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Aclidinium bromide (Tudorza PressAir), umeclidinium bromide (Incruse Ellipta), and glycopyrrolate (Seebri Neohaler) are other long-acting anticholinergics approved for the long-term maintenance treatment of COPD. These agents have been shown to improve lung function and are well tolerated.[113–115]

J.O. should be started on a long-acting bronchodilator, such as salmeterol or tiotropium. Once-daily β-agonists such as indacaterol or olodaterol are additional options to consider. Recently approved anticholinergics such as aclidinium bromide, glycopyrrolate, or umeclidinium bromide are other potential options. It should be noted that the tolerability and efficacy of the available long-acting bronchodilators are comparable. The choice of agent is largely based on considerations such as the frequency of drug administration, the patient's ability to use the inhalation device correctly, and any out-of-pocket costs incurred by the patient. J.O. should also be instructed to continue her albuterol two puffs every 4 hours as needed for breakthrough symptoms. A follow-up visit should be scheduled to assess her response.

CASE 19-2, QUESTION 2: J.O. is started on tiotropium respimat, inhale 5 μg daily and returns to the office for a follow-up visit 3 months later. She has had significant benefit from the medication and has had decreased wheezing and a noticeable improvement in her exercise tolerance. She asks to have spirometry repeated to see whether her lung function has improved on the new medication. Spirometry is repeated, and no significant improvement is noted in her FEV_1. How can she feel better, with improved exercise tolerance, without an improvement in her lung function?

Increasing evidence suggests that bronchodilators, including LABAs and anticholinergics, may reduce exercise-related dyspnea in patients with COPD by decreasing dynamic hyperinflation.[116] This improvement may be independent of marked changes in spirometry performed at rest. Indeed, because of flow limitation, these patients who exercise can have significant worsening of air trapping, which can worsen lung compliance and adversely affect respiratory muscle mechanics. A number of studies have shown that alleviation of such dynamic hyperinflation may be an important mechanism whereby bronchodilators improve exercise tolerance in patients with obstructive lung disease.[116]

CASE 19-2, QUESTION 3: J.O. seemed to do reasonably well for a number of years, but now, 3 years later, she has noticed progressive dyspnea on exertion. She is now having difficulty carrying laundry up from her basement, and she has noticed that her overall activity level has been curtailed. Repeat office spirometry now shows an FEV_1/FVC ratio of 0.49 and an absolute FEV_1 of 49% of predicted. She now has a CAT score of 22 and has had two exacerbations in the past year. J.O. has been adherent with her tiotropium regimen and has had no other significant changes to her medical history. She remains smoke free and is not exposed to secondhand smoke in her home and work environments. What therapeutic intervention(s) should be considered at this point?

INHALED CORTICOSTEROID THERAPY

J.O. has had significant deterioration in status and repeated COPD exacerbations despite appropriate adherence to tiotropium. Before modifying therapy, proper inhaler technique, medication adherence, and impact of nonpharmacologic interventions should be assessed. Combination therapy with either LAMA + LABA or ICS + LABA should be considered in patients with persistent symptoms or who continue to experience exacerbations despite appropriate use and adherence to long-acting bronchodilator monotherapy.[1] Fixed-dose combination products are preferred, and several options are commercially available (Table 19-3). LAMA + LABA therapy may be preferred, given the absence of asthma or atopic conditions and without elevated serum eosinophil levels and other biomarkers associated with ICS response. Also, dual bronchodilator therapy has a lower incidence of pneumonia, when compared to regimens containing an ICS. An LAMA + LABA combination was superior to an ICS + LABA in preventing exacerbations and other patient-reported outcomes in those with a history of prior exacerbations.[117] Several corticosteroid LABA inhalers are available and indicated for COPD, including Advair (fluticasone–salmeterol), Symbicort (budesonide–formoterol), and Breo Ellipta (fluticasone–vilanterol). No convincing data suggest that one preparation is superior to the other in the treatment of COPD. However, a number of multicenter, randomized, controlled clinical trials have demonstrated the efficacy of ICS in COPD.[78,83] The data have supported the use of ICS in advanced COPD and in patients with frequent exacerbations. ICS responsiveness may be further predicted by the presence of elevated eosinophils (≥300 cells/μL) or underlying asthma.[1] Moreover, regular use of ICS can decrease the frequency of acute exacerbations and improve health-related quality of life in patients with an FEV_1 <60% of predicted.[22]

