

THE ASTHMA CONNECTION

SEPTEMBER 2005 | VOLUME 03

Out-of-Control: Causes and Theories Behind Low Symptom Control at High Medication Doses

• A Four-Part Continuing Education Newsletter Series •

ISSUE Three of a Four-Part Series

Out-of-Control: Causes and Theories Behind Low Symptom Control at High Medication Doses

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Supported by an educational grant from Genentech, Inc. and Novartis Pharmaceuticals Co.

Learning Objectives:

- 1) Identify patients with severe asthma as defined by the appropriate clinical guidelines
- 2) Identify other conditions that should be excluded when evaluating a patient with possibly difficult-to-control asthma
- 3) Evaluate patient for conditions that can cause exacerbation of asthma symptoms or confound treatment options
- 4) Employ measures to increase adherence to treatment in this population
- 5) Understand the pathophysiology of severe asthma and how it impacts treatment decisions

Difficult-to-control asthma is an uncommon disease. The American Thoracic Society (ATS) says it is likely that less than 5% of those with asthma do not have their symptoms adequately controlled, even when high doses of inhaled corticosteroids (ICS) are used.¹ It is also a poorly understood disease, and that can make it a frustrating one to treat for both the healthcare practitioner and the patient.

There is little agreement on the terms used to describe difficult-to-control asthma. Brittle asthma, severe asthma, steroid-resistant asthma, refractory asthma, and irreversible asthma all are names given to essentially the same constellations of symptoms. For the purposes of this newsletter, we will use difficult-to-control asthma.

There are also many different definitions of what constitutes difficult-to-control asthma. Most definitions are focused on the severity of symptoms, exacerbations, airflow, and physical limitations in those patients who are already receiving high doses of steroids. Barnes and Woolcock defined “difficult asthma” as “failure to achieve control when maximally recommended doses of inhaled therapy are prescribed.”^{2(p1209)} Harrison defined it as “being present in a patient with a confirmed diagnosis of asthma whose symptoms and/or lung function abnormalities are poorly-controlled with treatment that experience suggests would usually be effective.”^{3(p555)}

Accreditation

This program has been approved for 1 contact hour Continuing Respiratory Care Education (CRCE) credit by the American Association for Respiratory Care, 9425 N MacArthur Blvd Suite 100 Irving, TX 75063.

This program has been approved for 1.0 contact hours of continuing education by the American Academy of Nurse Practitioners. Program ID 0506268

National Jewish Medical and Research Center is provider approved by the California Board of Registered Nursing Provider Number CEP 12724 for 1.0 contact hours

One thing that most are in agreement about is that difficult-to-control asthma imposes a burden on both the patient and the healthcare system. Vollmer and colleagues found that both acute and routine asthma healthcare utilization increased as the number of asthma control problems increased. Acute care episodes were 3.5 times more likely in patients with 3 to 4 control problems.⁴

Anis et al found that those who inappropriately used short-acting β -agonists (high doses of short-acting β -agonists and low doses of inhaled corticosteroids) saw a significantly higher number of physicians for their prescriptions, were admitted to the hospital more frequently, and were more likely to be admitted to the hospital under emergency conditions.⁵

Guidelines from the National Asthma Education and Prevention Program (NAEPP) define the patient with severe persistent asthma as one who has continuous symptoms during the day and frequent symptoms at night. They will also have forced expiratory volume at one second (FEV₁) less than or equal to 60% of predicted and peak expiratory flow (PEF) variability of more than 30%. There are also major physical limitations.⁶

Many patients with severe persistent asthma, as defined by the NAEPP, may be well managed by a combination of controller medications. However, asthma management is suboptimal in a significant number of these patients even when high-dose ICS and other controllers are used.

The ATS defined refractory asthma on the basis of medication requirement, frequency of exacerbations, and airflow restrictions. These symptoms were grouped by major characteristics such as treatment with oral corticosteroids for 50% or more of the year and treatment with high-dose ICS.

Minor characteristics included daily treatment with controller medication, symptoms requiring use of a short-acting β -agonist on a daily or near-daily basis, persistent airway obstruction as seen by FEV₁ less than 90% predicted, and diurnal PEF variability greater than 20%. Other symptoms of refractory asthma include 1 or more urgent care visits per year, 3 or more oral steroid “bursts” per year, prompt deterioration with 25% or less reduction in steroid dose, and a near-fatal asthma event in the past. Finally, other conditions must be excluded, exacerbating factors treated, and the physician should feel the patient is generally adherent to the prescribed treatment. By definition, there must be at least 1 major and 2 minor characteristics present before refractory asthma can be diagnosed.¹

Prior to making the diagnosis of severe asthma, we need to exclude other conditions that may mimic asthma or make the disease worse.

