Chapter 6
Medical Management of Asthma

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Introduction

Asthma is a chronic inflammatory disorder of the airways characterized by bronchial hyperresponsiveness (BHR) to a variety of stimuli and widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. Patients with asthma frequently have symptoms which can lead to limitations of daily activities, interrupted sleep, hospitalizations, and emergency department (ED) visits, and in small but significant group of patients, asthma can cause death.

The goal of asthma treatment is to enable patients with asthma to lead a normal life with minimal or no symptoms or exacerbations. Asthma has been traditionally classified based on frequency of symptoms and degree of airway obstruction into the following categories: mild intermittent, mildpersistent, moderate persistent and severe persistent (Table 6.1) (Global Initiative for Asthma (GINA) 2006). However, this classification has been recently modified and emphasis has moved away from severity classification toward classifying asthma by level of control. According to a new classification, patients with asthma should be categorized as controlled, partly controlled or uncontrolled (Table 6.2). This new concept recognizes that asthma is a disease with variable presentation where an individual's asthma symptoms may change over months or years. While severity reflects the chronic, underlying state of the disease, asthma control better reflects the variable day-to-day pattern of asthma. Therefore, the emphasis is placed on the periodic assessment of a patient's symptoms and the responsiveness to treatment. Studies suggest that the close monitoring of patients in this manner may lead to better treatment and prevention of asthma symptoms (Bateman et al. 2004).

Various therapeutic regimens have previously been proposed for different asthma severity categories. The most updated set of guidelines for asthma management have been released by Global Initiative for Asthma (GINA) in November of 2006 (Global Initiative for Asthma (GINA) 2006). In this chapter, we will discuss the new guidelines for asthma management, including the properties, efficacy and safety of the most common asthma medications, as well as recommendations for their use. The medications will be divided as they are in the various guidelines, into short-term reliever medications and controller medications. It must be noted that not all controller medications are additionally anti-inflammatory.

Medications: Short-Term Relievers

Short Acting Beta-2 Agonists

Pharmacology

Short acting beta-2 agonists (SABA) relax bronchial smooth muscle by binding to beta-2 agonist receptors on a smooth muscle cell. This leads to increases in cyclic AMP (cAMP) and subsequent relaxation of a smooth muscle cell. Additionally, relaxation of airway smooth muscle by β agonists may also involve the opening of potassium channels, without the involvement of cAMP

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Table 6.1 Classification of asthma severity by clinical features before treatment (From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (2006). Available at http://www.ginasthma.org/)

Intermittent
Symptoms less than once a week Brief exacerbations Nocturnal symptoms not more than twice a month • FEV_1 or PEF ≥ 80% predicted • PEF or FEV_1 variability < 20%
Mild Persistent
Symptoms more than once a week but less than once a day Exacerbations may affect activity and sleep Nocturnal symptoms more than twice a month • FEV_1 or PEF ≥ 80% predicted • PEF or FEV_1 variability < 20 – 30%
Moderate Persistent
Symptoms daily Exacerbations may affect activity and sleep Nocturnal symptoms more than once a week Daily use of inhaled short-acting β_2-agonist • FEV_1 or PEF 60-80% predicted • PEF or FEV_1 variability > 30%
Severe Persistent
Symptoms daily Frequent exacerbations Frequent nocturnal asthma symptoms Limitation of physical activities • FEV_1 or PEF ≤ 60% predicted • PEF or FEV_1 variability > 30%

(Giembycz and Newton 2006). Other important activation pathways have been described as well, which are beyond the scope of this chapter. Finally, beta-2 agonists may also exert nonbrononchodilator, anti-inflammatory actions, which have been suggested from some studies (Giembycz and Newton 2006). Beta-2 agonist receptors can be found on many pro-inflammatory cells and immune cells, including mast cells, macrophages, neutrophils, lymphocytes, and eosinophils. However, the clinical significance of these anti-inflammatory actions remains to be fully determined.

