinal study found that 16% of patients with asthma developed features consistent with irreversible airflow obstruction after 20 to 30 years of follow-up.³⁷ The presence of a normal diffusing capacity for carbon monoxide (DLCO) can be useful to differentiate patients with asthma from patients with COPD; nevertheless, patients with asthma and a history of smoking may also present with a reduced DLCO.³⁸

Older adults with asthma are frequently divided in 2 groups: patients with a history of longstanding asthma and patients who develop late-onset asthma (age at diagnosis ≥ 65 years). Some studies suggest that between 40% and 50% of all older adults with asthma report a history of having a first attack after the age of 40 years.^{39,40} In contrast, COPD frequently becomes clinically apparent in the sixth and seventh decades of life, although early-onset COPD is seen, particularly in women with active smoking.

Patients with late-onset asthma tend to have higher baseline FEV₁, a more significant bronchodilator response, and less history of atopy, in contrast with patients with longstanding asthma, who tend to have less reversibility and more prominent atopic disease.⁴¹ Classic symptoms of asthma, including dyspnea, chest tightness, wheezing, or cough, are rarely helpful to establish a clinical diagnosis and distinguish between asthma and COPD among older adults.

There are several factors present in the elderly population that may make the detection and evaluation of obstructive lung diseases difficult. For example, advanced age is frequently associated with cognitive decline and depression, features that may preclude identification of clinical manifestations for several years before establishing diagnosis. In addition, studies have shown that the elderly have a sedentary lifestyle (individuals spent most of their time at rest), therefore avoiding activities that would be associated with respiratory symptoms.

Moreover, older adults appear to have an altered perception of dyspnea. Several studies have shown that older adults (60–83 years) are “poor perceivers” of bronchoconstriction and are less aware of significant decreases in FEV₁ than younger individuals after bronchoprovocation.^{42,43}

Finally, older individuals frequently have comorbid conditions (such as congestive heart failure, chronic aspiration, gastroesophageal reflux, and so forth) and may use medications that mask or trigger the presence of respiratory symptoms, contributing to underdiagnosis or misdiagnosis of the obstructive lung defect.

TREATMENT

The management of COPD in older adults is similar to that in the general adult population. The goals of therapy include controlling exposure to risk factors, symptom control, improvement of quality of life, limiting lung function decline, prevention of exacerbations, and decreasing mortality. Nevertheless, clinicians may be faced with unique challenges when treating elderly patients with COPD, including the following:

1. The presence of comorbidities, such as glaucoma, cardiac disease, or osteoporosis, is highly prevalent and complicates the use of commonly prescribed drugs.
2. Frequent use of multiple medications increases the risk for drug interactions.
3. A high prevalence of depression and other psychosocial factors interferes with treatment adherence and evaluation of treatment response.
4. Studies suggest that aging results in an impaired bronchodilator response because of an altered β_2 -adrenoceptor responsiveness in patients with COPD and asthma.⁴⁴

Smoking cessation

Among all the therapeutic interventions used in COPD, smoking cessation is the only one that alters the natural course of COPD by slowing the rate of decline in lung function, improving quality of life, and reducing mortality.^{45,46} Although smoking cessation is more beneficial when achieved in early stages of the disease, 1 study showed that even those who quit later in life (65 years of age or older) gained benefits (men gained 1.4–2.0 years of life; women gained 2.7–3.7 years).⁴⁷

Smoking cessation frequently requires a multidisciplinary approach that includes physician counseling and behavioral and pharmacological therapy. Unfortunately, the rates of smoking cessation attempts appear to be the lowest among older adults, despite the fact that studies have shown that elderly patients achieve sustained abstinence rates comparable to the general population.⁴⁸ Traditional agents used for smoking cessation (nicotine replacement therapy, bupropion, and varenicline)⁴⁸ have been safely and successfully used in older patients.⁴⁸ The use of varenicline has been associated with the highest sustained abstinence rate; nevertheless, recent reports suggest that this medication may be associated with exacerbation of underlying psychiatric disorders and increased suicidal ideation.⁴⁹ Although there are no studies specifically addressing these problems in the elderly, varenicline must be used with caution given the high prevalence of depression among older adults.

