Management of difficult asthma

Muzaffar Ahmad, M.D.
Joseph A. Golish, M.D.

Department of Pulmonary Diseases

It is convenient to divide asthma into two main groups: extrinsic and intrinsic asthma. This division is more a difference in triggering mechanisms than in pathophysiology, but it does enable us to formulate a management plan and, to a lesser degree, predict a response to that plan. In extrinsic asthma, the patient should have strongly positive immediate wheal and flare skin tests to antigens and, more importantly, a history to fit the positive skin test. Patients in whom such an association is not found are classified as having intrinsic asthma. Most patients with adult-onset asthma have intrinsic or a mixed type of asthma. Apart from differences in triggering mechanisms, there is also variation in location of airways obstruction (large versus small airways), in response to therapy, in drug requirements, and in degree of reversibility. All these factors make asthmatics an extremely heterogeneous group requiring individualized treatment.

Difficult asthma may be defined as asthma not effectively controlled by around-the-clock use of bronchodilators, by occasional bursts of corticosteroids, and by the addition of another nonsteroidal preparation. Most patients with difficult asthma will be in the group of intrinsic or mixed asthma. Extrinsic asthma is relatively less difficult to treat. After the diagnosis has been confirmed with appro-

priate history and skin tests, asthma is sometimes controlled by removing the offending antigen. However, in most instances, an around-the-clock oral bronchodilator must be added. Of the oral bronchodilators the theophylline compounds should be used as first-line drugs. The variation in theophylline dosage required is well known;[1] therefore, whenever possible, therapeutic levels between 10 and 20 μg/ml should be documented. If the asthma is not effectively controlled, a sympathomimetic drug such as ephedrine (12.5 to 50.0 mg every 6 hours) or terbutaline sulfate (2.5 to 5.0 mg/8 hr) can be added as tolerated. This basic program can be supplemented by inhalation of β_2 stimulators (isoproterenol hydrochloride, isoetharine, metaproterenol sulfate) and an occasional burst of corticosteroids. Fixed drug combinations should be avoided since these make individualization of dosage impossible. The barbiturates contained in some of these preparations reduce the effectiveness of steroids and theophylline by affecting their hepatic metabolism through hepatic enzyme induction. Furthermore, sedatives, tranquilizers, and expectorants used in the combination drugs have their own side effects.

Cromolyn sodium, an antiasthma drug, is not a bronchodilator and works through its ability to inhibit degranulation of the sensitized mast cell and to block the release of the mediators of anaphylaxis from that cell. The drug cannot counteract the effect once these agents are released. It is most effective in extrinsic asthma and should be used when the simpler measures mentioned fail to provide effective control. An adequate trial is a period of 3 to 4 weeks in a dose of 20 mg four times a day delivered through a spinhaler. In some instances, it may completely obviate the need for any other form of antiasthma therapy. It has also been found to have a steroid-sparing effect in some steroid-dependent asthmatics.[2] Cromolyn sodium also inhibits exercise-induced asthma.[3] Immunotherapy (hyposensitization) may be tried as an adjunct to the basic medical management program; however, its effectiveness has not been conclusively proved in clinical studies.

The most difficult cases of asthma are the intrinsic or mixed. These patients should be started on the same basic program used for extrinsic asthma. The clinical entities that mimic asthma should be considered and excluded. The common "asthma mimics" are laryngeal obstruction, endotracheobronchial tumors, cardiac failure, foreign bodies, allergic alveolitis, pulmonary emboli, and occupational asthma. Occupational asthma needs special attention since its recognition may be difficult because of atypical symptoms and often an obscure temporal association with exposure. It appears after repeated exposure; sensitivity increases with time, and reactions are elicited by smaller amounts of the offending agent. There is a long list of precipitating factors in occupational asthma, the discussion of which is beyond the scope of this article, but several excellent reviews have been published.[4] It must be remembered that the incidence of occupational asthma is generally low; however, if unidentified, it can be frustrating to treat by conventional antiasthma measures. The treatment is cleaning the environment or removing the patient from a troublesome work environment.