Efficacy

SABAs are the bronchodilators of choice in asthma and response to these agents (12% or greater improvement in FEV1) is a key element in the diagnosis of asthma. They are the most potent bronchodilators and should be used as rescue or reliever medications following the onset of bronchoconstriction for any number of reasons. In addition, they can be used prophylactically for the prevention of exercise-induced bronchospasm, being the most efficacious therapy for this condition.

General Usage

Most SABAs come as aerosol inhalers (metered dose inhalers (MDI)). The inhaled SABAs generally act within 10 min and have a duration of action of 4–5 h. A typical dose for the prevention and or treatment of acute episodes of bronchospasm is two inhalations as needed every 4–6 h. The majority of SABAs come in racemic form, 50:50 mixture of the left-sided (inert form) and right-sided (active form) enantiomers. Levalbuterol (Xopenex) is a right-sided Albuterol enantiomer and is typically dosed three times daily as needed. The drugs in this class are generally equally effective when used in comparable doses. These medications should not be dosed on a regular schedule, but rather as needed (Drazen et al. 1996).

Table 6.2 Levels of asthma control (From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (2006). Available at http://www.ginasthma.org/)

Characteristic	Controlled (All of the following)	Partly Controlled (Any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/ rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV_1)‡	Normal	< 80% predicted or personal best (if known)	
Exacerbations	None	One or more/year*	One in any week†

* *Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate.*
† *By definition, an exacerbation in any week makes that an uncontrolled asthma week.*
‡ *Lung function is not a reliable test for children 5 years and younger.*

The frequency of use of SABAs can also be used as a surrogate marker for asthma control, with an increase in use indicative of poor asthma control. Use of two or more canisters per month is associated with an increased risk of a severe, life-threatening asthma attack (Suissa et al. 1994).

Safety

The common side effects of SABAs are tachycardia, skeletal muscle tremor, headache, and irritability. The selectivity of these agents for the beta-2 receptor limits the cardiotoxicity of these drugs, which would occur through activation of the beta-1 receptor. However, at high doses, activation of the beta-1 receptor does occur. Hyperglycemia has been described, especially in children, with an overdose of SABAs. Hypokalemia has been noted in patients using high doses of albuterol, if they are already at risk for hypokalemia (e.g., diuretic use). These metabolic side effects are usually not seen with standard therapeutic doses of beta-2 agonists. Several recent studies have suggested that regular use of albuterol may lead to lower peak expiratory flow rates in patients homozygous for the arginine allele at codon 16 of beta agonist receptor (Israel et al. 2004).

Anticholinergics

Pharmacology

Acetylcholine, the most important neurotransmitter of the vagal nerve and parasympathetic pathway, plays a critical role in maintaining normal airway tone. In addition, it increases bronchial constriction by binding to muscarinic (M) receptors M3 on smooth muscle cells in bronchi and trachea. An additional important M receptor is the M2 receptor, which inhibits the release of acetylcholine from parasympathetic nerve endings in the airway. In contrast to antagonism of the M3 receptor, if the M2 receptor is blocked or downregulated, it may lead to increases in vagally induced bronchial constriction (Bowerfind et al. 2003).

Anticholinergic agents inhibit bronchial smooth muscle contraction by binding to M3 receptors and hence blocking the effects of acetylcholine. Ipratropium binds to M2 and M3 receptors with equal affinity, suggesting that its clinical efficacy may be limited by binding to the M2 receptor leading to increased release of acetylcholine and augmented bronchial constriction (Maclagan and Barnes 1989). Tiotropium is more selective for M3 receptors. Though it binds M2 and M3 receptors with equal affinity, it dissociates from the M2 receptor nearly ten times faster than from the M3 receptor (Disse et al. 1993). However, the clinical consequences for this remain difficult to discern.