Table 19-3

Inhaled Therapeutic Options for COPD

Medication Brand Name and Strength (per Inhalation)	Chemical Name	Device	No. of Doses[a]/Device or Box
Short-Acting β_2 Agonists			
[c]ProAir HFA 90 µg, [c]Proventil HFA 90 µg, [c]Ventolin HFA 90 µg	Albuterol	MDI	200[b]
ProAir, RespiClick 90 µg	Albuterol	DPI	200
[c]AccuNeb 0.63 mg/3 mL, 1.25 mg/3 mL	Albuterol	Nebulizer	Varies
ProAir® Digihaler™	Albuterol	DPI	200
[c]Proventil 2.5 mg/3 mL (0.083%),[e]5 mg/mL (0.5%) *concentrate*	Albuterol	Nebulizer	Varies
[c]Xopenex HFA 45 µg	Levalbuterol	MDI	200[b]
[c]Xopenex 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL, [e]1.25 mg/0.5 mL *concentrate*	Levalbuterol	Nebulizer	Varies
Short-Acting Anticholinergic			
Atrovent HFA 17 µg	Ipratropium	MDI	200[b]
[c]Atrovent 0.02% (0.5 mg/2.5 mL) vial	Ipratropium	Nebulizer	25ct, 30ct, 60ct
Short-Acting Anticholinergic + β_2-Agonist Combination			
Combivent Respimat 20–100 µg	Ipratropium + Albuterol	SMI	120[b]
[c]DuoNeb 0.5–2.5 mg/3 mL vial	Ipratropium + Albuterol	Nebulizer	30ct, 60ct
Long-Acting β_2-Agonists			
Serevent Diskus 50 µg	Salmeterol	DPI	60
Brovana 15 µg/2 mL vial	Arformoterol	Nebulizer	30ct, 60ct
Perforomist 20 µg/2 mL vial	Formoterol	Nebulizer	30ct, 60ct
Arcapta Neohaler 75 µg	Indacaterol maleate	DPI	30 blister units
Striverdi Respimat 2.5 µg	Olodaterol	SMI	60[b](*30 doses*)
Long-Acting Anticholinergics			
Spiriva HandiHaler 18 µg	Tiotropium	DPI	30 blister units
[d]Spiriva Respimat 2.5 µg	Tiotropium	SMI	60[b](*30 doses*)
Tudorza Pressair 400 µg	Aclidinium bromide	DPI	60
Incruse Ellipta 62.5 µg	Umeclidinium	DPI	30
Seebri Neohaler 15.6 µg	Glycopyrrolate	DPI	60 blister units
Lonhala Magnair 25 µg/mL	Glycopyrrolate	Nebulizer	60ct
Yupelri 175 µg/3 mL	Revefenacin	Nebulizer	30ct
Long-Acting Anticholinergic + β_2-Agonist Combination			
Anoro Ellipta 62.5–25 µg	Umeclidinium + Vilanterol	DPI	60
Stiolto Respimat 2.5–2.5 µg	Tiotropium + Olodaterol	SMI	60[b](*30 doses*)
Utibron Neohaler 15.6–27.5 µg	Glycopyrrolate + Indacaterol	DPI	60 blister units
Bevespi Aerosphere 9–4.8 µg	Glycopyrrolate + Formoterol	MDI	120[b]
Duaklir Pressair 400–12 µg	Aclidinium + Formoterol	DPI	60
Inhaled Corticosteroid + Long-Acting β_2-Agonist Combination			
[c,d]Advair Diskus 250–50 µg	Fluticasone + Salmeterol	DPI	60
[c,d]Symbicort HFA 160–4.5 µg	Budesonide + Formoterol	MDI	120[b]
[d]Breo Ellipta 100–25 µg	Fluticasone + Vilanterol	DPI	60
Inhaled Corticosteroid + Long-Acting Anticholinergic + β_2-Agonist Combination			
[b,d]Trelegy Ellipta 100-62.5-25 µg	Fluticasone furoate + umeclidinium + vilanterol	DPI	60
Breztri Aerosphere 160-9-4.8 µg	Budesonide + glycopyrrolate + formoterol	MDI	120[b]

DPI, dry-powder inhaler; MDI, metered-dose inhaler; SMI, soft mist inhaler.

[a]Generic formulations available.

[b]Only FDA-approved strength for COPD other strengths may be commercially available.

[c]Institutional sizes not included.

[d]Number of doses after initial priming.

[e]Nebulized solutions marked "0.5- mL concentrate" should be diluted with 0.9% sodium chloride solution.