Robinson and colleagues looked at 100 patients with difficult-to-treat asthma. Despite being prescribed high levels of oral steroids for at least 3 months, 12 of the patients studied did not have asthma and an additional 7 had coexisting diagnoses such as bronchiectasis.⁷

Newman and Dubester found vocal cord dysfunction (VCD) in 10% of adults who were referred to a tertiary medical center with “intractable asthma.”⁸

Among the alternative diagnoses that should be considered when making the diagnosis of difficult-to-treat asthma are: chronic obstructive pulmonary disease, vocal cord dysfunction (VCD), pulmonary embolism, mechanical obstructions, cystic fibrosis, bronchopulmonary dysplasia, viral bronchitis, foreign body aspiration, alpha-1 antitrypsin deficiency, and obstructive sleep apnea. These topics are discussed in greater detail in the second newsletter of this series.

Diseases That May Coexist with Asthma and How to Treat Them

After considering alternative diagnoses, the next step is to identify conditions that can coexist with and exacerbate asthma. Among the disease entities to consider are: gastroesophageal reflux disease (GERD), and chronic and allergic rhinosinusitis.

GERD. Typical symptoms include persistent heartburn and acid regurgitation, although many patients will have GERD without heartburn. In some instances, a cough and/or wheezing may be present, especially at night. The most widely accepted test is 24-hour esophageal pH monitoring.

There are 2 major areas of focus in treating GERD: medications and lifestyle changes. Proton pump inhibitors (PPIs) such as omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole block the production of an enzyme needed to produce stomach acid and are considered the most effective treatment. H₂ receptor antagonists (H₂RA), such as ranitidine, should be considered as a second-line medication, especially in PPI-resistant patients. H₂RAs are effective only if taken at least 1 hour before meals because they do not affect acid that is already present.

Other options include sucralfate and promotility agents such as metoclopramide and bethanechol. However, the latter medicines are less effective than the first 2 and the promotility agents have a higher side effect burden.

Lifestyle changes include actions such as not eating within 2 or 3 hours of bedtime to allow enough time for the stomach to empty and acid production to decrease. Patients should not lie down immediately after eating at any time of day. It may be helpful to elevate the head of the bed on 6-inch blocks. Finally, eating smaller, more frequent meals throughout the day and avoiding fatty or greasy foods, chocolate, caffeine, mints or mint-flavored foods, spicy foods, citrus, and tomato-based foods are important points to teach the patient.

Remind patients that alcohol increases the likelihood that acid from your stomach will back up. Smoking weakens the lower esophageal sphincter and increases reflux. Overweight and obese people are much more likely to have reflux. Maintaining good posture helps food and acid pass through the stomach instead of backing up into the esophagus. Taking over-the-counter pain relievers such as aspirin, ibuprofen, or prescribed medicines for osteoporosis can aggravate reflux in some people.

Surgery is also an option in GERD, especially in patients who are not optimally controlled with medications and lifestyle changes. Most

patients become symptom-free or have a significant improvement in their symptoms following surgery.

Chronic and allergic rhinosinusitis. Common symptoms of chronic rhinosinusitis include postnasal drip, throat clearing, increasing cough, and/or worsening asthma at night.

Treatment often focuses on improving nasal drainage and includes nasal washes with a saline solution and nasal steroids. Saline nasal washes and sprays cleanse mucous from the nose and allow medications to work more effectively. This treatment also works to remove allergens and other irritants from the nose and decrease swelling.

Intranasal corticosteroid sprays are often used following the saline wash. They are particularly effective in lessening the chronic inflammatory response, itching, sneezing, and rhinorrhea in these patients.

There is also no “rebound congestion” when the medications are terminated.

Other pharmacological interventions include both topical and systemic decongestants, antihistamines, and medications such as ipratropium bromide nasal spray or topical cromolyn sodium. Intranasal decongestants can cause rebound congestion if used for more than 2 or 3 days in a row. If the foregoing medications do not provide optimal control, a course of systemic steroid treatment should be considered in refractory patients, especially those with a history of sinonasal polyps (Table 1).

