Asthma: current strategies for treatment

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■ Mortality from asthma is increasing, raising questions about the goals and adequacy of treatment. It is important to understand the pathophysiology of asthma and the rationale and options for treatment. Asthma, a reversible syndrome of airflow obstruction, is not simply spasm of airway smooth muscle; rather, it is a disease characterized by mucosal edema, mucous hypersecretion, and epithelial damage in the airway. Appropriate medical therapy includes treatment with compounds that specifically suppress airway inflammation. The best approach to treatment may be an anti-inflammatory agent—preferably by inhalation—along with an inhaled direct bronchodilator, with objective measures of airflow limitation to assess disease severity.

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MORTALITY FROM asthma is increasing.[1–2] During the 1960s and early 1970s, the increased mortality was thought to be related to the use of beta-sympathomimetic agents and methylxanthines in treating this disease. But epidemiologic studies and retrospective case reviews argue against this assertion and suggest instead that much of the morbidity and mortality associated with asthma may be linked to inadequate control of the disease.[3]

An analysis of asthma mortality in England suggested that potentially avoidable factors were present in the vast majority of asthma deaths,[4] and it was recently concluded that asthma had been underdiagnosed and ineffectively treated.[5] Factors which were thought to account for underdiagnosis and undertreatment included the patient's inadequate perception of the severity of attacks, lack of objective criteria for treatment, withholding of specific anti-inflammatory medications, and failure to understand how rapidly airflow obstruction can become severe (especially in the setting of marked diurnal variation of airflow).[5] A recent epidemiologic study from Britain[6] supports these conclusions by suggesting that a recent decrease in morbidity for the average patient was associated with an increase in the use of anti-inflammatory medications.

These studies suggest potential causes of asthma mortality, but they must be regarded as preliminary. The prevalence of asthma has not yet been adequately studied, so it is unclear whether the increase in asthma mortality is related to increased disease prevalence or increased case/fatality ratio.[2] Nonetheless, these data highlight the necessity for proper identification, treatment, and monitoring of patients with asthma. Asthma must be thought of as a chronic inflammatory disease which for the most part requires continuous therapy.

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TABLE 1
BRONCHODILATOR THERAPY: PHARMACOLOGY AND DOSAGES

Drug	Recommended initial dosage‡	Duration of action	Selectivity and notes
Albuterol (Proventil, Ventolin)			
Aerosol* (90 µg/activation in 17-g can)	2 puffs q4-6h	3-4 h	Selectivity: $\beta_2 >> \beta_1 >>> \alpha$
Oral (2 or 4-mg tablets)	2-4 mg PO q6-8h	4-6 h	Also available as syrup (2 mg/5 mL) or elixir
Bitolterol (Tornalate)			
Aerosol (0.37 mg/activation in 300-dose container)	2 puffs q6-8h	5-8 h	Selectivity: $\beta_2 >> \beta_1 >>> \alpha$; used infrequently
Epinephrine (Medihaler-Epi)			
Aerosol (0.16 mg epinephrine base/spray in 233- and 350-dose containers)	2 puffs q4-6h	1-4 h	Selectivity: $\alpha = \beta_1 = \beta_2$; parenteral epinephrine labeled for use in acute asthma and hypersensitivity (anaphylactic) reactions
Nebulizer† (1%, 1.25%, 2.25% solutions)	1-4 deep inhalations of spray from 1-2.25% solution q4-6h	1-4 h	
SC or IM (1:1000 [1 mg/ml] or 1:200 solution)	0.3-0.5 mg SC or IM every 20 min to 4 h as required	1-4 h	
Isoetharine			
Aerosol (Bronkometer: 340 µg/activation in 200- and 300- dose containers)	2 puffs q4h	1-3 h	Selectivity: $\beta_2 > \beta_1 > \alpha$
Nebulizer (Bronkosol: 0.062%, 0.08%, 0.1%, 0.2%, 0.25%, 0.5%, 1% solutions)	3-7 deep inhalations of spray from 0.1-1% solution q4h	1-3 h	
Isoproterenol (Isuprel, Medihaler-Iso)			
Aerosol (80 µg and 131 µg/activation, 300- and 450-dose containers)	1 or 2 puffs q4-6h	0.5-2 h	Selectivity: $\beta_2 = \beta_1 >>> \alpha$
Nebulizer (0.031%, 0.062%, 0.25%, 0.5%, 1% solutions)	5-15 deep inhalations of spray from 0.031-1% solution q4h	0.5-2 h	
Sublingual (10-mg tablets)	10-20 mg SL q6h	1 h	
IV (0.2 mg/mL)	0.01-0.02 g IV, repeated as necessary	0.5-2 h	Indicated for bronchospasm during anesthesia
Metaproterenol (Alupent, Metaprel)			
Aerosol (0.65 mg/dose in 255-mg container)	2 or 3 puffs q6-8h	3-4 h	Selectivity: $\beta_2 >> \beta_1 >>> \alpha$
Nebulizer (available in unit dose [0.6%] and multidose [5%] vials; a unit dose vial is equivalent to 0.3 mL of 5% solution diluted to 2.5 mL)	1 unit dose vial q4-6h (or more frequently in emergency treatment)	3-4 h	
Oral (10-, 20-mg tablets)	10-20 mg PO q6-8h	4 h	Also available as syrup (10 mg/5 mL) or elixir
Pirbuterol (Maxair)			
Aerosol (0.2 mg/activation in 25.6-g can)	2 puffs q6h	4-6 h	Selectivity: $\beta_2 >> \beta_1$
Terbutaline (Brethine, Bricanyl)			
Aerosol (0.2 mg/activation in 10.5-g can)	2 puffs q4-6h	3-6 h	Selectivity: $\beta_2 >> \beta_1 >>> \alpha$
Oral (2.5-, and 5-mg tablets)	2.5-5 mg PO q6h	4-8 h	
SC (1 mg/mL)	0.25 mg SC q15-30 min (total dose should not exceed 0.5 mg in 4 h)	1.5-4 h	