Efficacy

Ipratropium has a slower onset of action (30–60 min to maximum effect) and is less potent than short acting beta-2 agonists in the majority of asthma patients. In acute severe asthma, the concomitant use of an anticholinergic has been shown to more rapidly and effectively improve FEV1 than beta agonists alone, although the absolute increase is small. In addition, there is some indication that their use may reduce the need for hospitalization (Rodrigo et al. 1999). Tiotropium has a long duration of action and is dosed one inhalation daily. It may have a small bronchodilatory response in asthma and decrease bronchial hyperresponsiveness (O'Connor et al. 1996). However, tiotropium is not indicated for use in asthma and its role in asthma therapy remains to be determined.

General Usage

Ipratropium bromide is typically dosed two to four inhalations every 4–6 h as needed. It is rarely used as first line bronchodilator therapy, but can be used as an adjunct to beta-2 agonist therapy, particularly in acute severe asthma. In chronic asthma, ipratropium can be used as a rescue inhaler in patients with intolerance to beta-2 agonists. Neither ipratropium nor tiotropium are approved for use in asthma. Of note, ipratropium is also available in combination with albuterol. There are no data to support efficacy of the combination in chronic asthma.

Safety

Common side effects include minimal mouth dryness or bad taste in the mouth.

Medications: Controllers

Glucocorticosteroids

Pharmacology

Glucocorticosteroids (GCs) suppress inflammation by inhibiting many steps in the inflammatory process. GCs produce anti-inflammatory effects by binding to glucocorticoid receptors (GRs), which are localized in the cytoplasm of target cells. The activated GR then translocates into the nucleus where it binds to the specific DNA sequences suppressing some genes while increasing others (Bodwell et al. 1998). In addition, GC bound to its receptor appears to inhibit binding of proinflammatory factors to DNA, inhibiting activation of inflammatory genes. The end effect is modification of behavior of target cells. The degree of histone acetylation may also be an important mechanism of controlling inflammatory gene expression and ineffective histone acetylation may contribute to lower steroid responses (Ito et al. 2000). There is strong evidence that GCs limit expression of multiple inflammatory cytokines and adhesion molecules, which in return decreases influx of inflammatory cells into the airway (Schleimer et al. 1997). They decrease numbers of osinophils, dendritic cells, mast cells, and T lymphocytes. The effect of GCs on B lymphocytes is modest and immunoglobulin levels may only be slightly decreased. Interestingly, GCs do not prevent mast cell degranulation (Otsuka et al. 1986) and they do not affect neutrophils, perhaps even augmenting neutrophil survival (Meagher et al. 1996). They decrease inflammation in the epithelial wall and marginally inhibit mucus secretion. Over time, they reduce BHR though rarely eliminate it (Kraan et al. 1988; Djukanovic et al. 1992a). GCs also inhibit nitric oxide (NO) production by inhibiting the enzyme inducible nitric oxide synthase. Recent studies suggest that measurement of sputum eosinophils, or perhaps exhaled NO to adjust inhaled GC therapy may improve control of asthma and/or lead to decreased medication use (Smith et al. 2005; Green et al. 2002).

Efficacy

GC inhalers have become the primary anti-inflammatory treatment for adults and children with asthma (Suissa et al. 2000; Djukanovic et al. 1992b; Barnes et al. 1998). GCs have a significant long-term impact on both FEV1 and BHR. The improvement in FEV1 takes days to weeks, while the effect on BHR takes several months. They are also efficacious in the treatment of asthma exacerbations, usually in a systemic form, leading to their occasional categorization as reliever medications. However, not all patients respond equally to GCs, with most studies suggesting about 70% response rates. Variability of response is believed to be dependent on genetic predisposition, asthma phenotype, as well as adherence to therapy (Szefler et al. 2002). Dose response curves for efficacy have been very difficult to generate in most studies of mild-moderate asthma. However, a clear dose response exists for safety parameters (see next section).