Although sinus surgery is available, it does not tend to be useful for patients with asthma and chronic rhinosinusitis. It is important to remember that surgery does not cure rhinosinusitis; therefore,

Table 1. General pharmacologic management of allergic rhinitis⁹

Agent	Sneezing	Itching	Congestion	Rhinorrhea	Eye Symptoms
Oral Antihistamines	++	++	+/-	++	++
Nasal Antihistamines	+	+	+/-	+	-
Intranasal corticosteroids	++	++	++	++	+
Oral decongestants	-	-	+	-	-
Intranasal decongestants	-	-	++	-	-
Intranasal mast cell stabilizers	+	+	+	+	-
Topical anti-cholinergics	-	-	-	++	-

- provides no benefit
 +/- provides little or minimal benefit
 + provides modest benefit
 ++ provides substantial benefit

This table represents a consensus of the Task Force’s opinion. Referral to and/pr consultation with all allergy/immunology specialist is recommended

From American Academy of Allergy, Asthma and Immunology. Diseases of the Atopic Diathesis. The Allergy Report. 2000;2:39. Used by permission. All rights reserved.

medical therapy must be continued. Medical management is the preferred treatment modality. However, surgery may be considered in those who do not respond to aggressive medical management.

Allergic rhinosinusitis, or hay fever, is an overreaction of the immune system to an environmental allergen. Symptoms include nasal congestion; sneezing—especially upon awakening; runny nose with clear discharge; postnasal drip; and runny, watery eyes. Allergy testing is often ordered to help focus environmental control measures (see Newsletter 1 in this series for information on environmental control).

The treatment for allergic rhinosinusitis is similar to that seen in chronic conditions. Nasal washes and intranasal steroids are often used, the latter to alleviate inflammation. Antihistamines may be used to inhibit the action of histamine on nasal and eye tissues.

Nasal decongestants decrease the swelling of the nasal tissue and the resulting feeling of stuffiness. Topical nasal decongestants cause rebound congestion and irritation of the nasal passages if used more than 2-3 days in a row.

Nasal cromolyn spray, available without a prescription, works by blocking the allergic reaction on the mast cell. It prevents or reduces the release of histamine and other chemical substances that cause the allergic symptoms.

Conditions that are Difficult to Differentiate from Asthma

The following conditions are clinically complicated and are difficult to differentiate from asthma. Serious consideration should be given to referring these patients to a tertiary care facility for treatment. Failure to properly differentiate these various conditions can result in wasted time, effort, and money.

Common Variable Immunodeficiency (CVID) and IgG Deficiency. Replacement therapy with intravenous immunoglobulin (IVIG) is helpful in managing the deficiency.

Allergic bronchopulmonary aspergillosis. ABPA is treated with systemic steroids. Anti-fungal antibiotics, in combination with systemic steroids, are used in some centers, but their role in maintenance therapy is unclear at present and requires further study.

Churg-Strauss Syndrome. CSS is a type of vasculitis that is seen in association with asthma. The presence of asthma is part of the diagnostic criteria for the disease. Prednisone is the medication most often used, but other immunosuppressive medications may be added if needed.

Eosinophilic bronchitis. Eosinophilic bronchitis is a condition in which a patient has many symptoms suggestive of asthma, including eosinophils in the sputum, but there is no evidence of abnormal lung function. The condition usually responds well to inhaled and/or systemic steroids for a short period of time.

Hypereosinophilic syndrome. As the disease is rarely curable, the focal point of treatment is to suppress eosinophil count and lessen tissue damage. Corticosteroids are the mainstay of treatment, although hydroxyurea, interferon- γ , monoclonal antibodies against Interleukin (IL)-5, and bone marrow transplants are also used. A

significant number of patients have a chromosomal translocation that produces a fusion protein with a tyrosine kinase, similar to that found in chronic myelogenous leukemia. These patients show a dramatic response to imatinib, a tyrosine kinase inhibitor.

Chronic eosinophilic pneumonia. Treatment is usually oral corticosteroids.

Newman and Dubester's series found 34% of their referred patients with intractable asthma had both VCD and asthma.⁸ Liou and colleagues noted that symptomatic GERD and chronic sinusitis were independently associated with severe asthma.¹⁰

Adherence

How well patients follow their medication regimen is another factor that can have an impact on difficult-to-treat asthma. Determining which exacerbations are related to disease progression and which are due to the patient not adhering to the prescribed drugs may be one of the more difficult pieces of this puzzle.