(CONTINUED)

PATHOPHYSIOLOGY

Current understanding of the mechanisms involved in this disease has developed from the observation of airway hyperresponsiveness or hyperreactivity to nonspecific stimuli[7-9] and the observation of early and late bronchial responses to "allergic stimuli."[10] These have led to the concept of asthma as an inflammatory disease of the airway.

In asthmatic patients, the airway responds to certain physical and chemical stimuli with abnormal bronchoconstriction (decreased forced airflow or increased airway resistance). Bronchial challenge—with cholinergic agonists, histamine,[11] exercise,[12] inorganic compounds such as sulfur dioxide,[13] and a host of organic compounds—causes exaggerated bronchoconstriction, or bronchial hyperreactivity, in asthmatic patients, as compared with nonasthmatic individuals.[7]

Initially, this bronchial hyperreactivity was thought to result from alterations in the size, geometry, and function of smooth muscle, or of alterations in the afferent and efferent fibers of the autonomic nervous system which invests the airway.[7] However, new research suggests that inflammatory processes in the airway may induce hyperreactivity by affecting local nerves, muscles, or vascular cells and tissues. Studies in dogs[14] and in humans[15] suggest that airway hyperreactivity after exposure to ozone is associated with the influx of inflammatory cells and the recovery of the mediators of inflammation from the airway lining fluid. Thus, airway hyperreactivity may result from change in the inflammatory milieu of the airway.

