Review Article

The Difficult-to-Control Asthmatic: A Systematic Approach

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Abstract

With the judicious use of inhaled corticosteroids, β_2 agonists, and leukotriene modifiers, most patients with asthma are easily controlled and managed. However, approximately 5% of asthmatics do not respond to standard therapy and are classified as "difficult to control."[1] Typically, these are patients who complain of symptoms interfering with daily living despite long-term treatment with inhaled corticosteroids in doses up to 2,000 μg daily. Many factors can contribute to poor response to conventional therapy, and especially for these patients, a systematic approach is needed to identify the underlying causes. First, the diagnosis of asthma and adherence to the medication regimen should be confirmed. Next, potential persisting exacerbating triggers need to be identified and addressed. Concomitant disorders should be discovered and treated. Lastly, the impact and implications of socioeconomic and psychological factors on disease control can be significant and should be acknowledged and discussed with the individual patient. Less conventional and novel strategies for treating corticosteroid-resistant asthma do exist. However, their use is based on small studies that do not meet evidence-based criteria; therefore, it is essential to sort through and address the above issues before reverting to other therapy.

Incorrect Diagnosis

It is important to remember that "all that wheezes is not asthma" (Table 1). When there is a lack of response to standard therapy, the diagnosis of asthma should be questioned and revisited. Obtaining pulmonary function testing with flow/volume curves (both inspiratory and expiratory) and documenting reversible airway obstruction or airway hyperresponsiveness become essential. A flattened inspiratory curve, for example, is indicative of upper airway obstruction (ie, vocal cord dysfunction). A methacholine challenge should be performed when there is a question of airway hyperresponsiveness. Normal test results will point away from asthma and lead to a search for other causes of respiratory difficulty. Hyperventilation and vocal cord dysfunction are two frequent masquerades and complicating factors of asthma and are discussed in more detail below. Nocturnal dyspnea can be an indication of uncontrolled asthma; although it can also exist in congestive heart failure or chronic obstructive pulmonary disease (COPD). Obstructive sleep apnea, although mainly giving rise to symptoms at night, is usually not dyspneic. The presence of nocturnal dyspnea, with or without cough, especially in the setting of cardiac dysfunction or coronary artery disease, should raise the concern for the presence of cardiac asthma. A long-time smoker with irreversible airflow obstruction can have underlying

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Table 1 Alternate Diagnoses to Consider in Difficult-to-Control Asthmatic Patients

Hyperventilation
Vocal cord dysfunction
Cardiac asthma/congestive heart failure
Chronic obstructive pulmonary disease
Gastroesophageal/supraesophageal reflux disease
Restrictive lung disease
Sleep apnea
Cystic fibrosis
Endobronchial lesions

COPD. Making the diagnosis between COPD and asthma may be difficult as the two can have significant overlapping clinical characteristics. COPD typically shows a generally progressive airflow obstruction, with or without airway hyperreactivity, and typically is irreversible or only poorly reversible. The distinction is important in tailoring therapy with the use of anticholinergics and a greater emphasis on health maintenance and rehabilitation for patients with COPD.[2,3] A restrictive pattern on pulmonary function tests should lead to a search for causes of restrictive lung disease. A careful history and physical examination may raise the suspicion of upper airway obstruction manifested classically as stridor. In a child with wheezing, the diagnosis of cystic fibrosis should always be on the differential, especially in the setting of failure to thrive or persistent diarrhea. Localized obstruction of a major airway arising from endobronchial lesions is a rare but potential cause of wheezing.

