

At some frequent interval, perhaps once a month, these would be reported to a central data collection center. Of course it would be ideal if each patient could be evaluated to determine if a food (and which food) was actually responsible for the symptoms, but this would be difficult to accomplish.

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High-dose systemic glucocorticoid therapy in the treatment of severe asthma: A case of resistance and patterns of response

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Glucocorticoids are a cornerstone in the treatment of severe asthma, and asthmatic patients who respond poorly to glucocorticoid therapy, ("steroid-resistant" asthmatic patients), are at significant risk for adverse effects while receiving little therapeutic benefit. These patients often receive a prolonged course of glucocorticoids before the initiation of alternative asthma treatments, because the length of an adequate trial or time course of a "normal" response is unknown, and there are no clear markers identifying such patients. This report describes a case of asthma resistant to high-dose glucocorticoid therapy and observations on the time course of clinical response of severe asthmatic children to high-dose glucocorticoids.

CASE REPORT

The patient was a 15-year-old male referred for inpatient evaluation of chronic severe, steroid-dependent asthma treated with alternate day or daily glucocorticoids since age 10 years. During the year before admission he had suffered a respiratory failure and was hospitalized three times. Medications included theophylline, oral and inhaled albuterol, and 30 mg prednisone every other day. Despite the controlled hospital environment, daily measurements of forced expiratory volume in 1 second (FEV₁) taken before bronchodilator use were variable. Twenty milligrams of prednisone three times daily was begun, however, marked lability in pulmonary function continued (Fig. 1, A).

A sleep study revealed no episodes of oxygen desaturation, however, a considerable deterioration in pulmonary function was noted during the night. After 5 weeks of high-dose glucocorticoid therapy (60 mg/day prednisone), bronchoscopy and bronchoalveolar lavage were performed. No foreign bodies or anatomic abnormalities were noted, but the airways and lungs were erythematous and edematous, with whitish mucoid drainage. Analysis of bronchoalveolar lavage fluid was consistent with chronic inflammation¹; total leukocyte count was 310/mm³, with a high proportion of macrophages (75%) and neutrophils (8%).

In the present case, evidence of ongoing airway inflammation was demonstrated despite 5 weeks of high-dose glucocorticoid therapy. To our knowledge this is the first report of bronchoscopy and bronchoalveolar lavage performed in a patient with "steroid-resistant" asthma, and documents that "steroid-resistant" asthma is associated with ongoing or persistent inflammation. Further studies are needed to deter-

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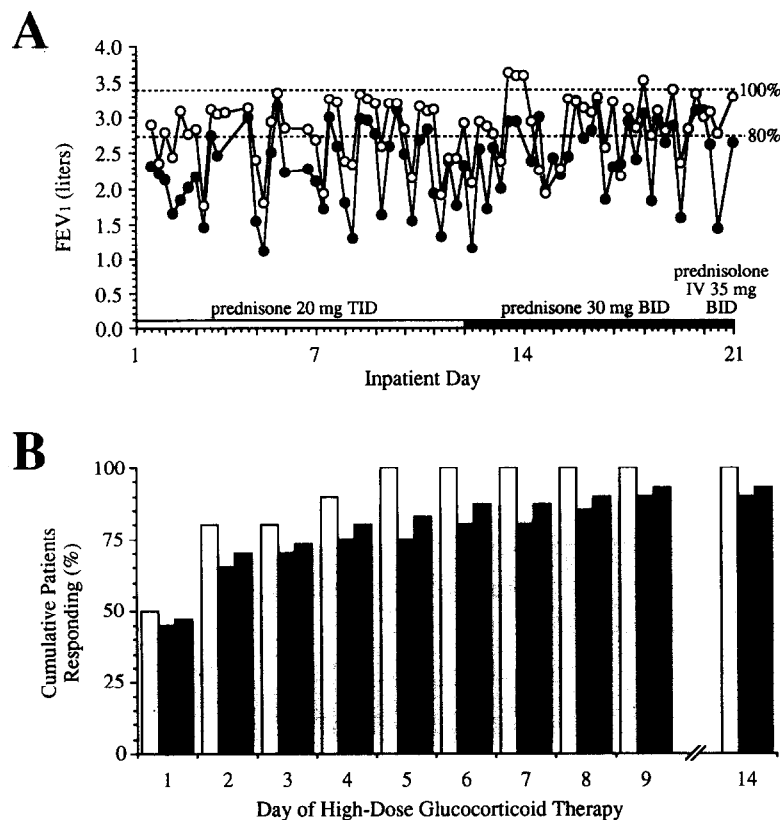


