Difficult asthma: Assessment and management, Part 1

Aidan A. Long, M.D., and Christopher H. Fanta, M.D.

ABSTRACT

A minority of asthma patients have disease that proves difficult to control with usual medications and experience ongoing symptoms, poor quality of life, and limitations in activity and/or frequent asthma exacerbations. This group of patients accounts for much of the expense associated with asthma care and is the focus of national and international collaborative study groups. Distinguishing between “difficult-to-manage asthma” and truly “therapy-resistant asthma” is helpful and promotes a systematic consideration of contributory factors. Critical evaluation of factors contributing to difficult-to-manage asthma including adverse environment, comorbidities, nonadherence, and incorrect diagnosis is recommended in a systematic fashion in Part 1 of this contribution.


In recent years, as modern asthma therapies have made good asthma control achievable in a majority of patients, difficult or refractory asthma has become the focus of intense interest from the perspectives of basic science, translational research, and clinical care. The following questions have come to the forefront: What is different about asthma in some patients such that it does not respond satisfactorily to conventional therapy with bronchodilators, inhaled corticosteroids, and leukotrienes modifiers; and how can we as asthma specialists best manage these patients?

In Part 1 of this review, we will discuss the scope of the problem, reference ongoing efforts nationally and internationally to study this subpopulation of asthmatic patients in a systematic way, and consider various working definitions of “difficult asthma.” We will focus on the assessment of difficult asthma, emphasizing the distinction between “difficult-to-manage” asthma and asthma that is truly therapy resistant. We will offer our recommendations for a systematic evaluation of the patient with difficult-to-control asthma and explore potential explanations for the failure of current treatments to provide adequate control in all patients.

In Part 2 we will consider treatment options for difficult asthma. We will focus on therapies approved by the Food and Drug Administration, including lipoxigenase inhibition with zileuton, anti-IgE monoclonal antibody therapy (omalizumab), and bronchial thermoplasty. We will briefly consider other therapeutic options not approved by the Food and Drug Administration for use in asthma, including ultrahigh-dose inhaled corticosteroids, long-acting anticholinergic bronchodilators, macrolide antibiotics, and vitamin D, along with other more toxic and experimental interventions, such as methotrexate, tumor necrosis factor α inhibition, and cyclosporine. Our discussion of the management of difficult asthma will conclude with consideration of specific asthma subtypes, each with potentially distinct therapeutic approaches.

The prevalence of difficult asthma is uncertain. Estimates have put the number at 5–10% of patients with asthma. Telephone surveys of randomly selected American households found the prevalence of active asthma, those who reported symptoms consistent with severe asthma (as defined by the criteria of Expert Reports of the National Asthma Education and Prevention Program) constituted ~18%. Because these telephone surveys were unable to collect information about lung function, it is likely that the true prevalence of severe asthma was underestimated.

Asthma severity reflects an intrinsic property of the disease process such that low-to-medium doses of inhaled corticosteroids, combined with long-acting bronchodilators and/or leukotriene modifying drugs, are inadequate to achieve control. However, many patients with severe asthma find their disease well controlled on high-dose inhaled steroids together with a second or third controller agent. These patients require inten-
sive treatment, but on this intensive regimen their asthma is mostly inactive and does not pose a problem for either the patient or his/her physician. They have infrequent symptoms, good functional capacity, normal or near-normal lung function, and infrequent asthma exacerbations.

Difficult asthma refers to the group of patients who despite being prescribed an appropriate and intensive treatment program for severe asthma continue to have frequent symptoms, have exercise limitation due to their asthma, have impaired lung function, and/or have frequent asthmatic exacerbations. Even if this group of patients with difficult asthma represents only 10% of all patients with severe asthma, one might estimate the prevalence of the problem to be ~2% of all patients with asthma or as many as half a million Americans. This small subset of patients with asthma bears a disproportionately large burden of morbidity and risk of mortality from their disease. They often have poor quality of life due to limitations imposed by their illness and toxicities caused by its treatment; and they typically require frequent medical visits, including emergent outpatient and inpatient care, with attendant large costs to the medical system.

