Airways Obstruction in Patients With Long-term Asthma Consistent With ‘Irreversible Asthma’*

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**Objective:** To describe a series of eight patients with long-term asthma and pulmonary function consistent with “end-stage,” irreversible obstruction.

**Design:** Retrospective descriptive analysis of patients with severe asthma.

**Setting:** A university-based allergy-immunology service with a large population of corticosteroid-dependent patients with asthma.

**Patients:** Eight patients with long-standing asthma and apparently irreversible airways obstruction despite long-term oral and inhaled corticosteroid therapy.

**Measurements:** Pulmonary function data, radiographic studies including chest radiograph and high-resolution CT of the chest, and serologic analysis to rule out allergic bronchopulmonary aspergillosis and α1-antitrypsin deficiency had been performed as indicated, and these results were obtained through chart review.

**Results:** The age of the patients ranged from 41 to 58 years, with a mean duration of asthma of 39 years (SD=12.4 years). No patient had evidence of any other pulmonary disease process. The mean duration of daily or alternate-day oral corticosteroid treatment was 15.8 years (SD=11.8 years). Despite intensive pharmacotherapy, all patients had an FEV1 57% (42±12%) with marked small airways disease as reflected in the forced expiratory flow between 25% and 75% of the FVC. Three of the eight patients demonstrated an accelerated decline in FEV1 despite continuous systemic corticosteroids.

**Conclusions:** We have described a series of eight patients with long-standing asthma who demonstrate irreversible airways obstruction despite long-term systemic and inhaled corticosteroids. The term “end-stage asthma” or irreversible asthma might be applied to these patients in whom fixed obstruction has occurred in the absence of other pulmonary diseases.

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**Key words:** end-stage asthma; irreversible obstruction

**Abbreviations:** ABPA=allergic bronchopulmonary aspergillosis; FEF₂₅₋₇₅% = forced expiratory flow between 25% and 75% of FVC; RV=residual volume; TLC=total lung capacity

Asthma traditionally has been considered a reversible disease of airflow obstruction, with no long-term, permanent damage to the airways. This has been contrasted with emphysema and chronic bronchitis, in which permanent structural alterations occur.1 In recent years, however, as the inflammatory nature of asthma has been appreciated, the possibility exists that long-term asthma could lead to chronic, irreversible airways obstruction has been acknowledged.

In 1977, Turner-Warwick2 reported some of her observations regarding patterns of asthma. She described three types of findings in patients with asthma: (1) those never achieving a normal peak flow, but showing a reversible component; (2) those having a reversible FVC but an irreversible decrease in FEV₁ and peak flow; and (3) the “drifter,” with irreversible airways obstruction gradually improving over weeks of intensive therapy.

Since that time, a number of studies have examined the effects of chronic asthma on pulmonary function. It has been demonstrated that FEV₁ de-
clines faster in patients with asthma (24 mL/yr) than in patients without asthma (6 mL/yr) or (50 mL/yr vs 35 mL/yr), suggesting that some permanent lung damage is occurring.5 Lung growth and senescence have been demonstrated to be adversely affected by severe persistent asthma during childhood and adolescence, although in most children with asthma, lung growth is apparently normal.5 Inhalations of corticosteroids have been shown to slow the rate of decline of FEV1, although those patients examined were selected for their unusually rapid rate of decline of FEV1 before treatment.6,7

A systematic examination of irreversible airflow obstruction in 59 patients with chronic asthma was published in 1984 by Brown and colleagues.8 They demonstrated that after 2 to 4 weeks of treatment with B-adrenergic agonists, theophylline, and in some cases, prednisolone, these patients had FEV1 values significantly below normal, and the difference was larger with increasing age and duration and severity of asthma. Only 48 of these patients received prednisolone and then only for 2 weeks. No patient was receiving long-term oral corticosteroids, and thus it is unclear whether a longer course of prednisolone therapy may have improved further these patients' FEV1.

In this study, we describe eight patients with severe, chronic asthma with irreversible moderately severe or severe airflow obstruction despite aggressive, long-term corticosteroid therapy.

MATERIALS AND METHODS

Eleven patients were identified by the attending physician staff of the Division of Allergy-Immunology as patients with severe asthma with an irreversible component of airflow obstruction. They were identified by recall from full-time faculty practices consisting of eight half-day weekly ambulatory clinics. All patients met the criteria for the diagnosis of asthma as defined by the Joint Task Force on Practice Parameters.9 Asthma was described as a disorder with reversible obstruction and airway inflammatory processes.9 Of these 11 patients, 1 was excluded because a large portion of her medical record was missing, and 2 were excluded because upon further review, they did not have a large irreversible component of their asthma. No patient was considered noncompliant with medications, especially prednisone or inhaled corticosteroids.