Pulmonary rehabilitation

Older adults with COPD frequently adopt a sedentary lifestyle that results in physical deconditioning and muscle weakness. Pulmonary rehabilitation represents a multidisciplinary intervention that consists of lower-extremity and upper-extremity exercise conditioning, breathing retraining, education, and psychosocial support aimed to break this cycle of inactivity and deconditioning. Although pulmonary rehabilitation does not directly improve lung mechanics or gas exchange, implementation of pulmonary rehabilitation has been associated with decreased dyspnea, improved health-related quality of life, fewer days of hospitalization, and decreased health care use.⁵⁰

A number of studies have investigated the effects of pulmonary rehabilitation in the elderly population. For example, 1 study compared the effects of a 2-week inpatient rehabilitation program between patients 65 to 74 years and patients >75 years and found similar improvements in exercise capacity, dyspnea, or health-related quality of life.⁵¹ Another study showed that although inpatient pulmonary rehabilitation was associated with greater improvements in walk distance in patients <60 years of age, pulmonary rehabilitation was well tolerated in older adults and resulted in significant improvements in functional capacity among elderly patients (including patients >80 years of age).⁵² Finally, outpatient pulmonary rehabilitation has also been associated with significant improvements in walk distance and lung function irrespective of age.⁵³

Pharmacologic treatment

Bronchodilator therapy. These agents are considered first-line treatment for COPD. Bronchodilators produce smooth muscle relaxation resulting in improved airflow obstruction, reduction in symptoms, improved exercise tolerance, and decrease in the frequency and severity of exacerbations. Despite these beneficial effects, bronchodilators do not affect the rate of decline in lung function (FEV₁) or survival.

β_2 -Adrenergic therapy. The GOLD guidelines recommend the use of short acting β_2 -adrenergic agents (≤ 6 hours) for symptomatic management of patients with COPD with all spectra of severity.⁸ Long-acting β_2 -agonist agents (LABAs) have longer duration of action (≥ 12 hours), and compared with placebo, these agents have been associated with a reduction in severe COPD exacerbations.⁵⁴ Nevertheless, a recent large multicenter study comparing salmeterol to placebo in patients with asthma found a trend toward more asthma-related deaths and prompted a black box warning issued by the US Food and Drug Administration advising against use of LABA as first-line therapy for asthma.⁵⁵ Finally, although adverse effects (ie, tachycardia, tremors, leg cramps, hypokalemia) of β_2 -agonist therapy may be more prominent in the elderly, previous studies have not found an increase in cardiovascular adverse effects associated with the use of LABA therapy, and a recent meta-analysis found a reduced risk for all-cause mortality compared with placebo.⁵⁴

Anticholinergic agents. These agents antagonize the muscarinic receptors, resulting in relaxation of bronchial smooth muscle tone and decreased mucus production. Two inhaled anticholinergic agents are commonly used in the United States: ipratropium bromide (short-acting) and tiotropium bromide (long-acting). In patients with COPD, use of tiotropium is preferred to ipratropium bromide because studies have shown

that tiotropium use results in a more significant improvement in lung function, reduction in frequency of COPD exacerbations, and reduced use of rescue medications.⁵⁶ Moreover, tiotropium bromide appears to have superior bronchodilator effects compared with LABA agents in patients with COPD.⁵⁷

Use of anticholinergic therapy is associated with common side effects among older individuals, such as dry mouth, cough, and worsening of narrow-angle glaucoma. In addition, patients with a history of prostate hypertrophy may develop severe urinary retention.

Importantly, the use of anticholinergic therapy has been associated recently with an increased risk of cardiovascular morbidity and mortality in some but not all studies. For example, a study that included >10,000 patients, the majority of whom were older than 60 years, found a nonsignificant trend toward increased hospitalization associated with myocardial infarction.⁵⁸ Similarly, a meta-analysis that included >14,000 patients with COPD found an increased risk for cardiovascular death, myocardial infarction, and stroke associated with inhaled anticholinergics.⁵⁹

In contrast, the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study randomized approximately 6000 patients to either tiotropium or placebo in addition to other, unrestricted respiratory medications for 4 years. Significantly lower rates of cardiac adverse events (relative risk, 0.84) and cardiac-related mortality (hazard ratio, 0.86) were observed in the tiotropium group.⁶⁰ In addition, the same group of investigators performed an analysis of 30 trials (including the UPLIFT data) that included 19,545 patients with moderate to severe COPD who were randomized to tiotropium or placebo. The authors found no increase in all-cause mortality, cardiovascular mortality, or cardiovascular events in the tiotropium group.⁶¹