Williams and colleagues retrospectively studied 405 adults with asthma who were members of a health maintenance organization (HMO) in Michigan. Adherence indices were calculated using medical records and pharmacy claims for ICS medications.¹¹

Overall, they estimated adherence to ICS was only 50%. Perhaps more importantly, adherence to ICS was significantly and negatively correlated to emergency department visits. After adjusting for possible confounders, each 25% increase in proportion of time without ICS medication, resulted in a doubling of asthma-related hospitalization. They estimated that hospitalization would have been reduced by 60% had there been no gaps in medication use.¹¹

The Quality of Care for Asthma Committee of the American Academy of Allergy, Asthma and Immunology (AAAAI), noted that nonadherence can take many forms. Indicators include not filling prescriptions, not taking the correct dosage or not taking it at prescribed intervals, and premature discontinuation of the drugs.¹²

Measuring adherence is not an easy task in this population. Garber et al found that self-report methods overall were highly concordant with the electronic measures in only 17% of the studies they reviewed. Interviews had significantly lower concordance with non-self-report measures. The researchers concluded that questionnaires and diaries tend to have moderate-to-high concordance with electronic measures. These 2 methods could be preferable to interviews for self-reported adherence.¹³

Bender, Milgrom, and Apter's review of adherence noted a sizeable literature establishing that patient self-reports greatly overreport adherence. Much of this self-report bias may come from a desire to impress staff, especially physicians, and even more so if the patients hold the health care providers in high regard.¹⁴

One area that is getting a closer look when discussing adherence measurements is objective monitoring through electronic devices.

Krishnan and colleagues measured patient compliance with both ICS and oral corticosteroid (OCS) prescriptions following release from the hospital by using self-reporting, canister weight, pill counts, and elec-

tronic medication monitor techniques. Poor adherence was defined as less than 50%. Electronically measured use of both corticosteroids dropped to less than 50% within 7 days. Self-report, canister weight and pill count all had low sensitivity for predicting poor adherence.

Poor adherence to both ICS and OCS predicted significantly worse symptom control.¹⁵

Weinstein's literature review looked at poor asthma outcomes. The use of multiple medications to control symptoms, coexisting disease states, the presence of anxiety or depression and high cost of care were all related to nonadherence. He also noted that without objective monitoring, physicians might not appropriately factor nonadherence into their clinical decision-making.¹⁶ These findings mesh nicely with Krishnan's results.

Factors effecting adherence

Bender and Bender reported on their analysis of 29 studies looking at reasons patients gave for nonadherence to medications.¹⁷ High emphasis factors in adults included: fear of adverse effects of medications, the belief that the medication does not help or is not needed, a sense of only an intermittent need for medication, inconvenience of medication use, cost of medication, and dislike of provider.

Lower emphasis level factors in adults included concerns about stigmatization, feelings of inadequate knowledge, forgetfulness, belief that asthma is not serious, and worry about diminishing effectiveness of the medication over time. Other factors included fear of addiction/dependence and lack of social support.

The authors also formulated a listing of concerns for 2 other subgroups. Children with asthma and their parents found the following most important: stigmatization, which seemed to be a more important influence in children than adults; fear of side effects, addiction,

and/or dependence; difficulty with administration of medication; and division of responsibility for treatment between child and caregivers.

The list of concerns apparently affecting adherence in low-income patients included difficulty obtaining medications (including transportation to and from appointments and the pharmacy in addition to monetary outlays), the cost of medication, fear of adverse effects, distrust of medical establishments, and interference of life hassles (ie, since a high percentage of their efforts center on maintaining basic needs, nonurgent medical care may be ignored).

The AAAAI Quality of Care Committee's report listed factors that impacted adherence and suggested interventional strategies for healthcare providers to consider.

Among the factors that they cited were:

- Patient factors, such as how they perceive the seriousness of their disease. The patient's health beliefs about their disease, the medications used, and the healthcare system also have an impact on adherence. Age, gender, race, ethnicity, and psychological factors are all factors the healthcare team should take into account.
- Treatment factors, such as a preference for oral medications over ICS, less frequent dosing, and difficulty of use.
- Poor patient–physician communication, especially about the chronic nature of the disease, the need for daily therapy, the role of medications in treating the disease, and side effects.
- Socioeconomic concerns. Although the biggest problems usually involve lack of insurance (Table 2) and other financial concerns, language, education, and disability also play important roles.

Both the NAEP and AAAAI Committee stress that asthma education is a partnership between the patient and the healthcare team.

Table 2. Contact Information for Patient Assistance Programs of the Pharmaceutical Companies that Produce the Most Common Asthma and Allergy Medications.

AstraZeneca Pharmaceuticals

Foundation Patient Assistance Program

PO Box 15197

Wilmington, DE 19850-5197

800-424-3727

For information and an application: go to: www.phrma.org/pap/companies/index.cfm?company=18

Aventis, Inc.