General Usage

GCs come as inhaled, oral, and intravenous preparations. Inhaled GCs (IGCs) are also called ‘controller’ medications since they prevent asthma symptoms and exacerbations. They should be used on a regular basis once or twice a day but can also be used for acute exacerbations. However, all IGCs are not equal. Fluticasone and mometasone are the most potent IGCs, while flunisolide is the least potent (Martin et al. 2002). In addition, the IGCs are all dosed differently. FP is sold in three dose strengths, mometasone in one (220 μg/puff) and budesonide in one (200 μg/puff). Some are available as dry powder inhalers, while others are metered dose inhalers, now primarily with hydrofluoroalkane (HFA) as the excipient. HFA beclomethasone is formulated as a solution leading to a smaller particle size and the greatest lung delivery of the available GCs (Verbanck et al. 2006). The implications of this greater delivery are still not clear. Inhaled fluticasone is most commonly used as a combination inhaler with the long-acting beta agonist (salmeterol) and a similar combination of budesonide with the long-acting beta agonist formoterol has recently been approved for use in the United States. Dry powder inhalers do not require a spacer device. However, MDI formulations should still be dosed with a spacer. In all cases, rinsing the mouth after use is recommended to prevent oral candidiasis.

Safety

IGCs are preferred over the systemic glucocorticosteroids because of the lower level of systemic side effects

as compared to systemic GCs. However, all of the known side effects of systemic GCs have also been described with IGCs, but usually only at high doses (>600 μg of fluticasone) (Brus 1999). The common side effects of IGCs include oropharyngeal candidiasis and dysphonia. At higher doses, skin thinning and easy bruising, osteopenia/osteoporosis, cataracts, and glaucoma have all been reported. Hypothalamic-pituitary-adrenal axis suppression with use of IGCs does occur with higher doses, but the clinical significance in adults remains to be established. Fluticasone, budesonide, beclomethasone dipropionate, mometasone, and triamcinolone have all been shown to suppress the HPA axis (Brus 1999).

The side effects of long-term oral GC use include hypothalamic-pituitary-adrenal axis suppression, diabetes, osteoporosis, hypertension, obesity, skin thinning, muscle weakness, psychiatric disturbances, including mania and depression, cataracts and glaucoma. The rare but significant side effect of both short- and long-term use of systemic GCs is avascular necrosis of bone.

Cromones

Pharmacology

Cromones have been suggested to inhibit IgE mediated degranulation of the mast cells. They marginally reduce products of the early phase of mast cell activation, which include histamine, prostaglandin D2 as well as tryptase. They decrease eosinophils in the sputum and the airway (Calhoun et al. 1996; Manolitsas et al. 1995). However, the chief mechanism by which cromones are efficacious is not yet known.

Efficacy

Sodium cromoglycate and nedocromil sodium are representatives of this class of asthma medications. They inhibit both early and late asthmatic responses to inhaled allergens and they reduce airways reactivity resulting from exposure to a range of inhaled irritants, such as sulfur dioxide and cold air (Oseid et al. 1995; Koenig et al. 1988). They have no effect on BHR. They have no effect on chronic cough in children (The Cochrane Database of Systematic Reviews 2006).

General Usage

Cromones are less effective than IGCs (The Childhood Asthma Management Program Research Group 2000). Their current clinical role is mostly in patients with exercise-induced bronchospasm or in patients with mild persistent asthma who do not tolerate IGCs.

Safety

Cromones produce minimal side effects, such as occasional coughing upon inhalation of the powder formulation. Unpleasant taste is occasionally a side effect of nedocromil sodium.

Long Acting Beta-2 Agonists

Pharmacology

Long acting beta-2 agonists (LABA) relax airway smooth muscle and provide long-term bronchodilation for up to 12 h (probably less in severe asthma). Their general pharmacology is similar to short acting beta-2 agonists, but unlike SABAs, they have a longer duration of activation of the receptor. They include two inhaler preparations: salmeterol and formoterol. Salmeterol, a partial agonist of the beta-2 receptor, has an onset of action within 30 min, while formoterol, a full agonist has a more rapid onset of action. Like SABAs, they exert primarily a bronchodilator effect, with some in vitro studies to suggest they have anti-inflammatory effects. However, the clinical effect of LABAs has been insufficient to replace IGCs as primary therapy for asthma (Lazarus et al. 2001) and studies suggest that they should never be used alone. Nevertheless, LABAs and IGCs may have a synergistic effect. LABAs may augment the anti-inflammatory response of IGCs by increasing translocation of the glucocorticoid receptor into the nucleus of cells, which may contribute to an improved effect on inflammation (Eickelberg et al. 1999).