Hyperventilation

Symptoms of hyperventilation often go unrecognized and may frequently be attributed to asthma. In a study of 14 "pseudosteroid-resistant" asthmatics, half were found to have hyperventilation as a potential cause of their disease.[4] These patients typically note subjective dyspnea without any provoking triggers. Their difficulty often is with inhaling. They may complain that they "can't get a good breath" or "can't breathe" without any objective signs of respiratory distress. Although a methacholine challenge will invariably be negative, some may note a subjective response to rescue metreddose inhalers (MDIs) as proper inhalation techniques will slow the respiratory rate. For these patients, it may be beneficial to monitor peak expiratory flow rate (PEFR) before and after hyperventilation episodes to make patients aware of their breathing, and to retrain their breathing pattern.[5]

Vocal Cord Dysfunction

Vocal cord dysfunction (VCD) may be seen alone or accompanying asthma and may masquerade as mild or severe asthma. Some patients with VCD may be on aggressive medical regimens, including oral corticosteroids and immunosuppressive therapy, and may even be classified as having corticosteroid-resistant asthma.[6] Typically, patients complain of feeling "tight" but point to their throat, and for them, inhaling is more difficult than exhaling. These patients can quickly and unexpectedly go from well to severely ill, some following an irritant exposure but for most without any obvious trigger.[7] The attack is not necessarily trivial as there can be accompanying oxygen desaturation. On auscultation, wheezing is loudest over the larynx. Although an inspiratory cutoff on the flow volume loop is characteristic of VCD, the diagnosis is best made by direct visualization of the vocal cords, which, during an acute attack, will show paradoxical movement during inspiration.[8] VCD may or may not be a form of conversion disorder but has been found to follow physical or psychological trauma.[9] Physician awareness and patient awareness are keys to successful treatment that involves speech and psychotherapy.

Poor Adherence

Once the diagnosis of asthma is made, it is important to ensure adherence to the medication regimen and document the correct use of inhalers. For "difficult asthmatics," this is particularly necessary because, although counterintuitive, asthmatics who are more ill are actually less likely to

take their medicines.[10] Despite our best efforts, poor adherence is surprisingly still common, and even more so with MDIs compared with oral medications, with some studies documenting between 10 and 46% adherence.[11] The adolescent population in particular is notorious for noncompliance, some of the reasons being forgetfulness, denial, embarrassment, inconvenience, fear of side effects, a lack of efficacy of medicines, and laziness.[12] Even when patients are compliant, use of improper inhaler techniques may prevent appropriate delivery of the drug. Therefore, a patient demonstration of proper techniques should be part of every physician visit.

Exacerbating Factors

For difficult-to-control asthmatics who have ongoing exposure to allergens or other triggers, identifying and eliminating these may help with asthma management. Microbial volatile organic compounds released from excess indoor mould growth and water-intruded areas are increasingly being recognized as important irritants triggering asthma.[13] Although dust mite control measures are relatively easy to implement for those with dust mite allergy, noncompliance remains an important obstacle. Cost may become an issue for some families as environmental control measures are not covered by insurance companies.[14] Removing or just keeping the house cat away from the bedroom is easy advice, but, apparently, too often it is not followed. Patients with a history of asthma that improves on weekends or holidays should raise the concern for exposure to occupational allergens or irritants. For these, serial PEFR measurements and specific challenge testing may need to be performed to institute appropriate avoidance measures or, when necessary, removal from the workplace. A drug history is always important to gather in a difficult asthmatic as such well-known and extensively used drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) and β-blockers can be significant unidentified precipitators of life-threatening asthma.[15] One should keep in mind that aspirin and NSAIDS are in many over-the-counter cold remedies and are often overlooked. A simple question such as "What do you think causes your asthma?" may tease this out. Furthermore, identifying the aspirin-sensitive individual with aspirin-exacerbated respiratory disease or aspirin triad will help guide therapy (ie, aspirin desensitization).[16] Dietary additives have been reported to cause wheezing, although this is still subject to debate.[17]

Table 2 Concomitant Disorders that May Be Present in Asthmatic Patients

Gastroesophageal/supraesophageal reflux disease
Allergic rhinitis
Chronic rhinosinusitis
Hyperventilation
Endocrinopathies (eg, hyperthyroidism, carcinoid syndrome)
Allergic bronchopulmonary aspergillosis
Aspirin-exacerbated respiratory disease
Churg-Strauss syndrome/other vasculitides

Concomitant Disorders

Certain disorders that tend to accompany and exacerbate asthma should be kept in mind in difficult-to-control patients (Table 2).