TABLE 1
BRONCHODILATOR THERAPY: PHARMACOLOGY AND DOSAGES – CONTINUED

Drug	Recommended initial dosage‡	Duration of action	Selectivity and notes
Antimuscarinic drugs			
Atropine sulfate, nebulizer (0.2%, 0.5% solutions)	0.025 mg/kg diluted with 2-5 mL saline and given q6-8h	4-8 h	
Ipratropium (Atrovent) aerosol (18 μg/actuation in 200-dose metered-dose inhaler)	2 puffs q6h (or more frequently if necessary)	4-8 h	
Methylxanthines			
Theophylline and derivatives			For IV use in patients with normal hepatic function, a loading dose of 5 mg theophylline/kg body weight is given over 3 min, followed by an infusion of 0.7 mg/kg/h; in congestive heart failure or hepatic disease, maintenance dose should be corrected for percentage content of theophylline base
Aminophylline (79% theophylline)			
Oral (100- and 200-mg tablets)	300 mg PO q6-8h	6-12 h	
Oral, controlled release (225-mg tablets)	225-675 mg PO q8-24h	8-24 h	
Oral, solution (105 mg/5 mL)	200 mg PO q6-8h	6-12 h	
Rectal, solution (300 mg/5 mL)	200 mg rectally q6-8h	6-12 h	
IV (250 mg/10 mL, 500 mg/2 mL)	See Notes	6-12 h	
Oxtriphylline (64% theophylline [Choledyl])			
Oral (100- and 200-mg tablets)	200 mg PO q6h	6-12 h	Also available as syrup (50 or 100 mg/5 mL) or elixir
Oral, sustained release (400- and 600-mg tablets)	400-600 mg PO q12h	8-24 h	
Theophylline			
Oral (Elixophyllin, Slo-Phyllin); 100-, 125-, 200-, 250-, 300-mg tablets and capsules	3 mg/kg PO q6-8h	6-12 h	Also available as syrup (26.7 or 50 mg/5 mL) or elixir; for IV use in patients with normal hepatic function, a loading dose of 5 mg/kg is given over 30 min, followed by infution of 0.5-0.7 mg/kg/h; in congestive heart failure or hepatic disease, the maintenance dose should be decreased. When theophylline salts or complexes are used, the dose should be corrected for percentage content of theophylline base
Oral, sustained release (Elixophyllin SR, Theo-Dur, Theo-24, Uniphyl); 65-, 130-, 260-, 300-mg capsules, tablets)	9 mg/kg/d PO, given as a single daily dose or in 2 or 3 divided doses	8-24 h	
IV (theophylline and 5% dextrose); 200, 400, or 800 mg/container)	See Notes	6-12 h	
Theophylline sodium glycinate (44.5-47.3% theophylline [Synophylate])			
Oral (330 mg/15 mL elixir)	330-660 mg PO q6-8h	6-12 h	
Dyphylline			
Oral (200- and 400-mg tablets)	15 mg/kg PO q6h	6-8 h	Although dyphylline is a theophylline derivative, it is not metabolized to theophylline and is not measured by conventional assays for serum theophylline; parenteral solution not for IV use
Elixir (33.3 and 53.3 mg/5 mL)	15 mg/kg PO q6h	6-8 h	
IM (250 mg/mL)	200-250 mg IM slowly; maximum, 15 mg/kg in any 6-h period)	6-8 h	

* "Aerosol" refers to pressurized metered-dose nebulizers; they should be activated twice, and directions for inhalation should be followed carefully. Accessory spacer devices have improved the efficacy of delivery of medication to the airways.
† "Nebulizer" refers to hand-held, bulb-operated nebulizers; they differ in the output and particle size of the aerosol generated and thus differ in the dose delivered per breath and in the relative distribution to the mouth and the airways.
‡ These are the recommended maintenance doses; patients may need to use the inhaler more frequently for full control of symptoms.

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Asthmatic patients show a distinct pattern of response to stimuli. In susceptible individuals, inhalational challenge to the airway with antigen provokes an early decrease in forced expiratory flows with a subsequent return toward baseline, followed by a further decrease in airflow after 3 or 4 hours.[10] In animal models of airway antigen exposure, these early[16] and late[17] responses are associated with the release of mediators of inflammation and the infiltration of inflammatory cells. Limited studies which assessed mediator release and cellular influx or activation after antigen challenge in human asthmatics suggest similar processes.[18,19] A recent study of mucosal biopsies in stable asthmatics has shown mucosal infiltration with inflammatory cells and evidence of chronic inflammation—both of which appeared to increase after antigen challenge.[20]

This research suggests that bronchial hyperreactivity and clinical asthma may be consequences of airway inflammation, with attendant effects on the local "effector" cells and tissues—epithelial, smooth muscle, nervous, and vascular. If this is so, then compounds that modulate or reduce airway inflammation may control exaggerated bronchoconstriction when it results from stimuli that initiate or potentiate inflammation. Indeed, studies have shown that anti-inflammatory compounds attenuate responses to antigen[21] and nonspecific stimuli such as sulfur dioxide.[22]

These recent studies confirm that asthma is a chronic disease of airway inflammation. More than an acute episodic illness, asthma is a continuous, persistent process needing long-term suppressive or prophylactic therapy.[5]

PHARMACOLOGY

Based upon the pathophysiology of asthma, its pharmacologic therapy can be divided into two categories: direct bronchodilators and anti-inflammatory compounds. Direct bronchodilators, which include the beta-sympathomimetic agents, anticholinergic agents, and methylxanthines, effect immediate bronchial relaxation by direct action on bronchial smooth muscle, resulting in an immediate decrease in airway resistance and an increase in forced expiratory flow. Anti-inflammatory compounds such as corticosteroids and cromolyn are widely used to suppress airway inflammation for long-term control of asthma.