In 1999 a European Task Force developed a consensus statement to highlight the importance of difficult asthma and to begin to consider a systematic approach to its evaluation and treatment. Soon thereafter, the American Thoracic Society released the results of its Difficult Asthma Workshop (2000); and thereafter an International Workshop assembled in Paris for the same purpose (2006). Their definitions of difficult asthma varied slightly, but the emphasis was the same: patients who despite treatment with oral or high-dose inhaled steroids continued to experience poorly controlled asthma, including acute asthmatic attacks. The criteria for difficult asthma developed by the American Thoracic Society Workshop group are shown in Table 1.

Ongoing collaborative scientific investigations into the biology of difficult asthma emerged from these conferences and used the definitions developed therein as inclusion criteria for patient recruitment. These include the European Network for Understanding Mechanisms of Severe Asthma and, in the United States, the Severe Asthma Research Program. Initial cross-sectional observations from these studies, each reporting findings from ~150–200 patients, include the following findings. As many as one-third of the patients require daily oral steroids; 25–40% have been hospitalized for asthma at least once in the preceding year; 12% have received intensive care unit treatment for their asthma; and common associated features are aspirin sensitivity, gastroesophageal reflux disease (GERD), rhinosinusitis, and a history of pneumonia.

Most recently, a group of investigators in the European Union have come together in the Unbiased Bio-

Table 1 Definition of refractory asthma (American Thoracic Society Workshop, 2000)

<table>
<thead>
<tr>
<th>Definition of refractory asthma (American Thoracic Society Workshop, 2000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory asthma is defined by the presence of one or both major criteria and two or more minor criteria.</td>
</tr>
<tr>
<td>Major criteria (required to achieve asthma control to the level of mild–moderate persistent asthma)</td>
</tr>
<tr>
<td>Treatment with continuous or near-continuous (&gt;50% of the year) oral corticosteroids</td>
</tr>
<tr>
<td>Treatment with high-dose inhaled corticosteroids</td>
</tr>
<tr>
<td>Minor criteria</td>
</tr>
<tr>
<td>Need for daily treatment with a controller medication in addition to inhaled corticosteroids</td>
</tr>
<tr>
<td>Asthma symptoms requiring daily or near-daily short-acting β-agonist use</td>
</tr>
<tr>
<td>Persistent airflow obstruction (FEV₁ of &lt;80% of predicted)</td>
</tr>
<tr>
<td>More than one urgent care visit for asthma per year</td>
</tr>
<tr>
<td>More than three oral steroid “bursts” per year</td>
</tr>
<tr>
<td>Prompt deterioration with &lt;25% reduction in oral or inhaled steroid dose</td>
</tr>
<tr>
<td>Near fatal asthma event in the past</td>
</tr>
</tbody>
</table>

Adapted from Ref. 3.

FEV₁ = forced expiratory flow in 1 s.

markers for the Prediction of Respiratory Disease Outcomes consortium of the Innovative Medicines Initiative. They have highlighted the potential value of distinguishing difficult asthma subtypes, including those prone to asthma exacerbations, those who have irreversible airflow obstruction, and those who are dependent on oral steroids for asthma control.

An industry-sponsored observational study of difficult-to-control asthma, called the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens, used less stringent criteria for patient recruitment, but enrolled ~4500 asthmatic patients from allergy and pulmonary practices across the United States. Patients were eligible if deemed to have “difficult-to-treat” asthma by their physician and either required intensive medication treatment or had frequent asthma exacerbations. A minority of patients in the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens were on high-dose inhaled steroids, and only ~50% were judged to have severe asthma. Nonetheless, this large cohort of patients again highlighted the “unmet need” of patients with difficult asthma. Depending on the level of lung function, within the preceding 3 months 44–48% of patients had an unscheduled office visit, 43–56% had a steroid burst, 4–9% had been hospitalized for asthma, and 13–19% required an emergency department visit.
Eight to 20% gave a history of intubation for respiratory failure due to asthma.

