BREATHE EASY

How to Approach Unresponsive Asthma

When challenged by asthma that won't adequately respond to treatment, what can a physician do? There are a few simple questions one can ask that should help to find a treatment that works.

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Despite an improved understanding of asthma and the many new treatments available for its control, a surprising number of patients appear refractory or unresponsive to the best management. Most patients with asthma have mild or moderate disease that responds well to simple treatments. Unfortunately, a proportion of patients suffer persistent symptoms, have recurrent exacerbations or have sub-optimal lung function, despite physicians' efforts.

Many terms are used to refer to failure to respond to asthma therapy, including "difficult asthma" and "refractory asthma." We will adopt here the term "unresponsive asthma" to address this subgroup of patients. The following review offers a sequence of questions designed to help the practitioner learn why his or her patient with asthma is apparently unresponsive to treatment.

DOES THIS PATIENT REALLY HAVE ASTHMA?

Misdiagnosis must always be considered when treatment fails. It was often said in the past that asthma was underdiagnosed, but there is now a trend towards overdiagnosis. A major factor in the misdiagnosis of asthma is over reliance on reported symptoms and therapeutic trials as a means of establishing the diagnosis. This approach is confounded by the well-known placebo effect when medication is prescribed. Consensus guidelines agree that the clinical diagnosis

of asthma requires objective evidence of variable airflow obstruction.[1] Many patients reporting respiratory symptoms, however, continue to receive asthma treatment without objective documentation of variable airflow obstruction or airway hyper-responsiveness.

Even when pulmonary function testing is requested, results may be misinterpreted. When a patient is suspected of having asthma, but spirometry is normal and unchanged by bronchodilator administration, the next appropriate step is to perform a methacholine challenge. Many patients do not reach this next logical step in the diagnostic work-up. One survey in primary care showed that only 10% of patients with suspected asthma, but normal spirometry in the pulmonary function laboratory, came back to perform methacholine challenge. Most of them received a clinical diagnosis based on the clinical presentation alone. Follow-up of these patients showed little concordance between their subsequent methacholine test results and the clinical diagnosis received.[2] Another study showed two-thirds of patients referred to an asthma center, and found to have no airway hyper-responsiveness by methacholine challenge testing, were regarded by their primary-care physicians as having asthma. These patients had been treated with an average of two daily anti-asthma medications for approximately two years.[3]

IF IT IS NOT ASTHMA, WHAT COULD IT BE?

Several conditions can present with asthma-like symptoms. The most common is chronic obstructive pulmonary disease (COPD). It can be difficult to distinguish asthma from COPD when symptoms present in middle-age and there is evidence of atopy or a family history of asthma against a background of tobacco smoking. Variability of airflow obstruction is the hallmark of asthma and establishes the diagnosis. COPD patients, however, can also present with some degree of variability in airflow obstruction (the "asthmatic component") and one must acknowledge that the two disorders may co-exist.

When assessing a patient with airflow obstruction that is incompletely reversed by simple bronchodilators in the pulmonary function laboratory, a two-week

