

*Clinical pearls***Managing severe asthma**Sally Wenzel, MD,^a and Stanley J. Szeffler, MD^b *Denver, Colo***Key words:** *Corticosteroids, severe asthma, difficult to control asthma, refractory asthma, childhood asthma, adult asthma***CURRENT CONCEPT OF SEVERE ASTHMA**

Severe asthma, although present in a relatively small proportion of the total population with asthma, comprises the group of patients with the greatest morbidity and who are in particular need of a careful evaluation and innovative approach to management. Task forces have been assembled by the American Thoracic Society and European Respiratory Society to discuss the definition, evaluation, and management of severe asthma.^{1,2} The American Thoracic Society focused its attention on refractory asthma and concluded that major characteristics included one or both of the following: (1) treatment with continuous or near-continuous ($\geq 50\%$ of the year) oral corticosteroids and (2) requirement for high-dose inhaled corticosteroids to achieve control at a level of mild-to-moderate persistent asthma and in association with 2 of the following minor criteria: (1) requirement for daily treatment with a controller medication in addition to inhaled corticosteroids, (2) asthma symptoms requiring short-acting β -agonist use on a daily or near-daily basis, (3) persistent airway obstruction ($FEV_1 < 80\%$ of predicted value, diurnal PEF variability $> 20\%$), (4) one or more urgent care visits for asthma per year, (5) 3 or more oral steroid “bursts” per year, (6) prompt deterioration with 25% or less reduction in oral or inhaled corticosteroid dose, and (7) near-fatal asthma event in the past.

From ^athe Division of Pulmonary Medicine, National Jewish Medical and Research Center, and the Department of Medicine, University of Colorado Health Sciences Center, and ^bthe Divisions of Pediatric Clinical Pharmacology and Allergy and Immunology, National Jewish Medical and Research Center, and the Departments of Pediatrics and Pharmacology, University of Colorado Health Sciences Center.

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Reprint requests: Stanley J. Szeffler, MD, National Jewish Medical and Research Center, 1400 Jackson St, Rm J313, Denver, CO 80206. E-mail: szefflers@njc.org.

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The European Respiratory Society called this group of patients “difficult/therapy-resistant asthma” and defined this disease as “that which is poorly controlled in terms of chronic symptoms, episodic exacerbations, persistent and variable airways obstruction and a continued requirement for short-acting β_2 -agonists despite delivery of a reasonable dose of inhaled corticosteroids.” They also indicated that these patients might require oral corticosteroids periodically or a regular dose of oral corticosteroids to maintain reasonable control of the disease.

Both groups define a patient whose symptoms are difficult to control despite adequate long-term controller therapy, including periodic or continuous use of oral corticosteroids. These patients have a poor quality of life caused by unpredictable asthma exacerbations and also are predisposed to significant adverse effects of medications, especially corticosteroids. They are also susceptible to a high frequency of comorbid diseases, such as gastroesophageal reflux and rhinosinusitis. Based on our combined experience at National Jewish Medical and Research Center in managing children and adults at a referral center specializing in the diagnosis and management of severe asthma, we will summarize a practical approach to the initial evaluation and management of these patients, as well as define areas in need of further research.

INITIAL EVALUATION

On evaluating a referred patient for the first time, one should confirm that the diagnosis is consistent with asthma. This is perhaps the most critical step. Patients with severe asthma should generally provide a history of frequent and significant asthma exacerbations despite levels of asthma control therapy consistent with moderate-to-severe persistent asthma. In addition, nocturnal exacerbations, exercise-induced asthma, and concomitant rhinitis-sinusitis are to be expected. Patients will often also provide a history of gastroesophageal reflux. If this information is not provided, and standard pulmonary function is equivocal, then further questions are needed to define whether these features are present but not previously recognized or managed appropriately.

Medical records should be carefully evaluated for prescribed medications, indication of medication adherence, pulmonary function tests, and evidence of evaluation for allergy, such as skin tests, RASTs, or a history of seasonal or environmental sensitivity. It is also important to determine whether the patient has been responsive to

the prescribed medications. Poor response might be due to poor adherence or possibly poor technique, specifically with inhaled medications. It is always useful to observe the patient administering his or her inhaled medications in the office setting.