For the remaining eight patients, a retrospective chart review was performed, with history, physical examination, radiographic (posterior-anterior chest radiography and high-resolution CT), laboratory, and pulmonary function data obtained from the medical record. The FEV1 determinations were generated from the best of three efforts. The most recent spirometric parameters were not very different from the patients' recent serial findings.

All patients had been evaluated previously for allergic bronchopulmonary aspergillosis (ABPA), and this diagnosis was ruled out in all eight by either negative immediate-type skin testing to Aspergillus fumigatus, or if this was positive, by negative serologic evaluation including total serum IgE, gel diffusion for precipitating antibodies to A fumigatus, and serum IgE and IgG antibody indexes.10 All patients had been evaluated for other possible pulmonary disorders, and all diagnoses but asthma were excluded by the appropriate studies. Other conditions considered and excluded are as follows: COPD, pneumoconiosis; bronchiolitis obliterans; recurrent pneumonia; hypersensitivity pneumonitis; sarcoid; α1-antitrypsin deficiency; and ABPA.

All patients were treated with regularly scheduled inhaled corticosteroids and as needed B-agonists, and all but one are currently considered oral corticosteroid (prednisone) dependent. The dose of prednisone used was the lowest dose required to prevent hospitalizations, severe symptoms, impaired functional status, or the need for emergency therapy for asthma. In every case, periodic attempts were made to reduce or discontinue prednisone therapy. Prednisone was administered as an alternate-day, single early-morning dose whenever possible, with courses of daily prednisone as needed for exacerbations. In addition, higher doses of prednisone (40 to 60 mg daily for 1 to 2 weeks when the patient was in stable condition) used to try to raise the spirometric values did not result in additional bronchodilation. Antibiotics were administered for purulent bronchitis, rhinitis, or sinusitis. In the 1970s and 1980s, and until 1991, theophylline was used on a regular basis for prednisone-dependent patients with asthma. The eight patients used high-dose inhaled corticosteroids (beclomethasone dipropionate, 672 to 840 µg/d, or flunisolide, 2,000 µg/d). For dust mite and mold (fungi) sensitivity, zippered mattress and pillow encasings were employed. Allergen immunotherapy had been administered to one patient (patient 3), although he was not receiving such therapy currently.

RESULTS

The clinical characteristics of the eight patients are shown in Table 1. The mean age of the patients was 50.1±5.9 years (range, 41 to 58 years). The average duration of asthma in the patients was 39 years (range, 36 to 51 years). All patients were treated with continuous oral corticosteroids (daily or alternate-day prednisone) and inhaled corticosteroids for a mean duration of 15.8 years (range, 1.5 to 32 years). Seven of eight patients are maintained currently on a regimen of oral prednisone, with six of them requiring alternate-day prednisone.

Only three patients had ever smoked cigarettes, and these three had a cumulative smoking history of 2, 5, and 10 pack-years. One patient had a history of asbestos exposure at work for approximately 10 years, but showed no evidence of asbestos-related pleural or pulmonary disease. No other occupational exposures were contributory. All but one patient demonstrated IgE to various allergens on allergy skin testing, but there was no common allergen to which all of these seven patients were positive. One patient was dog sensitive and continued to keep a pet dog, denying that the dog was a trigger of his symptoms.

The pulmonary function data for these patients are presented in Table 2. All patients currently have an
FEV₁ that is ≤57% of the predicted value for height and age (mean, 42±12%). In addition, all patients have a remarkably decreased forced expiratory flow between 25% and 75% of FVC (FEF₂₅₋₇₅%), which is consistent with severe small airways disease. These parameters did not increase despite high-dose, inhaled corticosteroids and regular prednisone supplemented with extra courses to try to improve overall respiratory status. The patients demonstrate an obstructive defect on formal pulmonary function testing, with no evidence of restrictive disease (decreased total lung capacity [TLC], residual volume [RV], or diffusion of carbon monoxide) in any patient. Patient 7, who had an RV of 71% and TLC of 94%, was obese. Of the eight patients studied, four had FEV₁ values that improved or remained stable over time, and four had values that worsened (Fig 1). Of the four patients with pulmonary function that worsened, three demonstrated a decline in FEV₁ by ≥90 mL/yr, despite continuous (daily or alternate-day) prednisone and inhaled corticosteroids for 6 to 15 years in addition to bronchodilators.

Radiographic studies in these patients, consisting of the chest radiograph and/or high-resolution CT of

### Table 1—Clinical Data

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<tr>
<th>Patient</th>
<th>Present Age, yr</th>
<th>Age at Diagnosis, yr</th>
<th>Age at Presentation to Us, yr</th>
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<th>Current Prednisone Dose, mg</th>
<th>Smoking History, Pack/yr</th>
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Mean±SD 50.1±5.9 39.0±9.8 15.8±11.8

*ASP=Aspergillus fumigatus; RW=ragweed; T=tree; G=grass; DM=dust mite; qd=daily; qod=every other day.

