Asthma:

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ABSTRACT: Education can help improve compliance with inhaled corticosteroid therapy or correct faulty metered-dose inhaler (MDI) technique. Options for patients with poor MDI technique include use of a spacer or an alternative device, such as a nebulizer or a dry powder inhaler. If therapy is ineffective, consider alternative conditions that mimic asthma, especially vocal cord dysfunction and upper airway obstruction. Treatment of comorbid conditions, such as gastroesophageal reflux disease or rhinosinusitis, may improve control. In refractory asthma, it is crucial to identify allergic triggers and reduce exposure to allergens. If another medication needs to be added to the inhaled corticosteroid, consider a long-acting β-agonist, leukotriene modifier, or the recombinant monoclonal anti-IgE antibody omalizumab.

A 23-year-old woman's asthma symptoms have worsened during the past year. Specifically, she notes increased wheezing during the day and more nighttime attacks that wake her up. She has been using her inhaler several times each day and almost every night. During the past year, she has been hospitalized twice because of her asthma; in the past month, she has made 3 unscheduled office visits and 1 emergency department (ED) visit.

This woman's case exemplifies the fact that asthma cases are on the rise. From 1980 to 1995, the prevalence of asthma rose from 30.7 per 1000 Americans to 56.8 per 1000. Asthma is also an increasingly common cause of ED visits and hospitalizations; the annual costs of treatment total approximately $7.5 billion. More than 5000 deaths each year are attributed to asthma, and this number is rising.

As the prevalence of asthma increases, you are more likely to encounter patients in whom standard therapies seem ineffective. Although some of these patients do have severe, refractory disease, other factors may be hindering asthma control (Table 1).

In this article, we discuss how to detect and manage the most common causes of ineffective asthma therapy. We also present therapeutic options for patients who need additional medication to achieve control of their disease.

NONCOMPLIANCE

The burden of responsibility for asthma therapy lies with the patient. Thus, compliance is crucial to successful treatment. A number of factors can contribute to poor compliance in asthma therapy, including:

• Inadequate understanding of the disease and its treatment (current guidelines for therapy are highly complex).
• Side effects and/or fear of their occurrence.
• Insufficient communication between patient and physician.

Consequently, noncompliance commonly underlies presumed treatment failure. Inhaled corticosteroids remain the cornerstone of therapy for many asthmatic patients. Unfortunately, these are also among the medications associated with the poorest rates of compliance. One reason is patients' poor understanding of the role of inhaled corticosteroids. Studies show that most patients who use an inhaled corticosteroid believe that the medication "opens the airways," and therefore use it only when they think they need it. Many others are afraid to use inhaled corticosteroids regularly because of fear of side effects.

The key to compliance is education. Take time to teach patients about the disease, its pathogenesis, and its triggers. Frequent follow-up visits are an ideal way to provide time for education, to assess compliance, and to remind patients to continue appropriate therapy. Discuss "action plans" for the management of exacerbations. Make sure patients understand the importance of maintenance therapy despite a lack of symptoms; in particular, stress the need to use inhaled corticosteroids regularly.

Ask patients if they are concerned about side effects, and reassure them about the safety profile of these agents. Many patients have irrational concerns (eg, weight gain and muscle buildup) that can
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For patients who cannot or will not use inhaled corticosteroids as instructed, prescribe alternative agents. Long-acting β-agonists provide effective relief of asthma symptoms, although they do not address the underlying inflammation and are not recommended as monotherapy. Cromolyn and nedocromil are mast cell stabilizers that can be useful in patients with mild disease, but compliance may be poor with these agents as well, since they must be used 4 times a day even when the patient is symptom-free.

The leukotriene modifiers block the formation of mediators in the asthma inflammatory cascade. They have shown some efficacy as monotherapy but are not as potent as inhaled corticosteroids. Nevertheless, they remain a useful alternative to inhaled corticosteroids. A study based on prescription refill rates suggests that patients are twice as likely to comply with leukotriene modifier therapy as with inhaled corticosteroid therapy. For patients with severe uncontrolled asthma, multidrug therapy may be necessary. However, the need for multiple medications (taken at different intervals) is an invitation for noncompliance. Even for patients with severe disease, try to keep the regimen as simple as possible.