The clinical pharmacology of these compounds has been recently reviewed.[23,24] The important principles are outlined here.

Direct bronchodilators

Beta-adrenoceptor agonists have been widely used in the treatment of acute bronchospasm. While their direct action is to relax smooth muscle by stimulating beta-2 receptors, they have other beneficial effects when given by inhalation: they promote mucociliary clearance and may have synergistic effects with corticosteroids or cromolyn on inflammatory cells to modulate airway inflammation. They may also help to reduce mucosal edema.

Clinical trials have shown that inhalation provides the most effective delivery of beta agonists with the fewest side effects. Oral beta agonists have a greater toxic-to-therapeutic ratio.[25] A growing clinical consensus prefers adequate regular use of aerosolized beta agonists over oral therapy in treating chronic disease, and over subcutaneous or intravenous therapy in treating acute disease (*Table 1*).

The rise in asthma mortality over the last three decades has been paralleled by an increased use of beta-agonist medications. Despite concern that the rise in mortality may be related to "overuse" of beta-agonist compounds, no data substantiate this contention. Scattered reports suggest "catecholamine toxicity,"[26] but retrospective studies associate these trends in mortality with underuse rather than overuse of medications. Another implicating factor is the widespread belief that regular use of these medications will cause them to become less effective. Controlled studies have shown that this phenomenon—tachyphylaxis—is not observed in asthmatic patients.[27–29]

Anticholinergic and antimuscarinic drugs. The effect of atropine and similar compounds on airway resistance and forced expiratory flows[30] and the clinical utility of these compounds in relieving bronchospasm[31,32] have been known for some time. It is thought that these compounds relax airway smooth muscle by blocking muscarinic receptors, thus inhibiting tonic vagal discharge and reflex vagal stimulation.

Because of systemic side effects of atropine and a negative effect on mucociliary clearance, anticholinergics fell out of favor. But with the advent of ipratropium bromide—a quaternary ammonium congener of atropine—this class of compounds is now of major importance in the treatment of bronchospastic disease. When delivered as an aerosol, ipratropium is not appreciably absorbed from the airway, and has no adverse affects on mucociliary clearance.[33] Additionally, a recent study found no evidence of tolerance to the bronchodilating effects of atropine-like compounds (*Table 1*).[34]

Methylxanthines. Asthma has been treated with methylxanthines for more than 100 years. Though once thought to cause bronchodilation by inhibiting phosphodiesterase in airway smooth muscle, serum concentrations necessary to inhibit this enzyme are not reached in clinical use.[35] Current understanding of the action of methylxanthines focuses on their role as an antagonist of adenosine.[36] It is thought by some that theophyllines do not affect airway inflammation or bronchial hyperreactivity. They are weak bronchodilators compared to the inhaled agents.[37] The role of methylxanthines in the treatment of acute and chronic reversible airway obstruction is being reevaluated.[38]

Although traditional teaching has been that "adequate" dosing of theophylline requires blood levels between 10 and 20 mg/L, recent work suggests that much of the bronchodilation is seen at levels up to 10 mg/L, and that the small additional effect seen at higher levels occurs with increasing toxicity.[39] Methylxanthines may have an additional role in chronic obstructive airway diseases because of their apparent beneficial effect on respiratory muscles (*Table 1*).[40]

Anti-inflammatory compounds

The anti-inflammatory mechanisms of corticosteroids in the airway are not completely understood. Although they appear to modulate the production of various inflammatory compounds (including prostaglandins, leukotrienes, and peptide hormones), the exact mechanism or mechanisms responsible for decreasing inflammation in the airway are yet unclear.