Gastroesophageal Reflux Disease/Supraesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is more common in patients with asthma, with an estimated prevalence of 34 to 80%.[18] However, the diagnosis of GERD/supraesophageal reflux disease (SERD) is not always clear-cut. In one study, 40 to 60% of asthmatics, 57 to 94% of those with otolarynogologic symptoms and 43 to 75% with cough were shown to have SERD without classic reflux symptoms.[19] To make the diagnosis, a 24-hour pH monitoring dual-probe study can correlate episodes of reflux with cough or other symptoms of asthma. Although a negative study can exclude acid-related symptoms, a positive study does not necessarily guarantee the success of acid suppression therapy. Often a therapeutic trial of

medical therapy for GERD may be both diagnostic and therapeutic, with testing reserved for more uncertain or recalcitrant cases. Twice-daily proton pump inhibitors have been shown to have some therapeutic success, but it may take several weeks before an improvement in symptoms is noted.[20] Furthermore, lifestyle changes consisting of elevating the head of the bed, waiting at least 2 hours between dinner and bedtime, and eating smaller and more frequent meals with reduction or elimination of substances that can exacerbate reflux (eg, alcohol, caffeine, nicotine), in addition to weight loss, are strongly recommended.

It is important to mention that hyperventilation and other forms of dysfunctional breathing may exist concomitantly with asthma, although the prevalence for this is unclear.[21] Teasing this out can be a challenge, and tailoring therapy will likely be even more difficult. Recognizing the coexistence of dysfunctional breathing, however, can help prevent unnecessary step-up of asthma therapy.

Other Diseases

There is increasing evidence that the upper and lower airways represent "one continuous airway," in which a pathologic process affecting one can affect the other. Therefore, uncontrolled allergic rhinitis or chronic rhinosinusitis can affect asthma control. Treatment of allergic rhinitis with nasal corticosteroids, for example, has been shown to improve symptoms of asthma and airway hyperresponsiveness.[22] Identifying and managing upper respiratory inflammation is therefore important, especially in the group of difficult-to-control asthmatics. Endocrinopathies such as hyperthyroidism or hypocorticalism and carcinoid syndrome may lead to exacerbations and will need to be concomitantly treated. An elevated immunoglobulin E level in a persistent asthmatic with evidence of centrilobular bronchiectasis should lead to a full evaluation for allergic bronchopulmonary aspergillosis. Patients with Churg-Strauss vasculitis may also have particularly severe and difficult-to-manage asthma, the presence of which should be suspected in the setting of serum eosinophilia or a mononeuritis multiplex.

Table 3 Potential Contributing Socioeconomic and Psychological Factors in the Difficult-to-Control Asthmatic

Socioeconomic risk factors
Poverty
Race
Access to medical care
Adherence
Psychosocial issues (eg, crime, violence, unemployment)
Environment (indoor and outdoor allergens and irritants, eg, tobacco smoke, NO_2)
Differing cultural practices
Psychological factors
Negative emotions
Functional symptoms
Anxiety/panic disorders
Depression

Socioeconomic Factors

When there is no obvious medical reason for refractory asthma, socioeconomic factors must be taken into account (Table 3). These include issues of poverty and race, access to medical care, adherence, psychosocial issues, and environmental risk factors. These particularly apply to the inner-city population of children and young adults, which has seen the greatest increase in the prevalence and severity of asthma in the past 20 years.[23] Poverty appears to underlie other socioeconomic risk factors. The specific role that race plays is less certain and harder to tease apart. Poverty influences access to medical care, which has been associated with increased hospitalizations and emergency department visits.[24] For many of the urban poor, the closest emergency room becomes the only access to medical care. This is compounded by the closing of many inner-city hospitals in recent years owing to inadequate funds. For those attempting to access the proper services, barriers may include a lack of transportation or child care, a lack of available after-work clinic hours, or an inability to communicate in English.[25] Obvious problems arise when the emergency room becomes the primary access to care. Adherence to scheduled follow-up visits and to medications can be affected, influencing the quality of care. For a population