**INHALER TECHNIQUE**

**Metered-dose inhalers.** Unless they are used correctly, metered-dose inhalers (MDIs) do not properly deliver asthma medication; thus, improper technique may result in inadequate treatment—which both patient and physician may mistake for failure to respond. Even with optimal technique, only 10% to 30% of the medication in an MDI actually reaches the patient's lungs. This leaves little doubt as to why patients with improper MDI technique often have uncontrolled disease. Here again, the solution to the problem is education. Instruct the patient in one of the various recommended techniques for MDI use. In one method (Box), the patient actuates the MDI during a slow deep inhalation over 3 to 5 seconds, followed by a 10-second breath hold. Although laboratory studies suggest that better delivery is achieved when the inhaler is held 2 inches from the mouth, no clinical difference has been demonstrated between this approach and that of sealing the lips around the inhaler; moreover, some patients may have difficulty in holding the inhaler away from the mouth.

After instruction, observe the patient's technique. There are a number of common pitfalls in MDI use to be alert for. It may be difficult for some patients—especially those who are very young or very old—to coordinate actuation and inhalation. Others find slow inhalation difficult. Stopping inhalation at the time of actuation is another common mistake.

**Spacers.** One alternative for those who are clearly unable to learn proper technique—especially those who have difficulty in coordinating inhalation and actuation—is a spacer or holding chamber. A spacer can greatly reduce drug deposition in the oropharynx by facilitating delivery. This is certainly the best choice for younger children.

To use the spacer, patients discharge the MDI into the chamber and within 3 to 5 seconds begin to slowly inhale. A spacer is no panacea, however. It still requires some coordination, and it can decrease the output of an MDI because of deposition and static electricity in the chamber. Spacers may also reduce compliance, since these bulky devices are inconvenient to carry (although you can recommend that a patient use a spacer when at home and an MDI alone when out).

**Dry powder inhalers.** Another popular alternative to the MDI is the dry powder inhaler, which the pharmaceutical companies developed to comply with laws to eliminate fluorocarbon use. These devices may improve delivery for patients who are unable to use an MDI properly. Their drug delivery has been shown to be equivalent to or slightly better than that of MDIs. Note that a dry powder inhaler requires a somewhat different technique than that used with an MDI. Many require a more rapid inhalation of 1 to 2 seconds. Also remind patients that they will destroy the dose if they exhale into the device first.

**Nebulizers.** Yet another option is aerosolized delivery via a nebulizer. Although the drug delivery of a nebulizer is equivalent to that of a properly used MDI, a nebulizer may provide better delivery for patients who are unable to learn other methods. An aerosol corticosteroid (budesonide) is available for nebulizer use in children. The main drawback of the device is its size, which makes it suitable mainly for use in the home.

**ASTHMA MIMICS**

Keep in mind that "all that wheezes is not asthma." When asthma does not respond to traditional therapy, it may be because the patient has another syndrome that mimics asthma, or because he or she has a comorbid condition that complicates it (Table 2).

The 2 most common syndromes that mimic asthma are vocal cord dysfunction and upper airway obstruction. Both may result in dyspnea and apparent wheezing, yet show little or no response to standard asthma therapy.
**Vocal cord dysfunction.** Also called "factitious asthma," vocal cord dysfunction causes recurrent, severe shortness of breath, and inspiratory stridor that is easily confused with wheezing; the condition typically occurs in women between the ages of 20 and 40 years. Keep in mind that concomitant asthma may be present. Patients often present in respiratory distress, and inspiratory stridor is the principal finding on physical examination, although this is often mistaken for wheezing. Arterial blood gas levels are usually normal, but there may be alveolar hypoventilation with increased carbon dioxide concentration. Results of pulmonary function tests are also usually normal, although they may demonstrate a flattened inspiratory loop consistent with extrathoracic obstruction. The condition is psychogenic; many patients have depression, anxiety, or post-traumatic stress disorder secondary to childhood abuse. The physiologic basis is the paradoxic adduction of the vocal cords on inspiration (they normally abduct during both phases of the respiratory cycle). The diagnosis is thus confirmed by direct visualization of the cords. A bronchoprovocation test may also help rule out true reactive airway disease. Once asthma is excluded, gradually discontinue the patient's asthma medications.