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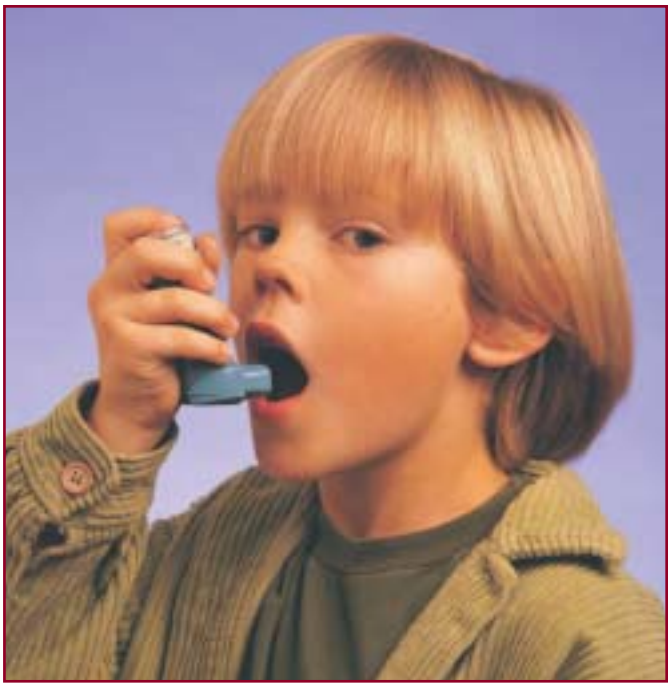
oral steroid trial can be diagnostically useful. If two weeks of prednisone in a dosage of 40 mg/day to 50 mg/day returns the FEV_1 to normal or nearly normal values, the diagnosis is asthma. If the FEV_1 is altered minimally by this approach, the most likely diagnosis is COPD. The measurement of carbon monoxide diffusion capacity (DLCO) is useful in distinguishing these two diseases; a low value suggests the diagnosis of emphysema. Patients with asthma typically have a normal or slightly elevated DLCO.

Other diagnoses to be considered include: left ventricular failure, angina, deconditioning, cystic fibrosis, localized obstruction, factitious asthma and vocal cord dysfunction. The latter is an upper airway phenomenon characterized by voluntary or unconscious narrowing of the vocal cords that manifests with episodic wheezing and breathlessness. The diagnosis is confirmed by laryngoscopy during the acute episode.

The objective confirmation of variable airflow obstruction or airway hyper-responsiveness is essential to confirm the diagnosis of asthma, particularly in patients who seem to be unresponsive to therapy. Other diseases also should be considered.

IF THE DIAGNOSIS IS CORRECT, ARE THE REPORTED SYMPTOMS BEING CAUSED BY ASTHMA?

The diseases discussed above can co-exist with asthma and be responsible for the troublesome symptoms. It would not be surprising to find symptoms overlap if the patient suffers from more than one disease. It is important to exclude the possibility that the persistent symptoms experienced by some patients thought to have unresponsive asthma are actually being caused by an uncontrolled secondary disease that manifests with asthma-like symptoms.



IS THERE ANY PROBLEM RELATED TO THE TREATMENT?

When confirming the diagnosis of asthma in the patient with unresponsive disease, one must assess the adequacy of therapy. Three important issues must be addressed: adequacy of drugs prescribed, compliance with the prescribed therapy and adequacy of inhaler technique.

Several asthma guidelines describe appropriate drug therapy for asthma. All recommend the as-needed inhalation of short-acting $beta_2$ agonists for relief or prevention of episodic symptoms. Frequent and persis-

Figure 1. Dose counter (Doser) attached to the top of MDI. The total of doses remaining in the canister as well as the total daily doses are recorded. From Simmons et al. J Allergy Clin Immunol 1998; 102(3): 409-13.

tent symptoms are an indication for a regular maintenance therapy, typically an inhaled corticosteroid. Other drugs such as long-acting beta$_2$ agonists, leukotriene receptor antagonists and theophylline, are potentially useful adjunctive medications. We will not review the details of pharmacologic treatment here. Readers are referred to the many asthma guidelines, including the Canadian Asthma Consensus Report.[1] The authors will focus in this section on two common causes of therapeutic failure: poor compliance and inhaler misuse.

Compliance

It is estimated that compliance with regular, preventive therapy for asthma is about 40% of the prescribed doses.[4] This low rate is explained, in part, by the variable nature of asthma; failure to take a preventive medication may not have immediate consequences if the patient's asthma is temporarily quiescent. Moreover, inhaled corticosteroids produce their clinical benefits gradually and, after withdrawal, their benefits disappear slowly. The noncompliant patient may remain well for many months. It is difficult to monitor compliance with inhaled medications, which exert their effects topically, as no objective measurement of the therapeutic agent is possible in clinical settings. Many of the factors that physicians use to estimate compliance, such as the patient's education, income, gender and disease severity, correlate poorly.[5] Compliance must be measured objectively.