Efficacy

LABAs relax airway smooth muscle and provide long-term bronchodilation for up to 12 h. They are the

preferred add-on medication to IGCs in patients inadequately controlled on IGCs alone, being more efficacious than doubling the dose of the IGC (Lemanske et al. 2001). Addition of LABAs to IGCs improves asthma symptoms, decreases asthma exacerbations and improves lung function (Pauwels et al. 1997; Bateman et al. 2004). Although they are effective bronchodilators when used alone, several studies suggest that using LABAs as single agents has an unacceptable safety profile and may lead to increased risks of fatal and near-fatal asthma exacerbations (Nelson et al. 2006).They reduce BHR for 24 h and demonstrate 12-h protection against exercise challenge. However, there is loss in bronchoprotection with exercise challenge at later time points after chronic treatment with LABAs (Edelman et al. 2000a). Another concern has been the possibility that LABAs may blunt the response to short acting beta-2 agonists. However, most studies suggest this does not occur (Korosec et al. 1999).

General Usage

Long acting beta-2 agonists are dosed via the inhaled route twice daily. In the United States, these medications are approved for use as a maintenance therapy for asthma. They should be used if a patient's symptoms are not adequately controlled with low to medium dose IGCs or if severity of disease requires two controller medications. In asthma, LABAs should only be used in combination with IGCs, never alone. Salmeterol is marketed in combination with fluticasone in a single dry powder disk device or metered dose inhaler. Formoterol has just recently been approved in the United States for use in combination with budesonide in an MDI. In Europe, formoterol (alone or in combination with the GC budesonide) has been also used a rescue medication in addition to its maintenance role, but use in this manner has not yet been approved in the United States. Salmeterol and formoterol are also approved for the prevention of exercise induced bronchospasm.

Safety

The common side effects of LABAs include tachycardia, skeletal muscle tremor and hypokalemia. β2-agonists have produced myocardial ischemia in susceptible individuals. All β2-adrenergic agonists can increase the QT_c interval. Recently, LABAs received a black box warning after publication of the Salmeterol Multicenter Asthma Research Trial (SMART) (Nelson et al. 2006). In this particular, trial there was a significant increase in asthma-related deaths in patients receiving salmeterol versus placebo. In Caucasians, the addition of IGCs prevented any increased risk, while a similar protective effect was not observed in African Americans. The mechanism for these safety concerns is not clear. Although focus has been on the effect of genetic polymorphisms, future large-scale studies are needed before the effect can be confirmed.

Methylxanthines

Pharmacology

Methylxanthines have many possible mechanisms of action. Their bronchodilatory effect derives from inhibition of phosphodiesterase and subsequent increase in intracellular cyclic 3(,5(-adenosine monophosphate (cAMP) and cyclic 3(,5(-guanosine monophosphate (cGMP) concentrations. However, this effect is not fully seen at therapeutic concentrations of methylxanthines (Rabe et al. 1995). Additionally, they may exert anti-inflammatory properties by preventing the translocation of the proinflammatory transcription factor nuclear factor kappa B (NF κB) into the nucleus and by increasing the activity of histone deacetylase during the transcription process (Ito et al. 2002). Theophylline has also been shown to have immunomodulatory effects on T lymphocytes. It is noteworthy that the anti-inflammatory effects may be exerted at lower plasma concentrations.

Efficacy

Theophylline should be used as an add-on therapy to IGCs in asthma. However, LABAs have been proven to be more effective and safer as an add-on therapy to IGCs than theophylline (Wilson et al. 2000). Therefore, theophylline should be used in selected patients with severe persistent asthma or nocturnal asthma as an add-on therapy to IGCs in patients who did not tolerate LABAs. Of note, theophylline does not have a significant effect on BHR.