1 Northwestern University Allergy Immunology Service.

### Table 2—Pulmonary Function Data

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Mean±SD 1.62±0.80 2.69±0.81 1.37±0.41 2.48±0.67

*DCO=diffusion of carbon monoxide.
the chest, disclosed no significant structural or infiltrative findings in any patient. The high-resolution CT examinations demonstrated mild pleural thickening in three patients and minimal bronchiectasis was seen in three. No bullous disease, emphysematous changes, or interstitial lung disease was demonstrated in any patient.

As mentioned earlier, no patient had ABPA based on skin testing and serologic analysis. Patient 1, with a remarkably elevated RV and hyperinflated lungs but no bullous disease on radiographic examination, was evaluated for α1-antitrypsin deficiency. His α1-antitrypsin level was within the normal range, and his phenotype was MM, thus ruling out this disorder. This syndrome was ruled out in the other patients by the chest radiograph and high-resolution CT of the chest in that there were no emphysematous bullae or attenuated vascular markings associated with bullous formation.

**DISCUSSION**

Asthma has become recognized as an inflammatory disease of the airways. Although many authors have suggested that this inflammation, if left unchecked, can lead to permanent airways damage, few have clinical data demonstrating this point. In this report, we have described eight patients with long-term asthma who, despite aggressive anti-inflammatory treatment, continue to have moderately severe to very severe airflow obstruction. This finding was also present in the small airways, as reflected by the extremely low FEF25-75% seen in all eight patients with severely reduced FEV1 values. In contrast to a previous study4 that utilized only a 2-week course of systemic corticosteroids, we have shown that the airflow obstruction in our patients is irreversible despite prolonged treatment with daily and alternate-day prednisone and maximal inhaled corticosteroids. We were unable to identify other explanations than seemingly irreversible asthma for the deterioration of lung function despite allergen avoidance, intensive pharmacotherapy, and in one patient allergen immunotherapy. The total cigarette smoking histories included 5, 10, and 2 pack-years in patients 2, 4, and 7, not an explanation for the irreversible obstruction that resisted therapy.

Asthma has been demonstrated in numerous studies to lead to structural changes in the airways. In 1984, Sobonya12 analyzed lung biopsy specimens from six nonsmoking asthmatics with severe, long-standing “allergic” asthma who had not died of status asthmaticus. He found that two of these patients had small airways that were abnormally small, with inflammation and fibrosis seen in the airway walls. The other four had normal small airways. Others have shown, both at autopsy and by bronchoscopic biopsy, the presence of inflammation and extensive remodeling in the airways of patients with asthma.13-17 Basement membrane thickening has been demonstrated to be due to collagen deposition.18 The airway remodeling seen in asthma has been demonstrated to be linked to indexes of asthma severity and contributes to airways hyperactivity.17,19

The macroscopic effects of these structural changes have been examined radiographically. In fact, Kinsella and colleagues20 in 1988 compared the chest CT results often seen in patients with asthma and “irreversible airflow obstruction” with the results of 10 smokers with COPD. However, there was no mention of exactly how the diagnosis of “irreversible” obstruction was made. They found that the patients with asthma demonstrated only hyperinflation without emphysema, while the smokers demonstrated prominent emphysema. However, these scans were not made with high-resolution CT, so thin section analysis was not utilized. Paganin and colleagues21 in 1992 utilized high-resolution CT in their study of 57 adult patients with chronic asthma. Thirty-six (63.1%) patients had normal chest radiographs. Abnormal CT findings were present in 71.9% of the patients studied, with mucoid impaction, lobar collapse, bronchiectasis, bronchial wall thickening, and acinar pattern emphysema seen. However, after 2 weeks of corticosteroid therapy (methylprednisolone, 2 mg/kg/d), the mucoid impaction and lobar collapse were reversed. The bronchiectasis, bronchial wall thickening, and emphysema remained, seen in 10%, 4%, and 4% of patients, respectively. They postulated that these abnormalities likely were secondary to bron-

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**Figure 1.** Trends of FEV1 percent predicted over time for each patient.

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<table>
<thead>
<tr>
<th>Date</th>
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<th>Peak Flow % Pred</th>
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chial destruction by the inflammation from asthma. These findings contrast with those seen in our study, as our patients had normal or minimally abnormal radiographic studies. This may be due to an inadequate course of corticosteroids (2 weeks) in the patients of Paganin et al, as opposed to the long-term oral and inhaled corticosteroid treatment our patients received.