Electronic dosage recorders are now available for both research and clinical applications. These include the Chronolog® [6] (Forefront Technologies Inc., Lakewood, Co, U.S.A.), Turbuhaler® Inhalation Computer and Doser® [7] (Figure 1). This last device records the consumption of medication from a pressurized metered dose inhaler (MDI) over specific period and displays the number of remaining doses. The Diskus® inhaler has a dosage counter incorporated, which helps not only physicians to verify the compliance but also acts as a reminder to the patient.[8] In addition, it is always possible to review the patient's pharmacy records. One or more objective measurements of compliance should be used when faced with an asthma patient unresponsive to therapy (see Table 1).

Inhaler misuse

Although the pressurized dry suspension MDI has been prescribed for almost fifty years, it is commonly misused. Approximately 40% of newly referred patients in

Table 1

Measures which may be useful when poor compliance is an issue

- Address the patient's compliance with medication at every consultation. Probe sympathetically to determine the reason for non-compliance (*i.e.*, fear of corticosteroids, financial barriers, *etc.*)
- Teach patients the role of each anti-asthma medication, including the appropriate method of administration.
- Assess the adequacy of inhaler technique at every visit (see section entitled Inhaler Misuse).
- Decrease the dosing frequency of the drugs. Maintenance therapy should not be prescribed for administration more than twice daily.
- Consider combination inhalers to simplify a multi-drug regimen.
- Use different techniques, such as the use of written home-management plans, diagrams and leaflets, to motivate the patient to keep up the treatment.
- Involve patients in their treatment decisions.

Adapted from: Chapman KR, Walker L, Cluley S, et al: Improving patient compliance with asthma therapy. Respir Med 2000; 94:2-9.[9]

specialized centres or pulmonary function laboratories do not use their inhalers properly. This is not altogether surprising, as most caregivers also are unfamiliar with proper inhaler techniques.[10,11] Dry powders are considered simpler, but not free of misuse problems. Patients acquire habits of poor inhaler technique over time, even if they had performed adequately before. This makes the regular evaluation of inhaler technique necessary.

It can be difficult to judge the adequacy of inhaler technique by visual inspection. The use of objective monitoring of inhaler technique is ideal. Patients whose asthma responds transiently to $beta_2$ agonist, but poorly to a controller medication, are often having problems with inhaler technique. Short-acting $beta_2$ agonists are administered in a dosage that is on the plateau of the dose response curve, resulting in enough drug being deposited even with poor inhaler technique. This does not happen with inhaled steroids. These depend more on optimal inhaler technique and airway deposition of the drug for beneficial results to occur.

IS THERE ANY EXTERNAL FACTOR CONTRIBUTING TO WORSENING OF THE DISEASE AND TO THERAPEUTIC FAILURE?

Environmental and other external factors

Exposure to many environmental antigens can result in poor asthma control. Continuing exposure to domestic antigens, such as cockroach antigen and fur-bearing pets, increases airway inflammation. Amongst the non-allergic exposures, tobacco smoke is the most important. Asthmatic children whose parents smoke are more likely to have emergency department visits than children with asthma whose parents do not smoke.

For dust-mite-sensitive patients with asthma, removal to a dust-mite-free environment can produce gradual improvement in asthma scores and a decrease in bronchial hyperreactivity. This is not feasible, however, in clinical practice. Several interventions can reduce allergen exposure in the patient's usual environment. Most of them require considerable effort and a long-term lifestyle change. These include the use of mattress and pillow encasements, laundering bedding in hot water, removal of dust-catching drapes and carpeting, avoidance of stuffed animals and reduction of the household's

and bedroom's relative humidity. For patients allergic to their fur-bearing pets, removal of the animal is advised, although patients are usually reluctant to consider this step. To further complicate this issue, the benefits of adopting these lifestyle modifications are not dramatic. Modest improvements in symptoms occur slowly.