General Usage

Methylxanthines come as oral and IV preparations. IV aminophylline was used extensively in the past for treatment of acute asthma exacerbations. However, aminophylline has fallen out of favor since it is less effective than nebulized beta-2 agonists and it may have significant side effects. Theophylline is an oral preparation, which should be administered only as a sustained release preparation.

When theophylline is used, levels should be kept below 10 mg/ml. Little data suggests that higher concentrations are more effective, but higher concentrations are associated with greater risk of toxicity.

Safety

At higher doses (10 mg/kg body weight/day or more), theophylline has the potential for significant adverse effects. Gastrointestinal symptoms, nausea, and vomiting are the early symptoms of theophylline intoxication. More serious side effects of theophylline intoxication include tachycardia, arrhythmias as well as seizures and death. Generally, serious toxic effects do not occur at serum concentrations below 15 μg/ml. Monitoring of serum concentrations is advised when high-dose theophylline therapy is started and at occasional intervals thereafter. However, certain conditions or concomitant medications can alter theophylline metabolism. For example, febrile illness, pregnancy, and antituberculosis medications reduce blood levels while liver disease, congestive heart failure and use of certain drugs including cimetidine, certain quinolones, and macrolides increase the risk of toxicity. Lower doses of theophylline are associated with less frequent side effects, and there is less need for measurement of plasma levels in patients on low-dose therapy.

Leukotriene Modifiers

Pharmacology

Leukotrienes (LTs) are important mediators of inflammation in asthma. Cysteinyl LTs (LTC4, LTD4 and LTE4) are produced by eosinophils, mast cells and basophils and long recognized as important contributors to allergic responses. LTB4 is produced by neutrophils and macrophages and its role in asthma is less clear. Cysteinyl LTs are important bronchoconstrictors and potent chemoattractants for neutrophils and eosinophils.

Leukotriene modifiers (LMs) act by blocking the cysteinyl leukotriene receptor (cysLR) 1 (Montelukast, Zafirlukast) or by preventing all leukotriene production through inhibition of the 5 lipoxygenase enzyme (Zileuton). Differences in efficacy of the two subclasses has never been confirmed. CysLR1 antagonists have a small effect on BHR following allergen challenge (Hui et al. 1991) and have been shown to modestly decrease inflammatory cell influx after allergen challenge (Kane et al. 1996; Calhoun et al. 1998). LMs decrease sputum, tissue and blood eosinophils (Pizzichini et al. 1999; Nakamura et al. 1998). They have a small effect on exhaled NO levels (Bisgaard et al. 1999; Wilson et al. 2001).

Efficacy

LMs are administered orally. They improve lung function, decrease asthma symptoms, and decrease asthma exacerbations (Reiss et al. 1998; Suissa et al. 1997). They inhibit exercise-induced bronchospasms and aspirin-related reactions in patients with sensitivity to nonsteroidal anti-inflammatories (Dahlen et al. 1998; Villaran et al. 1999; Edelman et al. 2000b). Patients' response to LMs is variable and it seems to be greatest in a subset of asthmatics in whom LTs are a major contributory factor to the asthma (Hasday et al. 2000). It appears that 30–50% of asthmatics respond to these medications (Malmstrom et al. 1999). As a general rule, LMs are less effective as controller asthma medications than IGCs, perhaps on the basis of the lesser overall percentage of responders.

LMs can be used as single therapy in mild persistent asthma (as a "nonpreferred" alternative to inhaled GCs) and in exercise-induced asthma. LABAs are generally more effective than LMs when added to IGCs in improving asthma control and decreasing exacerbations (Nelson et al. 2000; Fish et al. 2001). Although commonly used in conjunction with IGCs and LABAs in more severe asthma, there are no objective data to support that therapy with these three controller medications is an effective option.