Although patients with severe asthma often are suspected of having airway remodeling, it is difficult to identify this feature, especially in children. One indication might be a progressive escalation of treatment with or without a gradual loss of pulmonary function over time.³ The amount of information obtained from the initial history, physical examination, and medical records will determine the direction of subsequent medical evaluation and treatment decisions. If the history is consistent with severe asthma, then the medical evaluation will focus on defining the level of reversibility and concomitant medical illnesses. If the history of asthma is suspect, then the medical evaluation will focus on a careful differential diagnosis.

APPROACH TO EVALUATION

The initial evaluation is highly dependent on the history the patient provides, the physical examination, and the details of the past medical evaluation. Initial testing should include spirometry before and after a bronchodilator to evaluate the level of pulmonary function and degree of reversibility. This information will also serve as a baseline for assessing response to changes in therapy. Evidence of low pulmonary function and bronchodilator reversibility should prompt an assessment of response to oral corticosteroid therapy. Inspiratory and expiratory flow-volume loops are also helpful in assessing potential upper airway abnormalities that can masquerade as asthma, especially during an episode of respiratory distress. In adults with or without obstruction on spirometry and with a questionable history, a methacholine challenge test to evaluate bronchial hyperresponsiveness (a cardinal feature of asthma) with a laryngoscopy to evaluate upper airway dysfunction yields helpful information in a large percentage of patients.

Past evaluation for allergy and environmental triggers should be reviewed and further testing obtained based on the patient's specific history, especially in relation to pet exposure, indoor allergens, and seasonal allergens. In rare circumstances, assessment for food allergies, especially in children, might uncover a previously unsuspected food sensitivity and prompt a dietary avoidance measure to test for response.

Past radiologic tests should be reviewed for suggestions of other disorders that might masquerade as asthma, such as hypersensitivity pneumonitis, aspiration, or restrictive lung disease. The combination of abnormalities in pulmonary function and a suggestive chest radiograph could prompt consideration for additional diagnostic testing, such as high-resolution computed tomographic scanning, panels for hypersensitivity pneumonitis, body plethysmography, and evaluation for gastroesophageal reflux.

Because sinusitis is a frequent coexisting disease in severe asthma, a sinus computed tomographic scan could

prompt treatment for this disorder. In addition, patients who have received extended courses of oral corticosteroids and high-dose inhaled corticosteroids should be carefully evaluated for adverse steroid effects, including measures of growth in children, bone densitometry for osteopenia, and a slit-lamp ophthalmologic evaluation for cataracts and increased intraocular pressure. Findings in these areas will not only direct specific treatment for these complications but also direct the treatment regimen to steroid-sparing therapies. In patients with little evidence of steroid side effects despite a history of treatment, an evaluation for medication adherence could prove helpful, such as morning cortisol and blood eosinophil measurement as a baseline to assess response after a prescribed course of steroid therapy.

If the diagnosis remains consistent with severe asthma, an evaluation with a trial of oral corticosteroid therapy for poorly controlled asthma or an escalation in treatment will provide useful information when the clinical assessment is combined with measurements of spirometry before and after the treatment course.⁴ Attention to medication technique for inhaled medications is important and could identify problems with patient education.

FOLLOW-UP VISITS

Periodic follow-up visits are important in assessing response to therapy and also in directing further evaluation. Failure to respond to the usual course of treatment could prompt referral to a specialty center or the application of additional diagnostic tests or immunomodulator therapy. Referral centers that specialize in managing patients with severe asthma have access to tests that are not routinely available, such as induced sputum, exhaled nitric oxide measurement, methacholine challenge tests, body plethysmography, and bronchoalveolar lavage and biopsy that will add to the medical evaluation.⁵⁻⁷ Application of these techniques are helpful in defining the heterogeneous nature of severe asthma. In addition, these centers incorporate a careful evaluation of the psychosocial features that might contribute to poor control of asthma, such as learning disorders, depression, anxiety, and poor self-image, to name a few areas of concern.