When diagnosis of intrinsic asthma has been reestablished and the basic plan has not provided effective control,

other occult triggering factors should be looked for and appropriately treated. Most important of these are sinopulmonary infections. Sinus infections in particular may not be apparent and should be studied by direct examination and roentgenograms of the sinuses. It is difficult to control asthma without controlling sinusitis if present. This at times requires somewhat radical sinus operations such as a Caldwell-Luc procedure or a definitive frontal sinus operation. Severe asthma may also be caused by the aspiration of gastric acid in patients with hiatus hernia and demonstrable gastroesophageal reflux. Intensive medical regimens to reduce reflux and acidity may bring notable abatement of symptoms.[5] Surgical restoration of effective lower esophageal sphincter function has proved to be curative in some reported studies.

Several drugs may precipitate bronchospasm in asthmatics. Aspirin is one of the most important of these. Sensitivity to aspirin is more common in asthmatics with nasal polyps (about 15%). It is our policy to advise any asthmatic who has nasal polyps not to use aspirin, even when there is no history positive for aspirin sensitivity. Many over-the-counter compounds contain aspirin. The mechanism of producing bronchospasm may be through interference with prostaglandin synthesis. Other aspirin-like compounds such as indomethacin can also induce asthma. Most aspirin-sensitive asthmatics can tolerate sodium salicylate or acetaminophen, but a few may also have bronchospasm following ingestion of these compounds. About one third of aspirin-sensitive asthmatics have an idiosyncratic reaction to tartrazine (FD & C, yellow dye, No. 5), and since this food color is used in many products, testing an individual for asthma after its ingestion may be worth while. Propranolol may precipitate bronchospasm because of beta-adrenergic blockade and should be avoided by asthmatics.

A small subpopulation of asthmatics not necessarily with extrinsic asthma respond well to around-the-clock use of antihistamines. These patients should be identified in the laboratory by performing pulmonary function tests before and after administration of antihistamine and then documenting response to the treatment with antihistamine. A trial of around-the-clock use of the antihistamine added to the basic program would then be in order. Potassium iodide is thought to be a mucolytic agent, although there is no evidence to support this. There is another subpopulation of asthmatics who respond to potassium iodide on the basis of a mechanism other than the proposed mucolytic activity, and patients with difficult asthma should be given a therapeutic trial of potassium iodide around the clock.[6]

If all the aforementioned measures have been undertaken and adequate control still has not been achieved, corticosteroids should be added. They should always be added to a basic program. Patients with difficult asthma need corticosteroids for control and should always be given instruction about the risk to benefit ratio before steroid therapy is begun. An intermediate strength PPD test should be performed and, if positive, isoniazid prophylaxis must be used during the long-term use of corticosteroids. Slit-lamp examination should be done periodically to look for posterior capsular cataracts. High doses of prednisone (60 to 80 mg/day) should be given for the first few days and then tapered to as low a dose as possible to maintain effective control.

Sometimes a high dose "burst" of corticosteroids tapered to zero over the next few weeks is effective and the asthma can then be controlled by a conventional basic program. A fair number, however, will need maintenance corticosteroids, which should be kept below an adrenal-suppressive dosage when long-term therapy is indicated. If at all possible, alternate-day dosage should be given, because even with as much as 40 to 50 mg of prednisone, methylprednisolone or prednisolone on alternate days, the adrenal-pituitary axis is minimally suppressed. Unfortunately, however, steroid-dependent asthmatics may have trouble on the days they do not receive steroids. These patients should receive the single dose every morning, and split daily doses should be avoided as much as possible, since they can cause the worst adrenal-pituitary axis suppression. Prednisone or prednisolone should be prescribed for chronic use since either is appropriate for alternate-day therapy. When the effective maintenance dose has been established, an attempt should be made to replace it with the inhaled form of synthetic corticosteroid.