TABLE 2
ANTI-INFLAMMATORY THERAPY: PHARMACOLOGY AND DOSAGES

Drug	Recommended initial dosage*	Duration of action	Selectivity and notes
Cromolyn sodium (Intal)			
Aerosol (800 µg/actuation in 200-dose container)	2 puffs q6h	6-8 h	Nebulizer dose represents one spinhaler capsule or one 2-mL ampule of solution for nebulization; special nasal inhalers available for use in hay fever
Nebulizer (20 mg capsules for spinhaler; 20 mg/1 mL solution)	20 mg by nebulizer q6h	6-8 h	
Corticosteroids, aerosol			
Beclomethasone (Beclovent, Vanceril); 42 µg/actuation in 200-dose container	2-4 puffs q6-8h	12-24 h	Special nasal inhalers available for use in hay fever
Dexamethasone sodium phosphate (Decadron Phosphate Respihaler); 84 µg/actuation in 170-dose container	1-3 puffs 16-8h	12-24 h	Special nasal inhalers available for use in hay fever
Flunisolide (AeroBid); 250 µg/actuation in 50-dose container	1-2 puffs q12h	12-24 h	Significantly more expensive than beclomethasone; special nasal inhalers available for use in hay fever
Triamcinolone acetonide (Azmacort); 100 µg/actuation in 240-dose container	1-2 puffs q6-8h	18-36 h	
Corticosteroids, oral			
Prednisone (Meticorten); 5-mg tablets	5-60 mg PO q24h	18-36 h	Treatment of severe asthma may begin with dose of 30-60 mg/d, usually administered as single morning dose
Corticosteroids, parenteral			
Hydrocortisone sodium succinate (Solu-Cortef); 100-, 200-, 500-, 1000-mg vials	100-500 mg IV, for status asthmaticus requiring rapid-onset corticosteroid therapy; dosage (range varies from that listed to four times as much) may be repeated q6h as needed to control symptoms†	8-12 h	
Methylprednisolone acetate (Depo-Medrol); 20-, 40-, 80-mg/mL	80-120 mg IM q5-10d as alternative to oral corticosteroids for prolonged corticosteroid action in severe asthma	7-14 d	Used rarely, as a last resort; 4 mg methylprednisone is approximately equivalent to 5 mg prednisone
Methylprednisolone sodium succinate (Solu-Medrol); 40-, 125-, 500-, 1000-mg vials	30-60 mg IV for status asthmaticus requiring rapid-onset corticosteroid therapy; dosage (range varies from that listed to four times as much) may be repeated q6h as needed to control symptoms†	18-36 h	

*For control of symptoms, patients may require higher doses of inhaled steroids than these initial doses. Dosage is tapered slowly as condition improves; if possible, alternate-day therapy is substituted for daily dosage, or aerosol corticosteroids replace systemic agent; many patients require corticosteroid therapy only intermittently.
†From Summer WR. Status asthmaticus. Chest 1985;87(1 Suppl):87s.

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Inhaled forms of corticosteroids were developed to maximize efficacy and decrease the substantial side effects of long-term steroid therapy.[41] Even at high doses, inhaled corticosteroids exert minimal effects on the pituitary adrenal axis, and rarely manifest the toxicity of other methods of delivery.[42] Patients may use inhaled preparations for a number of years without serious systemic toxic effects. Local effects such as hoarseness and oral thrush have been noted, but these can be minimized with adequate cleansing of the mouth and pharynx, and by use of a spacer device (*Table 2*).

The clinical effects of cromolyn were initially thought to derive from its ability to prevent the degranulation of mast cells.[43] Now it is believed to have other properties, since it can inhibit the effect of SO_2 on the asthmatic airways—a process which many believe is not mast-cell mediated.[22] Cromolyn is not

appreciably absorbed from the airway, so it has minimal systemic side effects–most notably, local irritations in the upper airway (*Table 2*).

TREATMENT

The view that asthma is underdiagnosed and undertreated, joined with indications that airway inflammation contributes to the pathogenesis of this disease, leads to the prevailing treatment of asthma—a suppressive and prophylactic regimen with available anti-inflammatory compounds. The goals of treatment are to maximize or normalize forced expiratory flows and decrease the lability of airflow obstruction[44] while controlling symptoms.

Patients with asthma can have significant airflow obstruction, yet remain relatively asymptomatic; therefore, basing therapy on symptoms alone may be inadequate.[45] Treatment must be based on objective measures of pulmonary function in order to adequately assess and achieve the therapeutic objectives.