FIG. 1. A, FEV₁, measured before and after bronchodilator use shows marked lability despite high-dose glucocorticoid therapy (the first 3 weeks of hospitalization are illustrated). *Closed circles* denote measurements before bronchodilator use, and *open circles* denote measurements after bronchodilator use. Glucocorticoid doses are noted at bottom of graph, and 80% and 100% predicted values for FEV₁ are denoted by *broken lines*. **B,** Cumulative percentage of patients with a baseline morning pre-bronchodilator FEV₁ before bronchodilator use of 70% or greater who improved by more than 15% after initiation of high-dose glucocorticoid therapy. *White bars* denote patients who did not require maintenance glucocorticoids, *grey bars* denote patients who required maintenance glucocorticoids, and *black bars* denote all patients.

mine the mechanism for this potentially life-threatening form of asthma.

METHODS

To define the length of an adequate trial of glucocorticoids, data were collected from asthmatic inpatients over a 5-month period. All performed spirometry at least four times daily, both before and after bronchodilator use. We included those whose baseline morning measurement of FEV₁ before bronchodilator administration was 70% or less predicted before high-dose glucocorticoid therapy.

Response was defined as improvement of the morning FEV₁ measured before bronchodilator administration by 15% or greater over baseline. We focused on this particular measurement because it appears to be a sensitive and reliable indicator of pulmonary function in the patient with severe asthma, it is not "masked" by frequent bronchodilator treatments during the day, and is often the parameter most influencing the clinician's decision to start high-dose glucocorticoid therapy. Treatment was tapered on the basis of

clinical response. We evaluated the total number of patients responding on each day of treatment; data are described as the cumulative percentage of all patients who improved after high-dose glucocorticoid therapy.

RESULTS AND DISCUSSION

Thirty children with severe asthma (20 male, 10 female) were monitored (mean age, 12.3 years; range, 6 to 17 years). Twenty patients were receiving maintenance glucocorticoids when high-dose therapy was begun; the mean daily maintenance dose before high-dose therapy was 12.6 mg/day (range, 3.75 to 37.5 mg/day). Their mean high-dose treatment dose was 77.4 mg/day (range, 30 to 200 mg/day), whereas the mean dose for those not receiving maintenance glucocorticoids was 53.5 mg/day (range, 40 to 60 mg/day). Overall, the mean dose was 69.4 mg/day, divided into at least two daily doses.

All patients received optimal pharmacologic asthma

therapy before and during high-dose glucocorticoids, including theophylline, maximal doses of inhaled glucocorticoids, and inhaled albuterol at least four times daily. The last bronchodilator treatment of the day was administered between 10 and 12 PM in all patients. In addition, some received oral albuterol ($n = 16$), inhaled cromolyn sodium ($n = 12$), inhaled ipratropium bromide ($n = 2$), and intranasal glucocorticoids ($n = 23$).

Overall, 28 of 30 patients (93%) responded after high-dose glucocorticoid treatment (Fig. 1, B). A response generally occurred within the first 2 to 3 days of high-dose glucocorticoid therapy, with those not receiving maintenance glucocorticoids tending to respond sooner. Two patients, both of whom required maintenance glucocorticoids before high-dose therapy, did not achieve a 15% improvement of their morning FEV₁, measured before treatment with bronchodilator. No differences in glucocorticoid-induced adverse effects, atopic status, or symptomatology were observed between these nonresponders and the responders.

Previous investigators recognized that asthmatic patients resistant to glucocorticoid therapy must be identified early to allow for reduction of unnecessary exposure to glucocorticoids and the subsequent risk for adverse effects.² This also facilitates timely initiation of alternative asthma treatments. Unfortunately, it is often difficult to determine when an asthmatic patient truly is resistant to glucocorticoid therapy. Physiologic patterns of response in asthmatic patients have been described;³ however, no studies have characterized the time course of response to high-dose glucocorticoid

therapy in children with chronic severe asthma. Asthmatic patients have exhibited peak improvement in pulmonary function within 12 hours after a single oral prednisolone dose,⁴ and maximal improvement in pulmonary function has been observed 7 days after initiating twice-daily prednisone in acutely ill asthmatic children.⁵

Our observations characterize the time course of physiologic response for severe, steroid-requiring asthmatic children to high-dose glucocorticoid therapy. All who eventually responded to therapy did so within 10 days of initiating treatment. We conclude that asthmatic patients who do not respond within 10 days of beginning high-dose glucocorticoid therapy can be defined as clinically resistant and may be considered candidates for alternative asthma therapies.

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