Beclomethasone dipropionate (Vanceril, Beclovent) in a daily dose of 400 μg of the drug inhaled is approximately equal to 7.5 mg of prednisone in its effect on asthma.[7] Because of its topical action and minimal systemic absorption, side effects are few. The low incidence (5%) of symptomatic side effects (oropharyngeal candidiasis) contrasts favorably with the 30% rate of systemic side effects with prednisone. Symptomatic candidiasis is effectively treated with nystatin lozenges or suspension. In steroid-dependent asthmatic patients, the addition of topical steroids inhaled can lower the required dosage of systemic oral steroids. Inhaled steroid therapy should be added initially to oral steroid therapy in steroid-dependent asthmatics. Then after 1 to 2 weeks, while inhalation of topical steroid is maintained, the oral steroid (prednisone) dosage is gradually reduced at the rate of 2.5 mg/wk to the lowest maintenance level necessary to control symptoms. During acute exacerbations of asthma, temporary increases in systemic oral steroids may be necessary. No undesirable interactions have been reported during the concurrent use of adrenergic bronchodilator aerosols and beclomethasone dipropionate aerosol. If bronchodilator inhalation is required, it should be given before the topical steroid aerosol to aid deposition into the airways. In steroid-dependent asthmatics, cromolyn sodium may be effective in the reduction or cessation of steroids and should be given at least one 3- to 4-week trial.

Most asthmatics will respond to the therapy just described. However, a few extremely difficult-to-treat asthmatics (asthmatic bears) will not be effectively controlled by the measures mentioned. For these patients, other therapeutic trials are in order. Troleandomycin, a macrolide antibiotic, has been found to have a steroid-sparing effect that cannot be attributed to the antibiotic quality of this drug.[8] Addition of troleandomycin to their program helps about 60% of steroid-resistant patients. It works best with methylprednisolone, and the starting dose is 250 mg of troleandomycin three to four times a day. Response usually occurs within a week and then the antibiotic is tapered to 250 mg/day. Asthmatics who were completely uncontrolled on 60 to 100 mg of prednisone a day may be controlled on 250 mg/day of troleandomycin plus 12 to 16 mg of methylprednisolone every other day.

Such patients recover from the side effects of steroids, and sputum production decreases. Troleandomycin can cause the serum alkaline phosphatase level to rise, and occasionally liver toxicity may force discontinuance of the antibiotic. Troleandomycin also inhibits theophylline clearance. Therefore, the theophylline dosage should initially be reduced by half and then later adjusted, depending on the amount of troleandomycin used and on the measured serum theophylline levels.

Some patients may become unresponsive to aerosolized β-adrenergic stimulators due to overuse, and the removal of these agents is often helpful. A few patients may show a paradoxic response to an agent such as isoproterenol. They may have a bronchodilator effect for the first 15 minutes, followed by much longer bronchoconstrictor effect. These patients may be treated by more specific β_2-adrenergic stimulators such as salbutamol. Another subpopulation of asthmatics responds dramatically to inhalation of atropine sulfate[9] (2 mg of atropine sulfate in 1 ml of saline). Unfortunately, the around-the-clock program of atropine sulfate inhalation causes excessive dryness of the mouth. More recently, aerosol Sch 1000, a derivative of atropine, has been shown to be an effective bronchodilator in asthmatics without any marked side effects.[10] There also appears to be another small subpopulation of asthmatics whose major problem appears to be a hyperactive alpha-adrenergic system. Such patients may respond to treatment with phentolamine.[11] Immunosuppressive drugs of the antimetabolite variety (thioguanosine and 6-mercaptopurine) have been used with some success in asthma.[12] These may have a role in a small percentage of steroid-resistant asthmatics.

Status asthmaticus, a life-threatening emergency, must be treated aggressively with epinephrine (0.3 cc of 1:1000 every 30 minutes for a total of three doses), adequate hydration, supplemental oxygen and intravenous aminophylline (5.6 mg/kg in 30 minutes, followed by 0.4 to