Both the home and workplace environment should be examined for allergen and non-allergen exposures when asthma is unresponsive to usual therapy. History-taking is the most important part of this environmental assessment, but selective skin testing can be used to screen for common exposures of relevance (dust, moulds, pollens and pet antigens). Patients should be aware that environmental control measurements might produce a modest improvement in symptoms and may reduce medication needs.

Occupational exposures may be relevant for 10% to 30% of patients with asthma. It may be difficult to distinguish between pre-existing asthma that is aggravated by an irritant exposure in the workplace and asthma that is newly induced by an occupational exposure. Detection of occupational asthma requires a careful history, periods of peak flow monitoring and, when applicable, skin testing. It may be necessary to perform a challenge with the offending occupational substance(s). Although this approach is not part of the routine investigation of unresponsive asthma, it should not be overlooked.

Concurrent diseases

Allergic rhinitis and chronic sinusitis. These two conditions commonly accompany asthma and may make it worse. In addition, they can cause symptoms in their own right that could be misinterpreted as worsening asthma. The mechanism (or mechanisms) by which upper-airway disease worsens lower airway-disease is poorly understood. Inflammatory and mechanical factors have been postulated. Treatment of allergic rhinitis and sinusitis seems to result in improved asthma control and should be undertaken whenever a patient with unresponsive asthma also presents one of these nasal conditions.

Gastroesophageal reflux (GER). Many patients with asthma and GER report an increase in asthma symptoms during episodes of symptomatic reflux, and some patients will report an improvement in respiratory symptoms when their GER is treated effectively. The relationship between asthma and GER is controversial. Pathophysiologic mechanisms have been suggested to explain

the relationship of these two seemingly unrelated processes. The airflow obstruction of asthma is said to lower intrathoracic pressure while increasing intra-abdominal pressure, thereby favoring reflux of gastric contents in the esophagus. This acid perfusion of the distal esophagus could cause reflex bronchospasm through a vagal mechanism.

Despite the plausibility of this relationship, no placebo-controlled study has convincingly demonstrated that the treatment of reflux results in objective improvements in asthma control. It is possible that patients who describe a reduction in asthma symptoms while using anti-reflux therapy are exhibiting a placebo response or are confusing their reflux symptoms with asthma symptoms. Patients with both asthma and symptoms of GER should receive appropriate treatment based in anti-acid and anti-reflux drugs, as dictated by the severity of their reflux symptoms and independent of their asthma management. There is no reason to perform screening tests for asymptomatic GER in patients with unresponsive asthma.

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Others. Thyrotoxicosis may be related to worsening of asthma due to interaction between thyroid hormone receptors and glucocorticoid receptors, resulting in reduced effects of the corticosteroids. Measurements of thyroid indices may be warranted in patients with refractory asthma. Carcinoid syndrome is a rare cause of refractory bronchospasm.

Drugs: Nonsteroidal anti-inflammatory drugs, beta blockers and angiotensin converting enzyme (ACE) inhibitors

It is important to inquire about non-respiratory medication use, as several medications can contribute to poor control of asthma. For instance, acetylsalicylic acid (ASA)-sensitive asthma is often overlooked. Patients who suffer from severe asthma, and who ingest ASA or nonsteroidal anti-inflammatory drugs, may suffer severe or even fatal asthma attacks. Milder forms of the disorder also exist, in which the relationship between ASA and worsening asthma is less obvious. All beta blockers should be avoided in patients with asthma.

Previously unsuspected or mild asthma may grow markedly worse in patients who receive beta blocker prophylaxis for cardiovascular disease or, more subtly, receive beta blocker eye drops for glaucoma. ACE inhibitors are notorious for the tendency to provoke troublesome cough in individuals without underlying respiratory disease. Patients with asthma do not appear to have a greater propensity to suffer from ACE inhibitor-induced cough than others. ACE inhibitor-induced cough in a patient with asthma, however, can easily be misinterpreted as evidence of poor asthma control. ACE inhibitors should be stopped if there is suspicion that these drugs are worsening asthma.