Acute bronchospasm

Over the last 10 years, a number of studies have assessed the efficacy of direct bronchodilators and the role of suppressive, anti-inflammatory medication in the acute setting. A consensus is developing that inhaled beta-sympathomimetics are more effective than intravenous aminophylline or subcutaneous beta agonists, and are as effective as combinations of these medications.[46] One study suggested that, in the emergency setting, aminophylline did not contribute to bronchodilation but rather added toxicity to an adequate regimen of inhaled beta agonist (15 mg/h of inhaled metaproterenol).[47] Others have used 5 mg of albuterol with similar results. Although a recent meta analysis of aminophylline in the treatment of acute bronchospasm neither supports nor rejects its use,[48] there is a growing belief that theophylline may be more toxic than effective in this setting.[38,39,49]

Antimuscarinic agents, with or without inhaled beta agonists, may have a role in the treatment of acute asthma. Recent studies suggest that ipratropium plus a beta agonist may be more efficacious than a beta agonist alone.[50–52] Other trials however, dispute these claims.[53]

In acute asthma, corticosteroid therapy is important for the treatment of symptoms and improvement of forced expiratory flows. Corticosteroids administered in the emergency room decrease symptoms and reduce the need for recurrent acute treatment in the post-attack period.[54] A study of patients with acute bronchospasm found significant increases in forced expiratory flows in patients receiving corticosteroids, while those treated only with direct bronchodilators did not show sustained, progressive improvement.[55] Adequate doses of oral corticosteroids can be as effective as intravenous corticosteroids in the acute setting;[56] however, inhaled corticosteroids are not effective and may actually worsen airflow obstruction. It is suggested that patients previously using this therapy resume it once their condition has stabilized and begun to improve on oral corticosteroids.

Outpatient management strategy

The goal of outpatient therapy should be the prevention of attacks, relief of symptoms, and improvement in airflow obstruction (based on objective measures of pulmonary function). Symptoms of chronic asthma may be mild and transient, occur only during exercise or on exposure to cold air, or be chronic and persistent.

In very mild asthma, inhaled sympathomimetics or inhaled anticholinergics taken on a regular schedule (such as two puffs two or three times per day) appear to be the safest and most effective treatment to control symptoms and to maximize airflow. Oral beta sympathomimetics seem to be less effective, and have higher side effects than the inhaled form. Patients who would rather take pills may be treated for symptoms and airflow limitation with oral methylxanthines rather than inhaled sympathomimetics.

When symptoms occur only during exercise or cold exposure, prophylactic use of an inhaled beta agonist or cromolyn may be adequate. Some patients may complain of only nocturnal chest tightness and wheezing. Methylxanthines—in a 24-hour sustained release preparation (usually taken at bedtime) or twice-a-day preparations—have been suggested as treatment for this syndrome; the use of oral beta-sympathomimetics for this purpose has also been promoted.[57,58] However, because nocturnal symptoms are associated with significant bronchial hyperresponsiveness and daytime airflow limitation, patients with persistent night-time symptoms may have significant airflow lability, and may be at a higher risk for severe attacks. These patients should therefore be treated in a suppressive and prophylactic manner with anti-inflammatory agents.[59,60]

Patients with labile airflow or persistent airflow limitation—with or without significant symptoms—probably require treatment with anti-inflammatory agents. Inhaled corticosteroids can decrease bronchial

hyperreactivity, prevent the late asthmatic response to inhaled antigen, and decrease symptoms and airflow obstruction. Conventional inhaled anti-inflammatory agents are administered shortly after use of an inhaled direct bronchodilator, usually a beta agonist. The initial direct bronchodilation, in theory, improves deposition of the steroid aerosol in the airway. The patient uses these medications in sequence two, three, or four times a day (depending on the preparation used and patient preference). If symptoms dictate, the direct bronchodilator alone is used between this schedule. Higher doses of aerosolized corticosteroids than commonly recommended by the manufacturer are frequently necessary for adequate control of symptoms and improved airflow.[61] Even at high doses this medication is absorbed sparingly into the bloodstream, and systemic effects are infrequently seen.[42]

Pharmacologic recommendations

The initial control of moderate-to-severe bronchospasm is usually achieved by a short tapering course of oral corticosteroids with the introduction of an inhaled preparation during the taper. Inhaled corticosteroids are usually ineffective in the initial control of severe symptoms and may cause increased cough and wheezing in some patients until severe symptoms and airflow limitations are controlled. As the oral corticosteroids are tapered, the dose of inhaled corticosteroids may have to be increased to maintain airflow and prevent symptoms.