The TORCH study has defined the benefits and potential side effects of ICS in a broader patient population of COPD.[57] In this multicenter, randomized, placebo-controlled study, mean FEV_1 was 50% of predicted, but entry criteria did not require a history of repeated exacerbations. More than 6000 patients were randomly assigned to either an ICS (fluticasone 500 µg bid), inhaled salmeterol (50 µg bid), combined fluticasone 500 µg and salmeterol 50 µg bid, or placebo. Subjects were assessed for ~3 years. A significant benefit was seen as measured by decreased exacerbation rates in subjects taking either inhaled fluticasone or a combination of fluticasone–

salmeterol therapy. Also, an improvement was found in mortality with combination therapy that approached, but did not reach statistical significance. Overall adverse side effects with ICS were similar to those with placebo. An increased risk, however, was seen for lower respiratory tract infections with inhaled fluticasone or fluticasone–salmeterol. Of note, patients did not experience an increased risk of ocular manifestations or decreased boFFIgurene density with ICS treatment.

J.O. is already taking tiotropium, so a decision must be made regarding step-up therapy. Proper inhalation technique and adherence should be confirmed before escalating therapy. LAMA + LABA is the preferred regimen for this patient, given her persistent symptom burden and high frequency of exacerbations over the past year despite LAMA monotherapy. Tiotropium + olodaterol is one possible fixed-dose combination product that may replace tiotropium. J.O. is already familiar with the Respimat device, which may help maintain adherence. If J.O. is experiencing difficulty with using the respimat, several alternative long-acting dual bronchodilator products are available in different inhaled delivery devices.

CASE 19-2, QUESTION 4: J.O. calls the next day, having read something on the Internet regarding possible increased risk of death in people with obstructive lung disease who take long-acting bronchodilators. She is reluctant to take it. What should you tell her?

SAFETY OF LONG-ACTING BRONCHODILATORS

Although some evidence in asthma indicates that the use of long-acting bronchodilators may be associated with an increased risk of death, such evidence does not exist in patients with COPD. In fact, the TORCH study demonstrated no increased risk of death or adverse events among patients prescribed salmeterol compared with placebo.[57] Other trials designed to evaluate the safety of bronchodilator use have resulted in similar findings.[61,62,102,111] The patient should be reassured that long-acting bronchodilators are safe in COPD.

PULMONARY REHABILITATION

CASE 19-2, QUESTION 5: J.O. also wonders whether anything else other than her medication can be done for her. What advice might be given?

At this point, pulmonary rehabilitation should be strongly considered. In fact, a comprehensive multidisciplinary pulmonary rehabilitation program should be considered in any patient with COPD experiencing persistent shortness of breath despite pharmacologic management.[1,46]

Increasing evidence points to COPD as a systemic process,[118] and pulmonary rehabilitation addresses the systemic nature of the disease. Although the proximate cause of disability involves the respiratory system, leading to dyspnea on exertion, this, in turn, has systemic consequences. Although the changes may be fairly subtle to start with, most patients will gradually manifest increasing limitations in their activity. This results in substantial deconditioning. It is likely that this deconditioning, in addition to other factors such as systemic inflammation, adversely affect skeletal muscle function. Indeed, evidence is clear that oxidative capacity is diminished in patients with COPD,[47–49] which results in overall decreased aerobic capacity and increased lactic acid production for a given level of activity.[50] The increased acid load will lead to a greater requirement for ventilation, which makes dyspnea more severe. The more dyspneic the patient is, the less activity he or she will do, leading to more deconditioning and recapitulation of the downward spiral.

Pulmonary rehabilitation is an exercise-based, multidisciplinary program that seeks to address this cycle.[1] Most programs generally last 8 to 12 weeks and involve two to three sessions per week.[46] Education, particularly about medication use, as well as psychosocial counseling and breathing retraining are important components of the program. An important component of breathing retraining involves coaching patients how to use pursed-lip breathing effectively. Pursed-lip breathing involves pursing the lips together (as in whistling) during exhalation. This helps to slow down respirations and also provides a back pressure in the small airways, preventing dynamic airway collapse and exercise-induced hyperinflation. The major intervention, however, is exercise training, especially endurance training of the lower extremities (eg, using a treadmill or bicycle ergometer). Numerous studies have demonstrated that a rehabilitation program can significantly improve exercise capacity and quality of life, as well as decrease health care utilization.[51] This may partly be related to the beneficial effects of exercise on the oxidative capacity of the skeletal muscles.

J.O. should be referred to a local outpatient pulmonary rehabilitation program. A typical program involves 2-hour sessions, two to three times per week for 8 to 12 weeks. The sessions will involve education, breathing retraining, and strength and endurance exercise training.

basophils, eosinophils, neutrophils, macrophages, and leukotrienes, play important roles.[4] These additional mediators, attracted to the area through chemotaxis, sustain the inflammatory response.[4] Also, some chemotactic proteins can cause damage to the airway epithelium and expose local nerve fibers.[4] Continued exposure to the offending allergen can also prolong the late-phase reaction.