Treatment of vocal cord dysfunction is difficult, although speech therapy to teach the patient to relax the throat muscles may help. The role of psychiatric therapy still needs to be examined.

**Upper airway obstruction.** Although less common, this can have the same presentation as vocal cord dysfunction and is also frequently misdiagnosed as asthma. Possible causes of upper airway obstruction include benign or malignant neoplasm, increased soft palate tissue, tonsillar hypertrophy, foreign body aspiration, and goiter or tracheal stenosis. Consider this diagnosis in any patient with stridor and/or airway obstruction that is refractory to standard therapy. If not identified and treated, the condition can progress to critical airway obstruction and respiratory failure. As with vocal cord dysfunction, diagnosis of upper airway obstruction usually requires direct visualization of the oropharynx, either through physical examination or by bronchoscopy.

**Other mimics.** Other conditions that may be confused with asthma include chronic obstructive pulmonary disease, bronchitis, congestive heart failure, bronchiectasis, and recurrent aspiration. Each of these requires specific therapy and may need to be ruled out if an "asthmatic" patient fails to respond to standard asthma medications.

**COMORbid CONDITIONS**

**GERD.** Gastroesophageal reflux disease (GERD) is increasingly recognized as a trigger for asthma and often complicates its treatment. The exact nature of the interaction is not yet understood. Hypotheses include microaspiration of acid, which causes bronchospasm, or a reflex action in which refluxed acid causes an increase in vagal tone that in turn results in increased airway resistance. The reported incidence of GERD in asthmatic patients ranges from 30% to 90%. GERD is easily overlooked in patients with asthma, since as many as 25% of those who have both diseases have no symptoms of reflux, and many others do not link their GERD symptoms to their asthma. Only a good history can suggest the diagnosis. In fact, the comorbidity of GERD and asthma is now known to be so common that it is wise to question all patients with asthma about symptoms of reflux. In particular, consider GERD in any patient whose asthma worsens at night, when reflux is more likely to occur.

Antireflux therapy often ameliorates asthma symptoms. If you suspect GERD, a trial regimen of a proton pump inhibitor may be instituted without esophageal pH monitoring (the "gold standard" for diagnosis). Keep in mind that the dosage may need to be increased before clinical improvement is seen. In addition to drug therapy, lifestyle modifications--weight loss, low-fat diet, avoiding food before going to bed, and sleeping with the head of the bed elevated--can be beneficial. In patients with asthma who are receiving GERD therapy, monitor the clinical response and measure peak flow. If there is no evidence of improvement, change or discontinue antireflux therapy. If there is any question about the diagnosis or treatment of GERD in such patients, consider referral to a gastroenterologist.

**Drug-induced asthma.** Aspirin-induced asthma, or "triad asthma," is a syndrome that involves aspirin sensitivity, asthma, and nasal polyps. The syndrome can be triggered not only by aspirin but also by NSAIDs. As many as 30% of patients with asthma may have this sensitivity. Consider this syndrome in patients whose asthma is difficult to manage, because it can develop later in life and often goes unnoticed. Patients seldom see the connection between NSAID ingestion and their symptoms.

Strict avoidance of NSAIDs is the first line of therapy. The sinus component (polyps and/or sinusitis) can play a central role in this syndrome; treat it aggressively with nasal corticosteroids, polypectomy or surgical drainage, and antibiotics appropriate for sinusitis. Leukotriene modifiers are used to treat NSAID-induced asthma; these agents seem particularly effective and may become the mainstay of...
therapy. Other drugs may also exacerbate asthma. Always consider b-blockers—whether taken orally to control hypertension or used topically in ophthalmic preparations—as a possible cause of bronchospasm. If b-blockers are necessary, prescribe cardioselective agents.