DISORDERS OF PERCEPTION

Some patients with asthma are known to suffer from impaired perception of respiratory sensations. The so-called “poor perceivers” have blunted perception of respiratory sensations and do not perceive symptoms even when they experience considerable airflow

obstruction. Less often recognized are the "heightened perceivers." These patients may have controlled asthma, but report frequent symptoms and appear to respond inadequately to therapy. Psychological factors may account for these findings. It is important to determine the relation between patient symptoms and objective measures of lung function or disease severity, in order to detect abnormalities of perception in these patients. The patients should be treated and followed based on the objective measures.

DOES THIS PATIENT HAVE COMPLICATED ASTHMA?

This category includes the less common factors that could cause unresponsive asthma. Recent workshops have classified these patients as having truly "refractory asthma."[12] Such patients suffer from asthma that has been managed adequately, but still present with troublesome symptoms. Included in this group are patients with underlying diseases in which severe asthma is part of clinical manifestation.

Three subgroups are:

- Patients with asthma that does not respond to oral steroids (steroid-resistant asthma) or responds only at high doses (steroid-dependent asthma);
- Patients with particular patterns of uncontrolled disease with specific characteristics ("brittle asthma I and II");
- Patients with vasculitis (*i.e.*, Churg Strauss Vasculitis) or allergic bronchopulmonary aspergillosis (ABPA).

Steroid-resistant asthma

Some patients with unresponsive asthma do not respond to inhaled or oral steroids. All other causes that contribute to therapy failure discussed here should be excluded before considering this possibility. The absence of significant improvement (15%) in FEV_1, after a trial with prednisolone 1 mg/kg/day for two weeks, is required to confirm the diagnosis. Alternative therapies using non-steroidal immunosuppressive agents may be considered.

Steroid-dependent asthma

Asthma is controlled only with continuous use of oral or parenteral corticosteroids and attempts to discontinue or lower the oral steroid dosage result in asthma deterioration. These patients may have corticosteroid resistance secondary to inflammation and it seems that high doses of corticosteroids are able to overcome this resistance.

Lack of compliance to therapy and inhaler misuse are the most important reasons for unresponsiveness to asthma treatment.

"Brittle asthma"

This term is used to describe patients with asthma who have specific characteristics of poor control. It should be abandoned since does not refer to different pathophysiologic processes. Type I brittle asthma patients are those with marked and chaotic peak flow variability, that is, asthma is constantly present without response to standard therapy. They often have associated psychological problems (whether contributing to or caused by asthma control problems). Subcutaneous infusion of terbutaline has been reported to be effective.

Type II brittle asthma describes

patients who present with unexpected severe asthma attacks against a background of relatively good disease control and lung function. Some of these patients may suffer from poor perception of their disease. Type II brittle asthma patients have high a prevalence of food allergies. Some form of allergic airway edema or anaphylaxis may account for this specific pattern of unresponsive asthma. Epinephrine is the bronchodilator of choice to treat the exacerbations. Patients and relatives should be educated in its appropriate use.

Vasculitis and ABPA

Churg-Strauss is a vasculitic syndrome where asthma that is usually severe and difficult to control with inhaled steroids is associated with eosinophilia and systemic vasculitis. ABPA is another disease where severe asthma is present. Central bronchiectasis, eosinophilia and high levels of IgE are other features of this disease. Both conditions require treatment with oral steroids and may be misinterpreted as "unresponsive asthma." An atypical chest X-ray, or clinical features in a steroid-dependent patient, should result in prompt consideration of underlying vasculitis or ABPA.

CONCLUSION

Lack of compliance to therapy and inhaler misuse are the most important reasons for unresponsiveness to asthma treatment and should be addressed promptly when facing patients who do not adequately respond to treatment. Objective assessments can be helpful in assessing these factors. Procedures to increase compliance include the use of combined inhalers, decreased dosing frequency and involvement of the patient in the treatment decisions. The diagnosis of asthma should be always confirmed through the presence of variable airflow obstruction or airway hyperresponsiveness in these patients. Coexistent disease and alternative diagnosis causing the symptoms should be investigated. D_x

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