US Patient Assistance Center

10236 Marion Park Drive

PO Box 9950

Kansas City, MO 64134-9950

800-221-4025

For information and an application: g www.phrma.org/pap/companies/index.cfm?company=92

Bayer Corporation

Indigent Patient Program

PO Box 29209

Phoenix, AZ 85038-9209

800-468-0894, ext. 2765

For information and an application:

www.phrma.org/pap/companies/index.cfm?company=68

Boehringer Ingelheim Pharmaceuticals

Partners in Health Prescription Assistance

900 Ridgebury Road, PO Box 368

Ridgefield, CT 06877-0368

800-556-8317

For information and an application:

www.phrma.org/pap/companies/index.cfm?company=90

Forest Pharmaceuticals, Inc.

Indigent Care Program

13622 Lakefront Drive

St. Louis, MO 63045

800-678-1605 ext 207

Glaxo Wellcome, Inc.

Patient Assistance Program

PO Box 52185

Phoenix, AZ 85072-9711

800-722-9294

For information: www.ipp.gsk.com/

Merck & Co., Inc.

Patient Assistance Program

PO Box 4 (WP35-258)

West Point, PA 19486-0004

800-727-5400

800-994-2111 health providers only

Applications are available at:

www.phrma.org/pap/resources/2002-07-31.87.pdf

Pfizer Pharmaceuticals

Prescription Assistance

PO Box 66585

St. Louis, MO 63166-6585

800-707-8990

For information:

www.phrma.org/pap/companies/index.cfm?company=110

Schering Laboratories

Patient Assistance Program

PO Box 52122

Phoenix, AZ 85072

800-656-9485

Key points in the EPR-2 publication suggest that patient education should begin at the time of diagnosis. It is essential that all members of the team provide education. Teaching self-management is important and should be individually tailored to the needs of the patient as jointly developed treatment goals. Plans should encourage active participation by providing the patient with a daily self-management program and action plan for exacerbations, as well as promoting open communication. In addition, the expert panel for NAEPP suggests teaching the basic facts of asthma, roles of medications, skills (such as correct inhaler use and self-monitoring), environmental control measures, and implementation of rescue actions and then reinforcing these at every opportunity.¹⁸

Strategies to improve adherence

Several specific strategies are suggested by the AAAAI group. They point to practical recommendations from Green¹⁹ that include:

- Be brief. Roughly half of what is said will be forgotten within 5 minutes.
- Present the most important information first.
- Give a written summary of the information, at a sixth-grade reading level, without using medical jargon.
- Present information in small bits to make it more understandable. For example, discuss asthma symptoms prior to introducing the action plan.
- Customize general instructions to the specific patient.
- Supplement written instructions with oral interactions.
- Repeat instructions, repeat instructions, repeat instructions.

Medication selection can also have an impact on adherence. The AAAAI Committee noted that oral medications tend to be preferred over inhaled drugs and that no more than twice-daily dosing offers improved compliance when compared to more frequent administration. Others have shown that combining multiple medications into a single device increases the likelihood of proper usage. Just about anything that simplifies the regimen has a positive impact on adherence.

Use of prompts to remind patients to take their medications is also useful. Instead of just suggesting taking their medications twice a day, tie the medication use to routines that happen at more or less the same times every day. For instance, instructing patients to take their medications at breakfast and dinner or when awakening and at bedtime might lead to better use of the medications. Difficulty of use may also have an influence on medication usage, as may unpleasant tastes or odors.

If the patient and family feel overwhelmed, the order in which medication is introduced is also important. “Graduated regimen implementation,” as outlined by the AAAAI Committee, involves introducing new components of treatment after the patient has successfully mastered the earlier step.

They suggest adding 1 medication at a time, beginning with the 1 that is simplest to use. When the patient is not overwhelmed with

too much information at once, the positive reinforcement of mastering the first skill translates into greater confidence. Patients can then become comfortable with the next step.

Pathology of Difficult-to-Control Asthma

There are a number of scenarios being discussed in the literature about the pathology underlying severe asthma. However, as of now, there is no unified theory. In fact, there is emerging evidence that what we now call difficult-to-control asthma may be many forms of asthma with different pathologies requiring different treatment strategies.

The ATS working group discussed 5 different hypotheses.¹ One hypothesis is that refractory asthma is a form of mild/moderate asthma in which there is ongoing helper T-cell type 2 (Th2) triggered inflammation. The group pointed to autopsy studies of patients who died from status asthmaticus who often showed an inflammatory pattern consistent with Th2 cell inflammation. They also noted that biopsy and lavage studies of those with “steroid-resistant” asthma appear to show increases in eosinophils and Th2 cytokines when compared with steroid-responsive cohorts.