Inhaled corticosteroids. Inhaled corticosteroids (ICSs) have a profound effect suppressing airway inflammation and represent the cornerstone of therapy in asthma. In contrast, the role for ICSs in the treatment of stable COPD is less clear, despite the finding that multiple studies have shown that these agents play a key role in the prevention and management of COPD exacerbations. In older individuals, ICSs play an important role, because many patients are at risk for development of exacerbations, and the coexistence of asthma and COPD appears to be common. Nevertheless, in this age group, the use of ICSs is also sometimes debated because of concerns of increased risk for systemic side effects such as senile cataracts, bone density loss, or pneumonia.

Beneficial effects of ICSs in COPD

Lung function decline. Large studies have examined the effects of ICSs on lung function in patients with COPD. The Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study, the Lung Health Study II, the Copenhagen City Heart Study, and the European Respiratory Society Study on COPD failed to demonstrate an effect of ICSs on lung function over time. Similarly, a large meta-analysis that included almost 50 randomized control trials and more than 13,000 patients showed that ICSs were not associated with a reduction in FEV₁ decline or improvement in mortality.⁶² In contrast, another meta-analysis that included 8 studies (3715 patients) found a slight reduction (10 mL/y) in FEV₁ decline compared with placebo.⁶³ A more recent study, the Toward a Revolution in COPD Health (TORCH) trial, randomly assigned 6112 patients with moderate to severe COPD

to 1 of 4 arms of treatment: LABA (salmeterol), inhaled steroid (fluticasone), combination therapy (salmeterol plus fluticasone), or placebo. All active treatments slowed the lung function decline compared with placebo, and treatment with fluticasone for 3 years resulted in reduced FEV₁ decline (42 vs 55 mL).⁶⁴

Prevention of exacerbations. A significant number of trials have showed that the daily use of ICSs is associated with a reduction in the frequency of COPD exacerbation and improvement in quality-of-life scores. For example, the ISOLDE study showed that the use of fluticasone significantly reduced the number of exacerbations in patients with severe COPD.⁶⁵ Similarly, another prospective randomized trial compared triamcinolone with placebo and found a reduction in the number of exacerbations (28.2 per 100 person-years vs 21.1 per 100 person-years).⁶⁶ In addition, 3 meta-analyses concurred that treatment with ICSs (6-18 months of therapy) in patients with moderate to severe COPD results in a substantial reduction in the number of COPD exacerbations.^{62,67,68}

On the basis of these recent results, the GOLD guidelines recommend use of ICSs in patients with FEV₁ <50% and history of recurrent exacerbations (3 in the last 3 years),⁸ whereas the American Thoracic Society/European Respiratory Society guidelines recommend use of ICSs in patients with FEV₁ <50% and use of oral corticosteroids or oral antibiotics at least once within the last year.⁶⁹

Mortality. The use of ICSs has not been consistently associated with improved mortality. For example, 2 reports have suggested a possible mortality risk reduction: a study that included data from 7 randomized control trials reported a reduced mortality risk (HR, 0.75) compared with placebo,⁷⁰ whereas a meta-analysis showed improved survival in a subset of patients with severe and very severe COPD (HR, 0.66).⁶⁸ Nevertheless, these results have not been duplicated in most longitudinal prospective studies, and a large meta-analysis that included more than 14,000 patients (including the TORCH trial) showed that the use of ICSs has no effects on mortality.⁷¹

Side effects

The use of ICSs has been associated with common side effects such as oropharyngeal candidiasis and skin bruising. A common concern in elderly individuals is the development of cataracts. The relation between ICSs and development of cataracts is particularly difficult to evaluate in older adults because many patients have a history of concomitant use of oral steroids. For example, a meta-analysis reported that subcapsular cataracts were more common among patients receiving ICSs, although a more recent randomized trial did not confirm this association.⁷²