**Rhinosinusitis.** While it is well established that allergic rhinitis and asthma often coexist because of their strongly similar causes and inflammatory mediators, it is now believed that upper airway disease may contribute directly to the worsening of asthma symptoms. The precise mechanism of the relationship has yet to be elucidated, but it may involve neural reflexes (as is hypothesized in the relationship between GERD and asthma) or direct irritation from secretions draining into the respiratory tree. If symptoms dictate, consider treating allergic rhinitis that occurs in the setting of uncontrolled asthma with antihistamines and decongestants or nasal corticosteroids. In addition, studies suggest that antibiotic therapy for chronic sinusitis can dramatically improve pulmonary function test results.

**Allergy.** A number of allergic triggers clearly influence asthma severity. Identifying and reducing exposure to these triggers is a worthwhile goal for all patients with asthma; for those with refractory asthma, it is vital.

**Diagnosis.** The key to diagnosing and treating these triggers is a thorough history. Question the patient about seasonal and food allergies, environmental conditions in the home, pets, occupation, and hobbies (Table 3). If the history suggests that the patient’s asthma has an allergic component, then either radioallergosorbent test (RAST) serology—which determines the presence of specific IgE antibodies—or skin testing by an allergist may be indicated.

**Minimizing exposure.** Among the most common asthma triggers are outdoor allergens, such as pollens and mold spores. Unfortunately, these are also among the most difficult to avoid. Advise patients to remain indoors in an air-conditioned environment as much as possible during the appropriate season, especially during the afternoon when pollen counts peak.

Common indoor allergens include animal dander, dust mites, cockroaches, and mold. Cockroaches are a common trigger in inner-city environments. Instruct patients who live in such areas to keep their homes free of food debris and to use traps or baits if necessary. Dust mites are nearly ubiquitous in the United States and thrive in warm, humid conditions. They are found in carpets, mattresses, pillows, bed linens, clothes, upholstered furniture, and stuffed toys. Have patients encase their pillows and mattresses in impermeable covers and wash all linens frequently in hot water. Suggest that they remove carpeting if possible, at least from the bedroom. Instruct them to reduce humidity levels to less than 50% with an air conditioner or dehumidifier. A drier environment also helps control mold, which favors damp, humid conditions. Nearly all domestic animals produce secretions and dander that can be highly allergenic. The ultimate solution—to remove the pet from the home—is usually not accepted by the patient. When patients insist on keeping a pet, instruct them not to allow it in the bedroom and to bathe it weekly. Removal of carpets and upholstery can also help reduce pet-associated allergens.

Occupational exposure to allergens can usually be determined only by the history—either by asking patients about the presence of chemicals, dust, or fumes in the workplace or by documenting the presence of symptoms. Patients often report that their symptoms improve over the weekend and are exacerbated when they return to work. Air flow measurements that demonstrate reduced peak flow values while at work can be confirmatory.

Finally, be alert for irritants, such as air pollution, fumes, smoke, and sprays. Common sources include perfumes; cigarettes; cleaning agents; and indoor stoves, fireplaces, or heaters that lack proper ventilation.

**Immunotherapy.** IgE plays a central role in the pathogenesis of asthma. By modulating the immune response, immunotherapy can eliminate symptoms that would otherwise result from allergen exposure.

Because of the central role allergens often play in asthma, this might appear at first glance to be an ideal therapy for many patients. However, immunotherapy is not considered first-line therapy by any published guideline and is currently used in only a minority of patients. One drawback is the frequent injections every 2 to 4 weeks for a minimum of 12 weeks. In addition—although this rarely occurs—immunotherapy can result in a severe reaction in highly sensitive patients. Such reactions are especially serious in patients with comorbid conditions such as cardiac or chronic renal disease. Before initiating immunotherapy, be sure to perform an allergy survey, either by serum measurement of IgE antibodies (RAST) or by skin testing. Most allergists prefer the latter method because it provides a more obvious demonstration of an allergen's effect.