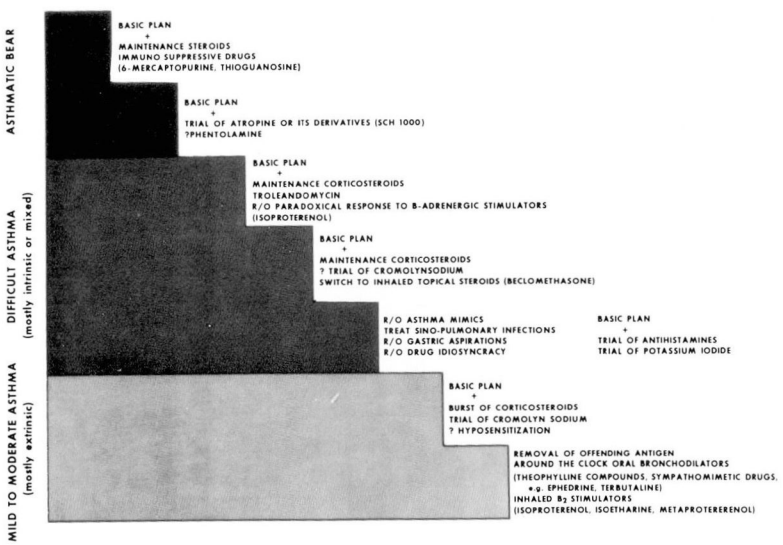

Figure. Step approach to treatment of difficult asthma.

0.9 mg/kg/hr as a maintenance dose). Corticosteroids should be employed early since their onset of action may require 6 to 8 hours. Recommended dosages and reported efficacy vary widely. We recommend an initial dose of 100 mg methylprednisolone sodium succinate intravenously to be repeated at 6-hour intervals. The dose can then be tapered, depending on the patient's response. Progressive respiratory failure often requires mechanical ventilation, and selected patients greatly benefit from bedside fiberoptic bronchoscopy through the endotracheal tube for removal of mucous plugs.

Summary

The approach to the management of difficult asthma should be a well-planned, individualized, step approach (*Figure*). This is mandatory because of the heterogeneity of asthma in adults and variations in the response of the patient to various antiasthma drugs. The basic plan should be adhered to, and steroids followed by steroid-sparing drugs should be added to that basic plan. An occasional patient may respond to treatment with phentolamine or atropine. An essential part of management is understanding on the part of the patient. Status asthmaticus responds to intense therapy with hydration, epinephrine, aminophylline, and steroids.

References

1. Jenne JW, Wyze E, Rood FS, et al: Pharmacokinetics of theophylline. Application to adjustment of the clinical dose of aminophylline. Clin Pharmacol Ther **13:** 349–360, 1972.
2. Munro-Ford R: Treatment of various types of asthma with disodium cromoglycate (Intal); a two year appraisal. Ann Allergy **29:** 8–18, 1969.
3. Palmer KNV, Legge JS: Disodium cromoglycate in exercise-induced asthma. Lancet **2:** 219, 1969.
4. Karr RM, Davies RJ, Butcher BT, et al: Occupational asthma. J Allergy Clin Immunol **61:** 54–65, 1978.
5. Overhold RH, Vorhees RJ: Esophageal reflux as a trigger in asthma. Dis Chest **49:** 464–466, 1966.
6. Siegal S: The asthma-suppressive action of potassium iodide. J Allergy **35:** 252–270, 1964.
7. British Thoracic and Tuberculosis Association. Inhaled corticosteroids compared with oral prednisone in patients starting long-term corticosteroid therapy for asthma. Lancet **2:** 469–473, 1975.
8. Spector SL, Katz FH, Farr RS: Troleandomycin; effectiveness in steroid-dependent asthma and bronchitis. J Allergy Clin Immunol **54:** 367–379, 1974.
9. Cavanaugh MJ, Cooper DM: Inhaled atropine sulfate; dose response characteristics. Am Rev Respir Dis **114:** 517–524, 1976.
10. Storms WW, DoPico GA, Reed CE: Aerosol Sch 1000; an anticholinergic bronchodilator. Am Rev Respir Dis **111:** 419–422, 1975.
11. Logsdon PJ, Carnright DV, Middleton E Jr, et al: Alpha-blockade in treatment of asthma. Lancet **2:** 232, 1972.
12. Asmundsson T, Kilburn KH, Laszlo J, et al: Immunosuppressive therapy of asthma. J Allergy **47:** 136–147, 1971.