As we begin our consideration of the assessment and treatment of difficult asthma, we offer our own working definition, derived from our daily personal experiences in clinical practice. We consider patients to have difficult-to-control asthma when, despite treatment with high-dose inhaled steroids, long-acting β-agonist bronchodilator, and a leukotriene receptor antagonist, they continue with poor asthma control (as defined by frequent asthmatic symptoms, suboptimal lung function, and/or frequent exacerbations) and/or can only achieve asthma control with daily oral steroids.

**ASSESSMENT: DISTINGUISHING DIFFICULT-TO-MANAGE FROM TRULY THERAPY-RESISTANT ASTHMA**

In approaching the challenge of the patient with difficult asthma, it is helpful to work through a systematic process to determine whether the patient fits into one of two broad categories, either “difficult-to-manage asthma” or “therapy-resistant asthma.” This distinction is of importance because a majority of patients in the former category may not be candidates for expensive innovative therapies while many patients in the latter category may indeed require innovative therapeutic approaches. There are many potential contributing factors to difficult-to-manage asthma, and it is possible that more than one might be at play in any given patient. The factors contributing to this category can be divided into the following groups:

1. **Adverse environment.**
2. **Nonadherence.**
3. **Comorbidities.**
4. **Incorrect diagnosis.**
5. **Psychosocial problems.**

Working through each of these potential contributing groups of factors in a systematic fashion will frequently identify the reason(s) behind the patient’s difficulty with controlling their asthma. Probing history taking is frequently sufficient to help identify issues related to an adverse environment, nonadherence, or psychosocial issues, whereas additional diagnostic workup will likely be required in the evaluation of comorbidities or alternative diagnoses.

**ADVERSE ENVIRONMENT**

In evaluating the patient’s environment for potential contributory factors in difficult-to-manage asthma, one needs to consider allergen and irritant exposure both in the home and in the workplace. It is well established that a majority of asthmatic patients, children more so than adults, have an atopic basis for their asthma. Several recent studies have highlighted the contribution of perennial aeroallergens such as house-dust mites, domestic animals, and environmental molds to asthma. For example, a study of randomly selected women from Detroit, MI, identified based on residence in specific ZIP codes, evaluated the association between physician-diagnosed asthma (identified in 19.9% of the 702 women studied) and evidence of sensitization to aeroallergens. It was determined that the odds ratio of being diagnosed with asthma was approximately five times higher in the setting of allergic sensitization to cat, four times higher for dog sensitization, and approximately double for sensitization to house-dust mites. Similarly, data from epidemiological studies indicate that the prevalence of sensitization to either cat, dog, or dust mites is >30% in asthmatic patients and significantly lower in nonasthmatic patients. Seminal studies documented a key role for dust-mite allergy in the development of asthma, and more recent studies from the inner-city asthma consortium and other investigators have highlighted the role of cockroach sensitization in relationship to emergency department visits for asthma.

The importance of determining the nature of the individual asthmatic patient’s particular allergic sensitivities has been increasingly highlighted by the emergence of evidence indicating that environmental control measures need to be both comprehensive and specific if they are to be effective. Several studies highlight that nonspecifically targeted strategies, such as provision of permeable dust-mite covers (without other dust-mite control measures), placement of HEPA filters (without other control measures), in the homes of unselected asthmatic patients, do not have any measurable effect on asthma outcomes. These studies have been interpreted to show that partial environmental control measures, applied indiscriminately to all asthmatic patients, are not likely to be helpful. In contrast, determining the nature of an individual asthmatic patient’s allergic sensitivities followed by focused and comprehensive environmental modification measures are far more likely to be of benefit. Thus, an allergy evaluation coupled with targeted education and follow through to ensure implementation of recommendations is a very important facet of optimally managing the patient with difficult-to-control asthma.