especially in need of adequate asthma control, studies have surprisingly shown that there is an overall low rate of prescribing of controller (37%) and relief (61%) medications.[26] Additionally, the likelihood of a scheduled visit with an established care provider (25%), of the use of controller medications (24%), and of the correct use of oral (44%) and inhaler (27%) medicines is also dramatically low.[27] The problem is compounded by the unfortunate reality that many of the poor cannot afford medicines, much less expensive ones.

The psychosocial risk factors that exist in certain neighbourhoods can have a large impact on asthma care. Stresses arising from crime, violence, drugs, gangs, and unemployment take time, energy, and focus away from appropriately caring for a child with asthma. Families are often headed by single women who balance work, child care, and other issues of daily living. Multiple caretakers may exist for these children, making effective communication and education particularly difficult and challenging. Furthermore, aggression, anxiety, and depression can be important issues in difficult living conditions and have been found to be risk factors for childhood asthma mortality.[28] Differing cultural practices can also represent barriers to effective care as certain individuals may choose to follow folk remedies for cures or to search other "healers" instead of seeking or complying with standard Western medical care.

Adherence can be a problem in any population, but additional barriers can exist for socioeconomically disadvantaged asthmatics. A lack of education or understanding of English, low household income, racial or ethnic minority status, and poor patient/physician communication are all factors associated with poor adherence.[29] Besides adherence to medications, avoidance of triggers in this population also proves to be difficult. A study of inner-city children showed that only one-third were able to avoid known asthma triggers most of the time and about two-thirds could not prevent exposure to cigarette smoke.[30]

Lastly, among socioeconomic factors, environmental exposure is also a major risk. The substandard housing that many of these patients live in contains high levels of indoor allergens, such as dust mite, mold, cockroach, and rodents, that are difficult to avoid and exterminate. Additionally, there can be exposure to tobacco smoke, volatile organic compounds, and nitrogen dioxide in the home. In highly polluted and industrial environments, limiting outdoor exposure to chemicals such as sulphur dioxide and ozone can be particularly difficult.[31]

Although the barriers against effective asthma care appear to be insurmountable in the socioeconomically disadvantaged population, it appears that, especially in this group, education is an important step in achieving better asthma control. A recent review of programs that have attempted to reduce the number of emergency department visits and hospitalizations in African American and Hispanic patients found that successful programs have incorporated intensive and repetitive patient education regarding asthma as an inflammatory airway disease, environmental control, controller versus "quick relievers," prevention of exercise-induced asthma, written action plans for acute exacerbations, and demonstrating proper techniques for using inhaler devices.[32] In addition, education by a nurse or pharmacist advocate, with time allotted for individual instruction, can be especially effective.

Psychological Factors

Existing psychological issues in a patient may make asthma particularly difficult to treat (see Table 3). Negative emotions, for whatever reason, even in normal patients, can influence the symptoms and management of asthma and should be recognized and addressed. When patients present with atypical symptoms or do not respond properly to medications, functional symptoms should be suspected. Psychiatric analysis may help determine this. In patients with comorbid asthma and anxiety disorders, treatment should be geared at controlling the asthma as asthma and sudden exacerbations are likely to cause anxiety and panic-like symptoms in the first place. Asthmatics with comorbid depression are especially difficult to treat. For this population, it is important and necessary to address and treat the depression before there can be any success with asthma therapy.[33]