Bronchoscopic studies also suggest that some patients, although by no means all, continue to show persistent eosinophil and lymphocytic inflammation despite high-dose steroids. This chronic inflammation may be related to long-term downregulation of binding affinity in the glucocorticoid receptor, upregulation of the less efficient glucocorticoid β -2 receptor, decreased efficiency of steroids to interfere with nuclear-transcription factor binding, or failure to suppress phosphorylation.

Another hypothesis considered was that refractory asthma entails a different kind of inflammatory process from that seen in milder forms. The ATS authors pointed to studies suggesting that neutrophils are present at higher levels in those with more severe forms of the disease.¹ Higher neutrophil levels are also found in those dying from status asthmaticus and in the sputum or bronchial washes of patients treated in the emergency department for status asthmaticus.

However, confusing this picture is the observation that steroids may actually prolong the survival of neutrophils by decreasing apoptosis. At this time, according to the working group, the relevance of higher levels of neutrophils to the pathology is unknown.

Refractory asthma that may be caused by a structurally remodeled airway leading to a fixed or irreversible obstruction is yet another path of inquiry being followed. Development of irreversible or only partially reversible disease, as defined by poor response to bronchodilators and steroids, is one of the markers of worsening asthma.

The participants in the ATS group noted that smooth muscle hyperplasia in the airways may be increased in patients with asthma who die of status asthmaticus. Subbasement membrane (SBM) thickening may also play a role in refractory asthma. Endobronchial biopsy studies show wide variability in SBM thickness and, when taken as a group, no differences are seen in those with refractory asthma (as defined by ATS guidelines) and those with milder forms.

However, when subjects with refractory asthma and high eosinophils were studied, thickened SBM and increased numbers of submucosal cells positive for transforming growth factor were found. The thickness of the membrane still did not correlate with physiological parameters such as spirometry results.

Another possible avenue of pathology suggested by the ATS authors is based on an altered distribution of inflammation and/or structural abnormalities. Autopsy studies note that inflammation and changes in structure extend to the small airways. Transbronchial studies in living patients indicate that inflammation extends to distal airways and possibly to the alveoli. These findings raise questions about whether refractory asthma is a manifestation of poor delivery of medications to the area. Studies have not yet been performed to evaluate whether these abnormalities differ in severe asthmatics when compared to those with less severe disease.

The final hypothesis outlined by the ATS working group suggests that refractory asthma may be 1 or more subtypes. If patients with severe asthma are grouped into those with and without eosinophils, those with eosinophils demonstrate responses that are consistent with Th2-type activation. Eosinophil-positive subjects also exhibited subtle physiological changes (especially in decreased forced vital capacity (FVC)/slow vital capacity (SVC) ratio) and a much higher level of near-fatal events.

“It is certainly possible, and even likely, that a combination of the above hypothesized events or other pathological elements not yet appreciated are involved in the pathogenesis of refractory asthma,” wrote the authors.^{1(p2347)}

Phenotyping

There have been many attempts to find phenotypes that explain the differences in asthma presentation. Miranda et al suggest that age at onset (earlier or later than 12 years-old) and presence or absence of eosinophils in the lung may be a way to differentiate the phenotypes.²⁰

Miranda’s cross-sectional analysis of data from 80 subjects with severe asthma found that those with early-onset severe asthma had significantly higher allergy sensitivity, more allergic symptoms, and a lymphocytic/mast cell inflammatory process. Later-onset severe asthma was associated with lower lung function despite shorter duration of illness. Greater levels of symptoms were seen in those with persistent eosinophils regardless of age of onset. This led the authors to suggest age at onset and eosinophil presence as possibly useful phenotypes.

Wenzel and her group compared their cohort of severe asthmatics by eosinophil status.²¹ Those who were eosinophil positive (e+) had associated increases in lymphocytes (CD3+, CD4+ and CD8+), mast cells, and macrophages. Neutrophils were increased in both groups, another linkage with severe asthma. Despite the lack of eosinophils and thinner SBM, FEV₁ was marginally lower in eosinophil negative patients. The authors noted that this finding suggests 2 distinct clinical subtypes of severe asthma exist.

The European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) undertook a cross-sectional study of clinical

phenotypes in Europe.²² Patients with severe asthma were almost identical in age distribution and duration of disease when compared to those with less severe forms. Patients with the worse disease remained symptomatic even though they had been maintained for at least 1 year on significantly higher doses of corticosteroids, inhaled long-acting β -agonists, and other anti-asthma medications. Other linkages suggested that those with severe asthma were more likely to be women and have an increased body mass index (BMI). The severe asthma cohort presented with a predominantly neutrophilic inflammatory manifestation, evidence of ongoing mediator release, but less atopy.