Another common concern is related to the development of osteopenia and osteoporosis. Loss of bone mineral density is of particular concern in older adults with COPD, who may have underlying osteopenia and high prevalence of vitamin D deficiency.⁷³ Nevertheless, the evidence to support the effects of ICSs on mineral density is controversial. For example, a randomized trial demonstrated that lumbar spine and femur bone density were decreased among patients who received ICS therapy, whereas another study failed to confirm these findings.⁷⁴ A recent meta-analysis included 3 studies that reported ICSs were not associated with an increased risk of bone fractures.⁷¹ Currently, the presence of osteoporosis or osteopenia does not represent a contraindication for the use of ICSs, although

physicians should perform appropriate evaluations to determine bone density status and consider supplementation with calcium and vitamin D as necessary.⁷⁴

Finally, an area of current controversy is related to the association of ICSs with the risk of pneumonia. A meta-analysis that included more than 10,000 patients reported an increased risk for development of pneumonia among patients who were treated with ICSs (relative risk, 1.34; $P = .03$).⁷¹ Another meta-analysis that included 17,000 patients also found an increased risk of pneumonia (RR, 1.60).⁷⁵ These findings have prompted some authors to suggest that ICSs should not be used alone but rather in combination with a LABA agent in patients with COPD.⁷⁶

Oxygen

In patients with COPD, 2 large multicenter trials, the Nocturnal Oxygen Therapy Trial (NOTT) and the Medical Research Council (MRC) trial, showed that in patients with COPD who have a resting $Pao_2 \leq 55$ mmHg on room air, the use of oxygen therapy for at least 15 hours daily improves survival, exercise tolerance, sleep, and cognitive function.⁷⁷ Nevertheless, other studies that included patients with less severe hypoxemia did not find an effect on survival,⁷⁸ and questions remain about the benefits of oxygen therapy in patients with mild hypoxemia or nocturnal desaturation. A multicenter randomized control trial (The Long-Term Oxygen Treatment Trial [LOTT]) is currently underway to determine the effectiveness of supplemental oxygen therapy for people with COPD mild hypoxemia at rest and desaturation on exercise.

Vitamin D

Vitamin D is a fat-soluble hormone whose main biological effect is to regulate calcium and phosphate homeostasis. In addition, vitamin D has pleiotropic actions in other systems in the body. In patients with COPD, some of these extracalcemic effects may be of particular importance: antimicrobial and immunomodulatory effects, regulation of skeletal muscle function, and regulation of proliferation, differentiation, and apoptosis of different cell types such as extracellular matrix in lung tissue.⁷⁴ Several factors commonly present in elderly patients, such as poor diet, sedentary life style, lack of sun exposure, and poor muscle mass, favor the development of vitamin D deficiency. As a consequence, vitamin D deficiency is highly prevalent among in this population of patients, with several studies reporting that 40% to 100% of the elderly in the United States and Europe are mildly or severely vitamin D-deficient.⁷⁹ Few studies have reviewed the relation between vitamin D levels and lung function. For example, spirometry data from the NHANES III study suggested that low levels of 25-hydroxyvitamin D strongly correlated with lower pulmonary function.⁸⁰ These findings have prompted some to hypothesize that vitamin D deficiency may play a role in the pathophysiology and natural history of COPD. Nevertheless, no other survey or large study has investigated or confirmed this possible association. Currently, vitamin D supplementation is recommended for patients with COPD with or at risk for osteopenia and osteoporosis. More studies are needed to investigate the therapeutic benefits of vitamin D supplementation beyond bone and calcium homeostasis in patients with COPD.

The prevalence of asthma and COPD continues to increase worldwide. Evidence suggests that both diseases are underestimated and underdiagnosed. These 2 diseases share many risk

factors and clinical manifestations and may be difficult to differentiate among older adults. Physiologic changes associated with aging and overlapping features of irreversible airflow limitation with variable airflow obstruction present a unique diagnostic challenge for the clinician, who in some instances may be unable to establish a diagnosis. International efforts are needed to increase awareness of the frequency and burden of these 2 diseases in the elderly. Standardization of definitions used to ascertain the presence of obstructive lung diseases are needed to improve our understanding of the real impact of these disorders in the aging population. Finally, to evaluate the real efficacy of pharmacologic agents commonly used for asthma and COPD in this population, it is key to include subjects with history of smoking or presence of overlapping syndromes in randomized clinical trials.

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