While the best all-around strategy is allergen avoidance, there may be a role for immunotherapy in
patients whose asthma is difficult to control. The National Asthma Education and Prevention Program recommends immunotherapy for the following patients:

- Those with severe asthma symptoms who have a proven reaction to an allergen that cannot be avoided.
- Those with symptoms that occur throughout the year.
- Those whose asthma is poorly controlled, who require multidrug therapy, or who have difficulty in tolerating their medications.\(^1\)

Also consider immunotherapy for patients with asthma who have persistent seasonal or nasal allergies.\(^1,3\) Although the results of clinical trials have varied widely, they show benefit for patients whose asthma is complicated by allergic rhinitis and for those with strong seasonal allergies. Before immunotherapy can become a mainstay of therapy, controlled trials that demonstrate its effect on disease severity are needed.\(^3\)\textbf{ADDITIONAL THERAPEUTIC OPTIONS}

After a thorough workup (Table 4), what more can you do for patients who continue to have asthma symptoms, even though they are compliant with their inhaled corticosteroid regimen, have good technique, and have no alternative diagnoses or comorbid conditions? Such patients need additional medication to control their disease.

One option is to simply increase the dose of the inhaled corticosteroid. This strategy may provide additional control. However, inhaled corticosteroids, especially at high doses, have been associated with growth retardation in children and with glaucoma, cataracts, skin bruising, and osteoporosis in adults. It is preferable to achieve control by adding another agent and by keeping the corticosteroid dose low or moderate.

\textbf{Long-acting b-agonists.} NIH guidelines recommend adding a long-acting b-agonist to an inhaled corticosteroid regimen if greater control is required.\(^2\) Many studies suggest that adding a b-agonist is preferable to increasing the corticosteroid dose—and is more effective at ameliorating symptoms and improving lung function.\(^4\) Long-acting b-agonists are particularly useful for controlling nighttime symptoms.\(^4\) A combination inhaler that delivers both a long-acting b-agonist and an inhaled corticosteroid in one device has the additional benefit of simplicity and may improve compliance.

\textbf{Leukotriene modifiers.} Although leukotriene modifiers are not as potent an additive agent as long-acting b-agonists, they also work in conjunction with inhaled corticosteroids to provide additional asthma control.\(^5\) In addition, leukotriene modifiers have the advantage of oral dosing, which is especially helpful for patients who have difficulty in using an MDI. They also are effective in patients with allergic rhinitis, which makes them an attractive option for those who have both allergic rhinitis and asthma. Finally, recent studies have suggested possible safety concerns about salmeterol, a long-acting b-agonist which in certain subpopulations (particularly African Americans) may be associated with worse outcomes.\(^6\) Leukotriene modifiers might be a good alternative in these subpopulations.

\textbf{Theophylline.} This once-popular methylxanthine derivative is now used only for add-on therapy because of its side effects (eg, tachycardia and numerous drug interactions). Use caution when prescribing theophylline, particularly in elderly patients who may have concomitant heart disease; be sure to monitor blood levels in such patients.

\textbf{Anti-IgE.} Recombinant human monoclonal anti-IgE antibody is a novel newer therapy.\(^7,8\) The anti-IgE antibody omalizumab has been studied in several large, multicenter, randomized, double-blind, placebo-controlled phase 3 trials.\(^9,19-21\) Their primary end points showed a reduction in asthma exacerbations, decreased need for inhaled corticosteroids and rescue medications, and amelioration of symptoms. Omalizumab is expensive; reserve this agent for patients with moderate to severe allergic asthma who have not responded to other measures. It is administered as a subcutaneous injection every 2 or 4 weeks.

\textbf{Systemic corticosteroids.} Although systemic corticosteroids have a poor side-effect profile, some patients may fail to respond to any other therapy, particularly during acute exacerbations. When these agents must be used, taper the dosage as rapidly as possible. Watch for and counsel patients about side effects, which include glucose intolerance, cataracts, and osteoporosis. For those who are receiving long-term systemic corticosteroids, bone densitometry measurements at the start of therapy and 6 months later may be indicated.\textbf{FUTURE THERAPY}

Several new asthma therapies are expected to be introduced over the next few years; these agents will provide more alternatives for patients whose disease is difficult to manage.

Inhaled corticosteroids will remain the mainstay of therapy; however, newer versions will feature increased potency, once-daily dosing, less risk of systemic side effects, and improved delivery. Combination inhalers will become increasingly more common, in response to the need for less complicated regimens and better compliance. Clinical trials are under way with phosphodiesterase-4 inhibitors.
inhibitors in the treatment of asthma. These oral medications are similar to theophylline but have a better safety and efficacy profile.

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