To date, the only additional treatment specifically approved for intervention in patients with moderate-to-severe asthma is omalizumab. Based on the appropriate patient profile (eg, serum IgE measurements), a trial might be initiated with a plan for reassessment over the first 3 to 6 months of treatment.⁸ Because response to various anti-inflammatory and immunodulator therapies is highly variable in this population, response should be carefully documented to determine continuation of the selected treatment. Although initial reports with treatments such as methotrexate, troleandomycin, gold, and intravenous gamma globulin were encouraging, experience over the past 20 years has been in general disappointing, except for the occasional patient who has an excellent response. Unfortunately, it is usually not clear whether the good

response is due to the medication or a potential placebo effect. Future applications of biomarkers and genetics might assist in predicting responders and nonresponders to the various treatments. An interesting observation is the frequent identification of *Mycoplasma* and *Chlamydia* species through electron microscopic evaluation of lung biopsy specimens in patients with severe asthma. This consideration prompts a trial of macrolide antibiotic therapy; however, this area is in need of further research to define appropriate diagnostic techniques and patients likely to respond to this therapy. In patients with adult-onset asthma, particularly when associated with aspirin sensitivity, a clinically significant response can be seen with a 5-lipoxygenase inhibitor.

SPECIAL CONSIDERATIONS IN CHILDREN

The evaluation previously summarized applies in general to both children and adults. However, one thing to consider in the evaluation of children is that the younger the child, the more one should consider other medical disorders. In our experience young children presenting with respiratory distress at an early age should be assessed for possible cystic fibrosis, congenital anomalies affecting the respiratory tract, aspiration syndromes, and immune deficiency. Frequent disorders associated with severe asthma identified in older children include gastroesophageal reflux and sinusitis.

Frequent school absence should prompt communication with the school to assess the possibilities of environmental exposures, family disorders, learning disability, and school avoidance caused by failing school performance. Because children often have difficulty with inhaled medication, administration with dry-powder devices, or even metered-dose inhalers with or without spacers, a trial of nebulized budesonide suspension could prove beneficial. In addition, for patients who do not show evidence of gastroesophageal reflux, a trial of low-dose theophylline therapy with appropriate precautions for drug interactions could provide benefit. Because omalizumab is only approved for children as young as 12 years of age, further studies are needed to define the safety and efficacy of this treatment in younger children. It is possible that this treatment might be more effective in children with severe asthma compared with adults because they are in the early stages of their disease progression.

SPECIAL CONSIDERATIONS IN ADULTS

Perhaps the most common cause of “severe asthma” in adults is a misdiagnosis. Therefore confirming the diagnosis is of critical importance. If the patient is smoking, strong advice must be given to stop because steroids do not appear to be as effective in smoking (compared with nonsmoking) asthmatic subjects.⁹ The role of obesity in increasing the severity of asthma is unclear, although it is apparent that asthmatic subjects in general have a higher body mass index than the general public. The contributing

role of perimenstrual asthma to severe disease also is poorly understood. However, numerous case reports exist for the improvement in asthma after initiation of oral contraceptives. Additionally, severe asthma in adults appears to differ quite dramatically by phenotype, being affected by age at onset and presence-absence of particular types of inflammation.¹⁰ Adult-onset asthma appears to be less allergic, such that measures targeted to remove allergens are less effective. In addition, aspirin sensitivity–triad asthma and occupational-related asthma are additional phenotypes to consider that might benefit from specific therapies, including aspirin desensitization, 5-lipoxygenase inhibitors, and removal from exposures. Finally, the presence of eosinophilic inflammation (as measured directly based on sputum or biopsy results or indirectly based on exhaled nitric oxide levels) suggests a phenotype of severe asthma that might benefit from higher doses of corticosteroids or alternative anti-inflammatory agents.^{11,12} If no measurable inflammation is present, anti-inflammatory approaches might be less beneficial.

WHEN IS A LUNG BIOPSY INDICATED?