Environmental exposure to allergens in the workplace can also be an important contributor to difficult-to-manage asthma. This effect has perhaps been best exemplified with respect to plicatic acid exposure in woodworkers in the Pacific Northwest; latex exposure in sensitive individuals in health care or glove manufacturing environments; animal allergies in laboratory animal workers; employees of breeding facilities, and, occasionally, workers in veterinary facilities; and yeast allergy among bakers. Exposure to...
nonspecific irritants, including volatile chemicals, tobacco smoke, and environmental pollutants, can also contribute to poorly controlled asthma and should be evaluated by a detailed history of the patient’s environmental exposures.31

Remediation of these adverse environmental exposures can be helpful but frequently requires significant time and resources on the part of the patient coupled with comprehensive education and reinforcement on the part of the caregivers. In the ongoing dialog between patients and caregivers, which is strongly endorsed by the national asthma management guidelines, routine reevaluation of environmental exposures is emphasized as an integral part of adherence in aiming for optimal asthma control in the long term.32 This aspect of caring for the asthma patient frequently suffers from inadequate focus in today’s fast-paced health care environment, in favor of reliance on medication adjustment.

Included in the notion of adverse environment, one might also consider exposure to pharmaceutical agents that might be contributing to difficult-to-manage asthma. Such agents potentially include β-blockers, aspirin, and nonsteroidal anti-inflammatory medications, each of which can significantly worsen asthma, or angiotensin converting enzyme inhibitors, which can cause coughing and might complicate the diagnostic picture.33 Based on review of oral challenge testing, it has been estimated that up to 20% of asthmatic patients experience worsening with exposure to aspirin or other nonsteroidal anti-inflammatory medications.34 Aspirin-exacerbated respiratory disease is frequently observed as an acquired phenomenon with a history of previous tolerance of this category of medications. This sensitivity to cyclooxygenase 1 inhibitors is not simply classic allergy, i.e., not typically related to immediate-type hypersensitivity, but rather is felt in large part to be related to abnormalities in metabolism of arachidonic acid leading to excessive production of leukotrienes.

ADHERENCE

Poor rates of adherence to prescribed medications are well documented in many chronic medical conditions, and asthma is certainly no exception to this problem. Data published in 2005 from analysis of United Health Care databases addressed the rate of refill of asthma controller prescription medications and showed that most monthly prescriptions were refilled between two to four times per year.35 At a minimum, this indicates that for more than two-thirds of the time most asthmatic patients are not taking the prescribed medications in the recommended doses. Other studies have indicated similar low rates of adherence with prescribed asthma medications and their associations with difficult-to-control asthma.36,37 In our current health care environment in United States, it is not easy for the treating physician to access data about medication adherence. However, one can sometimes gain insight from asking when the patient last refilled his/her controller medication or by looking at the renewal date on the medication if the patient happens to have it with them at an office visit.

The reasons for nonadherence are multiple. A recent patient survey sought to let patients identify the reasons for noncompliance with asthma medications. High on the list were fear of side effects, belief that the medication was not necessary, belief that the illness was not serious, a sense of the need for only intermittent use of medication, and concern that the medication would lose effectiveness over time.38 What is remarkable is that all of these factors are amenable to better education and could be potentially improved by better dialog between the asthma patient and the caregiving team. Although cost of medication is often cited as the primary reason for noncompliance, this ranks as number seven among reasons patients cited for nonadherence. Strategies to improve adherence with chronically prescribed medications have been evaluated, sometimes with disappointing results.39 Repeated patient education at office visits about the importance of maintenance therapy, including emphasis that medication efficacy will not be lost with continuous use, simplification of therapeutic regimens and exploration with patients about what factors contribute to their own noncompliance are likely to be most helpful.