Once a patient's airflow has been normalized and symptoms are in remission, a slow tapering of both inhaled anti-inflammatory agents and inhaled bronchodilators can be undertaken. A reasonable but uninvestigated goal is to taper the direct bronchodilator and to maintain the patient on the lowest dose of inhaled anti-inflammatory agents that maintains the patient symptom-free with normal spirometry and peak flow throughout the day.

In some cases, inhaled cromolyn can be substituted for inhaled corticosteroid therapy. A recent study[62] documented the efficacy of cromolyn treatment in improving airflow and controlling symptoms for adults with asthma. As with inhaled corticosteroids, higher than recommended doses may be necessary for adequate control.

In patients who are taking only oral corticosteroids, adequate inhaled doses of corticosteroids or cromolyn can decrease the dependency and side effects of oral corticosteroids. In these cases, doses of inhaled medication are increased while the oral corticosteroids are slowly tapered. In many cases oral corticosteroids can eventually be discontinued, though some patients will continue to require oral corticosteroid treatment in addition to inhaled anti-inflammatory compounds. If oral steroids are necessary, the lowest possible alternate daily dose that maintains optimal airflow is the preferred treatment.

It is controversial whether methylxanthines add any benefit to the above treatment protocols;[63] a prevailing feeling is that they probably do not add to adequate anti-inflammatory and inhaled beta agonist treatment.

Alternatives to steroid therapy. The frequency of side effects from long-term use of corticosteroids has prompted investigation of alternate or complementary anti-inflammatory agents. Recently, it has been suggested that the adjunctive use of methotrexate may permit the reduction of steroid dose in severely asthmatic patients who are steroid-dependent.[64,65] In patients who required oral corticosteroid therapy despite maximal inhaled corticosteroid therapy, methotrexate appeared to decrease oral corticosteroid dosage while maintaining or improving symptoms and forced expiratory flows.[65] Low-dose methotrexate was used, beginning at 7.5 mg per week orally or intramuscularly and adjusted up to 50 mg per week. Few side effects were seen, and these included nausea (with oral preparations), stomatitis, and transient transaminitis.

Other investigators have suggested that gold compounds might be useful in asthma.[66]

Spacer devices. The proper delivery of the aerosolized particles to the airway is critical to aerosolized therapy. Under the best circumstances, only 10% of an actuation from a metered-dose inhaler is delivered to the lungs, while 80% is deposited in the oropharynx.[67] In many patients, hand-mouth discoordination will cause this ratio to be even lower. Spacer devices allow maximum airway deposition by optimizing particle size and distribution, and by achieving a proper flow rate of the aerosol into the lung.[68,69]

Environmental factors

The environment may include many sensitizing agents, ranging from household allergens to occupational chemicals, which can promote and potentiate airway inflammation.[70] Removal or avoidance of these exogenous substances can be critical in controlling asthma. Simple measures such as removing pets, using rugs to control dust, placing plastic coverings on beds or pillows, and frequent cleaning of central heating and air conditioning systems may be all that is necessary to control symptoms and improve airflow.

Although "food allergies" are not thought to contribute significantly to adult asthma,[71] some asthmatic patients may be sensitive to certain chemical additives, such as sulfites and artificial food colorings. Avoiding foods with these additives may improve the patient's condition.[72] More complex economic and social issues may be involved when exposure to airway sensitizing agents results from their presence in the work place.[73]

Immunotherapy

"Allergy" testing (assessing intradermal skin sensitivity or serum immunoglobulin titers) and subsequent immune desensitization therapy is widely used in treating many "allergic" diseases, despite little evidence that desensitization is effective in treating asthma in adults. Some studies have shown specific decreases in bronchial reactivity after desensitization to a specific antigen,[74] but few studies document clinical improvement. Problems with standardization of antigen and appropriate patient selection have made these studies difficult to perform. Most physicians who treat asthma believe that immunotherapy to single, specific antigen is a last resort if asthma is inadequately controlled by avoidance and drug treatment.[75,76]

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