Genetics

The genetic genesis of asthma is a controversial area currently in flux. Studies of asthma phenotypes and their genetic linkages have produced results that can be charitably called “inconsistent.”

Hoffjan and collaborators undertook a literature review of genetic association studies. They showed that variations in 64 genes had been reported in at least 1 study to be linked to asthma or 1 of its traits. Of these, only 33 were replicated in a second study, 9 were not replicated either in a second study or a second sample of the same study, and 22 associations were shown only in a single study.²³

Study of genetic markers has proved equally confusing. Altmüller and others conducted a genome-wide scan on 201 asthma-affected sibling pairs. Several linkage regions were seen, although none with a $P < 0.0003$ could be found. They also noted that other researchers have shown asthma linkages to almost every chromosome and several genes, indicating that heterogeneity of the disease process extends into the genetic realm.²⁴ However, as was noted by Hoffjan,²³ most of these were weak and have not been replicated.

There are some very interesting possibilities being explored that may, in time, give us not only a better understanding of the disease, but also ways to assess risk and possibly tailor treatments in the future. Quite a few susceptibility genes have been identified and are being localized to a variety of chromosomes.

At this point, there is not a single gene that could be pointed to as representing the asthma phenotype. The current thought is that asthma is most likely going to be a multi-gene disease and will have an environmental component that will combine to produce the phenotype. It is doubtful that a single gene dominates the process of asthma.

Response to medications

There is an emerging body of research that indicates at least some subsets of patients with difficult-to-control asthma may not respond to the medications properly. This currently poorly-defined group has been called “steroid resistant” (SR) or “steroid insensitive” (SI) depending on the researchers.

There are a number of possible pathophysiological scenarios discussed in the literature. Leung and colleagues demonstrated that splicing of glucocorticoid receptor (GCR) pre-messenger RNA creates a second GCR (GCR- $_$) that does not bind to glucocorticoids and also antagonizes the activity of GCR- $_$.²⁵ Matthews and

his group suggest defective receptor translocations and altered patterns of histone acetylation may be a culprit.²⁶ Joos and Sandford noted in their review that polymorphisms in specific genes have been associated with responsiveness to β -agonists and leukotrienes.²⁷ At this time there is little consensus on what factors are important and how (or if) they may interact.

Prescribed medication regimens

When thinking about the impact of prescribed medications on control in these patients one consideration is the effects underprescribing has on symptoms. Yuksel and others retrospectively reviewed 1022 charts of patients treated in the emergency departments of 2 hospitals in Alberta, Ontario, Canada.²⁸ Despite being a high-risk group, patients were prescribed inhaled corticosteroids only about half the time. Sin and Tu found similarly low levels (40%) of ICS prescription in a Canadian population 65 years or older who had survived an acute asthma exacerbation.²⁹

Case Study

A 33-year-old white male who has been treated for mild intermittent lifetime asthma presents to the office with a complaint of increasing symptoms. He had seen his allergist who had placed him on fluticasone inhalation 220 mcg 2 puffs twice a day and salmeterol inhalation 1 puff 2 times each day. He had been on montelukast 10 mg daily and albuterol as needed before his recent increase in symptoms. He continued to have daily symptoms and was referred back to his pulmonologist to rule out any other pulmonary complications.

During the review of systems, he denied gastric reflux. Primarily he was concerned about increased nocturnal and early AM wheezing and increased use of albuterol during the day for shortness of breath.

Physical Exam:

Vital signs were all within normal limits.

The head, eyes, ears, nose, and throat examination showed a pale nasal mucosa with mild swelling. The tympanic membranes were normal. There was no adenopathy, thyroidmegaly, or jugular vein distention.

There was no active wheezing on auscultation and respirations were even and unlabored. A chest x-ray was within normal limits. Pulmonary function tests (PFT) revealed mild obstruction, which is a change since all previous PFTs had been normal.

A cardiac exam noted regular rate and rhythm although there was no S3 heart sound.

Externally, there was no cyanosis, clubbing, or edema.

Upon questioning about changes in the environment, at first he denied any changes but after a while admitted that he was living with a roommate who had 2 cats. He has tested positive for cat allergy in the past. He also admitted that he let the cat sleep in the bed with him. He had become attached to the cat and had not wanted his allergist to know that he was being exposed to a known trigger.

Summary

Difficult-to-control asthma is not yet well defined. However, most discussions of the disease include severity of the symptoms, number of exacerbations, as well as physical and airflow limitations in patients already receiving high doses of corticosteroids. The clinical picture is further confused by the presence of other conditions that mimic asthma or coexist with the disease. Finally, varying levels of adherence to medication regimens may also have an impact on proper case finding and treatment.