COMORBIDITIES

Evaluation and intensive management of comorbidities can also result in significant improvements in asthma outcomes for the difficult-to-manage patient. The comorbidities can be considered under several categories:

1. Allergic upper airway disease.
2. GERD.
3. Obesity.
4. Obstructive sleep apnea.

Upper airway allergic diseases, including allergic rhinitis, chronic rhinosinusitis, allergic fungal sinusitis, and aspirin-exacerbated respiratory disease, are all potential confounding factors in the atopic patient. Studies have indicated that a significant majority of patients with allergic rhinitis have abnormal bronchial hyperreactivity.40 Chronic sinusitis with or without nasal polyps may also be associated with increased bronchial reactivity and directly contribute to increased respiratory symptoms through postnasal drainage of secretions.41,42 One recent survey estimated that 54% of patients with severe asthma suffers with chronic rhinosinusitis, and twice as many patients with severe...
asthma have required sinus surgery than have patients with more moderate or mild asthma. Churg-Strauss syndrome, a condition in which patients with asthma develop eosinophilia and vasculitis manifesting with rhinosinusitis, pulmonary infiltrates, cardiomyopathy, and peripheral neuropathy, has been observed with a higher rate of frequency in patients who are able to reduce exposure to either parenteral or inhaled steroids as a result of use of alternative antiasthmatic medications, including leukotriene receptor antagonists and anti-IgE monoclonal antibody.43,44

The contribution of GERD to difficult-to-manage asthma has been the subject of considerable debate. The Severe Asthma Research Program estimates that 41% of patients with severe asthma has been diagnosed with GERD in contrast to only 12–16% of patients with mild to moderate disease.45 Therapeutic trials of proton pump inhibitors (PPIs) and other antireflux measures have been recommended in algorithmic fashion for the management of patients with severe asthma. A number of studies suggest positive outcomes to such a strategy, but a systematic review of this literature points to inconsistent results.46–47 A more recent study has raised additional concerns about the benefits of routine prescription of antireflux therapy for asthmatic patients in the absence of symptoms of gastroesophageal reflux. Mastronarde and colleagues evaluated 412 patients with poorly controlled asthma who had no or minimal symptoms to suggest GERD. These patients were empirically treated with high-dose PPIs (esomeprazole at 40 mg twice a day) for 6 months. The authors observed no change in the number of episodes of poor asthma control or in any of the components thereof, including symptoms, rescue medication usage, lung function, or quality of life. Strikingly, further analysis of the subgroup of patients who had an abnormal pH probe study, confirming silent GERD, showed that this group fared no better for asthma outcomes with this therapeutic approach than did the overall group.48 A recent randomized controlled trial evaluated the benefit regarding asthma symptoms of treatment with a PPI (lansoprazole) in a large number of children with poorly controlled asthma without overt GERD symptoms. The study documented no change in asthma symptoms or lung function attributable to lansoprazole, even in a subgroup with pH probe confirmed acid reflux disease. Children treated with lansoprazole were reported to have an increased risk of respiratory infections.49

An integral aspect of management of GERD is weight loss. Obesity itself, independent of GERD, has been linked epidemiologically to asthma. The association is complex and may relate to immunologic, genetic, or pulmonary mechanical factors. In at least one randomized study, weight reduction was shown to improve overall lung function, symptoms, and quality of life for obese persons with asthma.50,51 Obesity also contributes to obstructive sleep apnea, which can complicate assessment of nocturnal awakenings and dyspnea as a manifestation of asthma control.52

**ALTERNATIVE DIAGNOSES**

Many of the conditions mentioned previously as co-morbidities may in fact represent primary diagnoses causing respiratory symptoms frequently ascribed to asthma. Similarly, the distinction between chronic obstructive pulmonary disease (COPD) and asthma can be difficult. Therapeutic strategies for asthma can result in positive outcomes for COPD, and agents primarily introduced for COPD are showing benefit in asthma. Patients with severe air trapping or emphysema should be evaluated for α-1-antitrypsin deficiency, and the patient with airway obstruction and a chronic productive cough should be evaluated for diseases causing bronchiectasis, such as cystic fibrosis or allergic bronchopulmonary aspergillosis. Diagnostic testing for allergic bronchopulmonary aspergillosis typically reveals very high serum IgE levels (often in excess of 1000 IU/mL), skin test sensitivity to *Aspergillus*, specific serum IgE and IgG to *Aspergillus* and precipitating IgG antibody to *Aspergillus* (“serum precipitins”), and *Aspergillus* isolated on fungal culture of sputum.