Whether invasive studies, particularly bronchoscopy with endobronchial biopsy, lavage, or both, are clinically indicated in severe asthma is controversial. However, numerous bronchoscopic studies have suggested that pathologic changes exist in the airways of subjects with severe asthma, including the presence or absence of inflammation, colonization-infection with atypical bacteria, or both, which might indicate changes in therapy. In addition, certainly in children, but also in adults, bronchoscopic evaluation is often considered necessary to rule out structural abnormalities, aspiration, and infection. The procedure itself should only be done by a highly experienced bronchoscopist with appropriate technical and nursing support. The procedure is commonly done in children after achievement of general anesthesia, whereas in adults it is usually done during conscious sedation. Biopsy specimens should be taken from the subcarinae of the lower lobes and fixed in formalin, acetone, or both or frozen. Both frozen and acetone-fixed tissue allows for better morphometric evaluation and antigen preservation. Lavage in children to evaluate for aspiration or infection might also be warranted.

If the bronchoscopy is specifically performed to evaluate airway pathology, either to confirm the diagnosis of asthma or to better understand the level-type of inflammation present, it is likely the tissues should be evaluated primarily in institutions with a history of airway pathologic evaluation (in a quantitative manner, if possible). Because the pathologic changes associated with asthma can be subtle, it is imperative that both quantitative approaches and normal airways are available for comparison. The presence of airway eosinophils suggests that further anti-inflammatory therapy is indicated, whereas the absence of eosinophils or the presence of neutrophils might suggest that further increases in steroid doses are not

likely to be helpful.¹³ If neutrophils are observed, consideration should be given to infectious causes or perhaps those related to occupational exposures. Further prospective studies of treatment based on bronchoscopic findings are needed.

CONCLUSIONS

Patients with severe asthma pose a challenge to the clinician to verify the diagnosis, assess for coexisting medical illnesses, and define a more effective treatment regimen. Referral centers that specialize in the management of children and adults with severe asthma can assist the clinician in the office setting by providing a comprehensive assessment using tools that are not readily available. More information is needed on the application of biomarkers and genetics for individualizing therapy and developing new therapeutic strategies. It is important to continue to identify indicators that can reliably predict who will have severe asthma so that prompt early intervention strategies can be formulated. A systematic approach to overall care of severe asthma should lead to a reduction in morbidity and mortality associated with this disease.

REFERENCES

1. Chung KF, Godard P, Adelroth E, Ayres J, Barnes N, Barnes P, et al. Difficult/therapy-resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task Force on Difficult/Therapy-Resistant Asthma. European Respiratory Society. *Eur Respir J* 1999;13:1198-208.
2. American Thoracic Society Workshop. Proceedings of the ATS workshop on refractory asthma. Current understanding, recommendations, and unanswered questions. *Am J Respir Crit Care Med* 2000;162:2341-51.
3. Covar RA, Cool C, Szefer SJ. Progression of asthma in childhood. *J Allergy Clin Immunol* 2005;115:700-7.
4. Colice GL, Stamponi P, Leung DY, Szefer SJ. Oral corticosteroids in poorly controlled asthma. *J Allergy Clin Immunol* 2005;115:200-1.
5. Wenzel S. Severe asthma in adults. *Am J Respir Crit Care Med* 2005;172:149-60.
6. Szefer SJ, Leung DYM, editors. Severe asthma: a multidisciplinary approach, lung biology in health and disease series. New York: Marcel Dekker; 2001.
7. Payne DN, Balfour-Lynn IM. Children with difficult asthma: a practical approach. *J Asthma* 2001;38:189-203.
8. Oba Y, Salzman GA. Cost-effectiveness analysis of omalizumab in adults and adolescents with moderate-to-severe allergic asthma. *J Allergy Clin Immunol* 2004;114:265-9.
9. Tomlinson JE, McMahon AD, Chaudhuri R, Thompson JM, Wood SF, Thomson NC. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. *Thorax* 2005;60:282-7.
10. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol* 2004;113:101-8.
11. ten Brinke A, Sterk PJ, Masclee AA, Spinhoven P, Schmidt JT, Zwinderman AH, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. *Eur Respir J* 2005;26:812-8.
12. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715-21.
13. Wenzel SE. Phenotypes in asthma: useful guides for therapy, distinct biological processes, or both? *Am J Respir Crit Care Med* 2004;170:579-80.