There are also many ongoing controversies over the pathology of difficult-to-treat asthma. While the ATS working group has suggested 5 different possible hypotheses, a consensus regarding which one might best explain the condition has not been reached. Similarly, attempts to discover genotypes and genetic clues to why there are differing asthma presentations have not shed much light on the subject.

Overall, it appears likely that difficult-to-treat asthma is a name for many different processes that result in similar presentations.

It was explained to him that uncontrolled inflammation in asthma would result in remodeling and would make the asthma symptoms worse. He would, at the very least, need to remove the cat from the bedroom.

The patient was questioned about his actual medication use. He admitted that he did not like taking inhalers and was only using his montelukast. Further questioning brought out that he viewed the inhaler medication as being hard to use and inconvenient to carry around. He was also concerned about side effects and the possibility of addiction. Finally, he expressed long-term financial concerns related to the expense.

The health care team and the patient worked to jointly develop a way to treat his asthma, allow him to keep the cat, and lessen concerns about the medication. First, the patient was taught the effects (both therapeutic and adverse) of the medications. In addition to talking with him, he was given appropriate information on his medications to reinforce what was said. Steps were discussed to lessen the adverse effects as much as possible. This conversation lessened his fears about the side effects and eliminated the concerns about addiction.

It was also stressed that he would more than likely need more controller medications while the cat was in the house and that it should be expected that there might be changes in his other medications as well to compensate for the higher levels of exposure to feline triggers.

He agreed to use the inhalers and consider removing the cat from the bedroom.

To address the concerns about being able to afford medications, the Partnership for Prescription Assistance Web site (<https://www.pparx.org>) was provided for information on private and public programs available in his state to help pay for needed medications. He was also referred to the patient assistance programs of the pharmaceutical companies that produce the asthma and allergy medications he was prescribed.

POST-TEST

1. The NAEPP definition of severe-persistent asthma includes:
 - a) Continuous symptoms present during the day
 - b) Frequent symptoms during the night
 - c) PEF/FEV1 of 60% or less of predicted
 - d) All of the above
2. Indications of possible nonadherence include all of the following except:
 - a) Prescriptions going unfilled
 - b) Premature discontinuation of medication
 - c) Not taking proper dosage at prescribed intervals
 - d) Well-controlled symptoms
3. Pharmacological strategies to increase adherence include:
 - a) Lower frequency of medication when possible
 - b) Simplify the delivery of medication
 - c) When possible, combine several medications into 1 inhaled form
 - d) All of the above
4. In the study by Williams, et al, each 25% increase in the proportion of time without ICS medications resulted in _____ of asthma-related hospitalizations
 - a) No change
 - b) Doubling
 - c) Tripling
 - d) Quadrupling
5. According to the results of a study by Miranda and colleagues, those with early onset asthma had significantly higher/more _____
 - a) Allergy sensitivity
 - b) Allergy symptoms
 - c) Lymphocytic/mast cell mediation of their inflammatory process
 - d) All of the above
6. Studies have shown increased levels of neutrophils in some patients with severe asthma. If this is true, steroid treatment may worsen the problem because:
 - a) Neutrophils are poorly responsive to steroids
 - b) Steroids are thought to prolong neutrophil survival by decreasing apoptosis
 - c) A and B
 - d) None of the above
7. Treatment of chronic rhinosinusitis includes all except:
 - a) Nasal wash with saline
 - b) Topical intranasal corticosteroid
 - c) Routine use of topical decongestant
 - d) Antihistamines
8. Which of the following is considered to be a condition that exacerbates asthma and may make it harder to treat effectively?
 - a) GERD
 - b) COPD
 - c) Cystic fibrosis
 - d) Churg-Strauss Syndrome
9. Which of the following is a MAJOR characteristic of refractory asthma under the ATS guidelines?
 - a) Symptoms that require a short-acting β_2 -agonist on a near-daily basis
 - b) Three or more steroid “burst” treatments per year.
 - c) Treatment with oral corticosteroids for 50% or more of the year
 - d) A near-fatal asthma event in the past.
10. Lifestyle changes that may help relieve the symptoms of GERD include all except:
 - a) Raising the head of the bed on 6-inch blocks
 - b) Eating smaller, more frequent meals
 - c) Eating plenty of chocolates and citrus-based foods
 - d) Not eating 3 or more hours prior to bedtime

1. d 2. d 3. d 4. b 5. d 6. c 7. c 8. a 9. a 10. c

Answers:

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Making the Connection Between Understanding and Management of Difficult-to-Control Asthma

October Issue

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