A syndrome of a paradoxical movement of the vocal cords, often referred to as vocal cord dysfunction, can be mischaracterized as asthma with the patient making frequent urgent care visits and often being prescribed extensive antiasthma therapy. This condition represents involuntary vocal cord adduction during inspiration, which can give rise to many of the clinical signs
and symptoms of asthma, including loud expiratory wheezing. This condition is seen more frequently in female patients and also in association with exercise during adolescence, but it is not exclusive to these demographics. Accurate diagnosis can be difficult because it requires visualization of the vocal cords at a time when the patient is symptomatic. This condition is amenable to treatment by relaxation exercises, and referral to speech pathology can be helpful. Other entities that can manifest with cough and wheeze and potentially be misdiagnosed as asthma are listed in Table 2.

THERAPY-RESISTANT ASTHMA

It is increasingly recognized that asthma represents a syndrome rather than a single condition and that there is great clinical and pathological heterogeneity among the population diagnosed with asthma. This heterogeneity may extend to include genetically programmed differences in the way asthma patients respond to medications.

Variability in the response to corticosteroids in asthma has been shown in clinical trials involving both adults and children. The pattern of response appears to exhibit a normal distribution with a proportion of patients actually showing deterioration in lung function in response to treatment with inhaled steroids. A specific phenotype of steroid-resistant asthma has also been described and reported with differing prevalences among severe asthmatic patients. This phenomenon has been evaluated mechanistically and has been associated with abnormalities of the glucocorticoid receptor. Additionally, smoking has been linked to resistance to glucocorticoids by inactivating histone deacetylase 2.

Separately, other studies have shown that some patients appear not to experience a beneficial bronchodilator effect from either short-acting or long-acting β-agonists, and this clinical phenotype can be statistically linked to genetic polymorphisms resulting in Arg/Arg substitutions at amino acid position 16 in the β-adrenergic receptor. The clinical relevance of this observation remains an area of controversy. Many of the patients who have a blunted response to β-agonists do benefit from inhaled anticholinergics. Furthermore,
studies in children have shown that there is a subgroup of asthmatic patients who experience improvement in lung function with inhaled steroids but not from leukotriene antagonists and another subgroup who appear to experience no benefit from steroids but improved lung function with leukotriene antagonists.60

Based on the ideas described previously, we propose a checklist that can be useful in guiding the approach to the patient with difficult asthma (Table 3).

CHANGING UNDERSTANDING OF ASTHMA PATHOGENESIS

It is likely that persistence of the problems of difficult-to-manage asthma and therapy-resistant asthma relates in no small part to our incomplete understanding of asthma pathogenesis and, accordingly, inappropriately targeted therapies. Concepts of asthma pathogenesis continue to evolve. Because the initial concept of asthma as a disease primarily of bronchoconstriction related to smooth muscle contraction (1970s), through the increased understanding of the role of airway inflammation and bronchial hyperreactivity (1980s and early 1990s), followed by an additional focus on airway remodeling (late 1990s and early part of the 21st century), the paradigm continues to shift. The focus on Th2-type cytokine-dependent inflammation resulting from adaptive immune responses to allergens as the primary target of novel therapies is falling short in the clinic. The initial promise of anti–interleukin-4 (IL-4) and anti–IL-5 therapies from animal models of asthma has not borne out in clinical trials of human asthma.61 An initial trial of an anti–IL-13 monoclonal antibody, lebrikizumab, showed only modest benefit toward these aspects of asthma pathogenesis will relate in no small part to our incomplete understanding of asthma pathogenesis and, accordingly, inappropriately targeted therapies. Perhaps novel therapies targeted toward Th2-type cytokines or skewing adaptive responses to innate immune responses, including innate cell elaboration of Th2-type cytokines or skewing adaptive responses toward the Th2 pattern. Perhaps novel therapies targeted toward these aspects of asthma pathogenesis will prove beneficial in the future.62

REFERENCES