CLINICAL PRESENTATION AND ASSESSMENT OF RHINITIS

The diagnosis of rhinitis is not defined by one specific laboratory test; rather, it is related to the coordinated results of a thorough patient interview, including medication history, pertinent physical examination, and a limited number of relevant laboratory assessments.

Risk Factors

Several elements increase the risk of developing allergic rhinitis. Atopy, parental history, introduction of formula in infancy, exposure to maternal smoking at age younger than 1 year, serum IgE levels >100 IU/mL before age 6 years, ethnic origin other than White European, environmental pollution, birth during pollen season, no older siblings, late entry into nursery or preschool, and exposure to indoor allergens such as animal dander and dust mites as well as concomitant food allergies[26] are risk factors.[5]

History, Signs, and Symptoms

A history should be obtained from the patient that includes details of the onset (including seasonality),[3] character, frequency, duration, and severity of the patient's symptoms and any identifiable factors that provoke or relieve these symptoms.[5] Past medical history (including the age of onset of symptoms) and family history (eg, atopy) are also helpful.[5] Other symptoms such as sleep problems, snoring, repeated sniffing, and allergic salute and shiner should also be noted.[3]

Both allergic and nonallergic forms of rhinitis are common and can potentially coexist.[2] Diagnostic criteria suggestive of allergic rhinitis include nasal discharge, itching, sneezing, and nasal congestion.[3] Occasionally, patients will present with a decreased sense of smell.[5] Symptoms of allergic conjunctivitis include itchy, watery eyes,[5] which occur in ~50% to 70% of patients with allergic rhinitis. Their presence can be used to differentiate allergic rhinitis from other forms.[5] Persistent congestion and/or rhinorrhea[25] like changes in temperature, air conditioning, pollutants, tobacco smoke, and other irritants suggest that nonallergic triggers may be involved. The negative impact of rhinitis on a patient's quality of life can be substantial, and it is important to assess this during the patient interview. Symptoms and symptom-induced interference with necessary (ie, work, school) and enjoyable (eg, hobbies, family events) activities can lead to patient anger, sadness, irritation, and withdrawal.[5] The questions listed in **Figure 20-4** provide a guide to collecting the information needed to initiate and modify therapy based on the underlying causes of the rhinitis symptoms.

1. Which of the common symptoms of rhinitis is the patient experiencing?
    - Sneezing, nasal itching, runny nose, nasal congestion, postnasal drip, altered sense of smell, watery eyes, itching eyes, ear "popping"

2. What color are the nasal secretions?
    - Clear, white, yellow, green, blood-streaked, rusty brown

3. When did the symptoms first appear?
    - Infancy, childhood, adulthood

4. Were the symptoms associated with a change in state/environment?
    - After a viral upper respiratory infection, after a traumatic blow to the head or face, upon moving into/visiting a new dwelling, after obtaining a new pet

5. How often do the symptoms occur?
    - Daily, episodically, seasonally, constantly

6. For how long has this symptom pattern persisted?
    - Days, weeks, months, years

7. Which factors or conditions precipitate symptoms?
    - Specific allergens, inhaled irritants, climatic conditions, food, drinks

8. Which specific activities precipitate symptoms?
    - Dusting, vacuuming, mowing grass, raking leaves

9. Are other members of the family experiencing similar symptoms?

10. Which of the following are prevalent in the household?
    - Carpeting, heavy drapes, foam or feather pillows, stuffed toys, areas of high moisture (basements, bathrooms), tobacco use (by patient or others), pets

11. Does the patient have other medical conditions that can cause similar symptoms?

12. Is the patient taking any medications that might cause or aggravate these symptoms?

13. What prescription and nonprescription medications have been used for these symptoms in the past? Were they effective? Did they cause any unwanted effects?

14. What is the patient's occupation?

15. What are the patient's typical leisure activities?

16. To what extent have the symptoms interfered with the patient's lifestyle (ie, are they disabling or merely annoying)?
    - Greatly, somewhat, not much

Figure 20-4 Patient history interview.

Diagnosis

PHYSICAL EXAMINATION

During a physical examination for rhinitis, the patient's nose should be inspected for the position of the septum, appearance of the nasal mucosa, secretions, and any growths.[3] Common physical characteristics of patients with allergic rhinitis are clear nasal discharge, swollen nasal membranes,[4] allergic shiners (discoloration under the