The clinical implications of long-standing asthma have been examined by numerous investigators. Patients with asthma have been reported to have a faster decline in their FEV$_1$ than the general population. Inhaled corticosteroids have been shown to slow this decline, at least in patients with extremely high rates of decline to start. A longitudinal epidemiologic study in Copenhagen added important details to these findings. This study demonstrated that while patients with newly diagnosed asthma experienced a more rapid rate of decline of FEV$_1$ than the general population, patients with chronic asthma did not. Specifically, while the FEV$_1$ values of the patients with chronic asthma were below normal, further decline was at a normal rate. These findings suggest that, possibly, excessive damage to the airways occurs early in the disease process, with later lung function compromised but not declining at an abnormally rapid rate.

This observation is consistent with the findings in five of our patients. These patients had FEV$_1$ values which, while remarkably below normal, over time either improved, remained stable, or declined slowly (Fig 1). While these five patients were receiving daily or alternate-day corticosteroids and inhaled corticosteroids under our care, the pulmonary function had not deteriorated at a rate that would explain their severe airways obstruction. This would suggest that the bulk of the irreversible airways damage inflicted by asthmatic inflammation occurred years ago, possibly quite early in the course of their disease. We were unable to demonstrate emphysematous bullae or other abnormalities such as bronchiolitis obliterans on high-resolution CT. While it is unclear what precipitated such a dramatic loss of pulmonary function in these patients, it appears that in five of our patients, the current corticosteroid treatment has prevented further excessive decline in FEV$_1$.

One can speculate, then, that if aggressive anti-inflammatory therapy had been started earlier in the course of disease, some of this damage to the airways may have been prevented. This would be consistent with the findings of Agertoft and Pedersen, who showed that the extent of inhaled corticosteroid-induced increase in pulmonary function is related to the interval between the onset of asthma symptoms and the start of therapy, in both adults and children. Earlier treatment with inhaled corticosteroids reduced or prevented excessive decline of FEV$_1$. However, as illustrated in Figure 2, patient 3 had a deterioration over time despite alternate-day pred-

![Patient 3](image)

**Figure 2.** Pulmonary function data for patient 3 plotted against time. Data for July 1983 through January 1989 could not be located.
nison and inhaled corticosteroid therapy. He had received regular or nonscheduled β-adrenergic agonists and, previously, theophylline and nedocromil.

Three of our patients demonstrated a rapid, progressive decline in FEV\textsubscript{1} despite aggressive treatment with inhaled and oral corticosteroids. These three patients had FEV\textsubscript{1} values that declined faster than 90 mL/yr. This is in excess of the 20 to 50 mL/yr found in previous studies.\textsuperscript{3,4,24} One patient had continued exposure to a pet dog, despite allergy skin tests that clearly demonstrated the presence of IgE to dog. Although the patient adamantly denied dog sensitivity, it is speculative whether his continued dog exposure allowed the allergic inflammation to damage his airways. Another patient was known to be intermittently noncompliant with office visits.

Additionally, these eight patients may have some component of steroid resistance. While all patients studied responded to oral corticosteroids with reduced symptoms and improved respiratory status and spirometry, and their conditions deteriorated when lowering the prednisone dose was attempted, these patients may have been somewhat less responsive. They may have had an element of relative corticosteroid resistance, in which high levels of inflammatory cytokines are thought to block some of the anti-inflammatory effects of corticosteroids.\textsuperscript{25,26} This notion would be especially plausible in the patient with the continuous presence of a potent stimulus of allergic inflammation (his dog). It is possible that a prolonged course of very-high-dose daily prednisone therapy would have been necessary to avoid the progressive loss of FEV\textsubscript{1}.

In summary, we have described eight patients with long-standing asthma who demonstrate irreversible airways obstruction, refractory to long-term systemic and inhaled corticosteroids. Five of the eight patients would rate as having severe disease with FEV\textsubscript{1} percent predicted <50% with maximal inhaled corticosteroid and oral steroid use.\textsuperscript{27} We did not continue daily prednisone therapy when it became apparent that maximal improvement in respiratory status and FEV\textsubscript{1} had occurred. This irreversible condition may be due to undertreated inflammation early in the course of their disease or unusually aggressive asthma. The term “end-stage asthma” or irreversible asthma might be applied to these patients, who clearly have a component of asthma that is dissimilar from the traditional, reversible inflammation and bronchoconstriction. Pharmacotherapy with long-term alternate-day prednisone, courses of daily prednisone, and inhaled corticosteroids did not prevent the emergence of moderately severe to severe obstructive airways disease. Nevertheless, corticosteroids are valuable in treating such patients and hopefully may prevent additional deterioration of respiratory status and FEV\textsubscript{1}.

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