Other Issues

A few other categories of difficult-to-control asthma deserve brief mention. Premenstrual worsening of asthma can occur in some females and is typically poorly responsive to glucocorticoids but may respond to aggressive hormonal therapy.[34] Nocturnal worsening of asthma may persist in some individuals despite maximal doses of corticosteroids, necessitating more aggressive interventions. Brittle asthma can be extremely unstable, may be related to a lack of perception of symptoms and disease severity, may involve unidentified triggers, and therefore may respond only to individualized therapy.[35] Patients with "steroid-dependent asthma" can often be found on a "roller-coaster" pattern of recurring bursts of corticosteroid therapy, and for these, treating exacerbations long enough and with high-enough doses of steroids may be needed to achieve long-lasting effects. Steroid-resistant asthmatics are defined as those patients with persistent obstruction (< 15% improvement in forced expiratory volume in 1 second) and inflammation despite treatment with 40 mg prednisone per day for more than 14 days. This "resistance" may be relative as some patients may respond to higher doses of steroids.[36] On a molecular level, there appear to be two types of steroid resistance. The first type is less common and is believed to result from a reduction in the number of existing and functioning glucocorticoid receptors. Patients with this type do not experience improvement in their asthma, nor do they experience any side effects from the steroids. The second type is more common and involves a reversible binding defect of the steroid to its receptor. A third type may result from an increase in the catabolism of steroids and is seen most commonly in patients on mitochondrial enzyme oxidizing system stimulators, such as phenobarbital.[37] Finally, there are patients with prolonged severe asthma who develop remodelling of their airways and irreversible obstruction for whom early recognition can be essential to effective management.[38]

Some Other Therapeutic Approaches

A few medical regimens, although nonstandard therapy, have been shown to have some clinical benefit in refractory asthma. The use of a single dose of intramuscular triamcinolone for difficult adult and pediatric asthmatics has been shown to reduce objective measures of inflammation and the number of asthma exacerbations, respectively.[39,40] The reasons for these may be a combination of improved compliance, improved anti-inflammatory profile of parenteral steroids, and overcoming a relative steroid resistance. Omalizumab has also shown good clinical benefit for those moderate to severe persistent allergic asthmatics who have failed other therapy and should be considered for this group of patients.[41] Anti-inflammatory therapies such as tumour necrosis factor-α inhibitors that target other aspects of the immune system have shown some benefits in early clinical trials of selected asthmatics with a specific immune profile, although their safety and efficacy will need to be more fully determined.[42] Immunosuppressive agents such as cyclosporin A have been shown to have beneficial effects in some studies, but one must always weigh the potential side effects with the actual benefits.[43] Lastly, therapies in both preclinical and early clinical stages, particularly immunomodulating agents such as deoxyribonucleic acid (DNA) vaccines, hold promise for high therapeutic potential and may become future options for these patients.[44]

Conclusion

When confronted with a patient in whom asthma appears to be refractory to inhaled β_2 agonists, leukotriene modifiers, and high-dose inhaled corticosteroids, a systematic and logical approach should be adopted. The first step is to confirm the diagnosis and to exclude potential masquerades of asthma, such as hyperventilation, VCD, or COPD. Next, assess compliance by direct questioning or monitoring inhaler use or prescription filling. Have the patient demonstrate the correct inhaler technique in the office. Once these are confirmed, the presence or persistence of exacerbating factors should be vigorously sought. Have all provoking stimuli in the forms of allergens or irritants been removed from the daily environment of the patient? Are there any potential aggravating factors or concomitant disorders, such as GERD or upper air-

way disease, that have not been treated? Is the patient taking any other medicines that can affect the asthma? Finally, acknowledge any underlying socioeconomic or psychological factors and, when possible, address these with the patient. Are there any barriers to communication, and should the treatment regimen be simplified for the sake of adherence? Perhaps the patient fits into a special category of particularly unstable asthma or exhibits a particular asthma phenotype for which tailoring and individualizing therapy will be beneficial. Approaching and addressing these issues in a systematic manner will help prevent unnecessary and inefficient therapy and will lead to the improved management of the difficult asthmatic patient.

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