General Usage

Montelukast is dosed once a day, Zileuton four times a day and Zafirlukast is dosed twice a day. LMs are indicated for use as controllers in persistent asthma. LMs can be used as single therapy in mild persistent asthma (as a "nonpreferred" alternative to IGCs) and in exercise-induced asthma. They can also be used as add-on therapy to IGCs as opposed to doubling the dose of IGCs (Price et al. 2003). Montelukast was also approved for treatment of allergic rhinitis. Interestingly, two studies have suggested that LMs are effective in the treatment of acute asthma in adults (Camargo et al. 2003; Silverman et al. 1999).

Safety

Zileuton and Zafirlukast may cause elevation of liver enzymes. Reversible hepatitis has been reported with Zileuton (Liu et al. 1996). This generally occurs in the first 3 months of therapy and can be monitored for by monthly checks of AST and ALT. The reaction to Zafirlukast is less predictable and can occur at any time (Reinus et al. 2000). No liver enzyme abnormalities have been reported with Montelukast. LMs have been linked to emergence of Churg-Strauss vasculitis in patients with asthma. However, most experts believe that appearance of Churg-Strauss vasculitis is caused by reducing steroid dose and not ongoing treatment with LMs (Wechsler et al. 2000).

Anti-IgE Therapy

Pharmacology

The cross-linking of IgE bound to mast cells is well recognized as a critical contributor to Type I acute hypersensitivity reactions linked to allergic responses. The cross-linking of the IgE causes immediate activation of mast cells/basophils to release histamine, proteases and produce a variety of lipid mediators, including leukotrienes and prostaglandins. In addition, more recent studies suggest that IgE may play a role in chronic asthma as well.

Omalizumab is a humanized monoclonal anti-IgE antibody, which binds free serum IgE to prevent binding of the IgE to mast cells and thereby inhibit activation. The effect lasts for 2–4 weeks, dependent on the starting IgE level and the weight of the patient. The secondary effect of decreased IgE level is down-regulation of IgE receptors on the surface of mast cells and basophils (MacGlashan et al. 1997; Beck et al. 2004). Additionally, omalizumab decreases sputum, airway tissue, and blood eosinophils, as well as surface IL-4 level (Djukanovic et al. 2004).

Efficacy

Omalizumab has been shown to inhibit both the early and late phases of allergic reactions. In large-scale clinical trials, omalizumab decreases the rate of exacerbations and improves asthma symptoms in patients whose asthma is not controlled on IGCs alone (Busse et al. 2001; Soler et al. 2001). While there are data to support efficacy when added to IGCs + LABA, the effect is less strong than in milder asthma (Humbert et al. 2005). Omalizumab does not cause a clinically significant improvement in FEV1 nor a decrease in BHR. Omalizumab has not been shown to improve asthma symptoms acutely and should not be used for treatment of acute asthma exacerbations.

General Usage

Omalizumab is dosed subcutaneously one to two times per month. The dose is determined by the serum IgE level and the weight of the patient. It is indicated for the treatment of moderate to severe allergic asthma, as defined by an IgE >30 IU/ml and documented specific IgE (either through skin testing or RAST). Omalizumab is a very expensive medication (>$10,000/year) and patients treated with this medication should have failed more standard therapy before preceding to this medication.

Safety

The most common side effects of omalizumab include local injection site reactions. Both early and delayed anaphylactic reactions are rarely observed in individuals receiving omalizumab therapy (less than 0.1%) and

patients should be monitored for 2 h after injection. Patients should also have an epinephrine autoinjector (epipen) and be informed how to recognize and treat delayed anaphylaxis when it occurs. Omalizumab therapy has also been associated with increased incidence of neoplasms. Malignant neoplasms were observed in 0.5% of omalizumab-treated patients and in 0 .2% of control patients. There is presently an ongoing long-term clinical trial to evaluate whether there is causality between omalizumab and neoplasms.

Treatment of Asthma

Medication Administration Routes

Asthma medications can be administered via inhaled, oral, or parenteral routes. Inhalers are the preferred method of delivery for most asthma medications because of direct deposition of medication to the airways and few systemic side effects. On the other hand, the newer biological therapies in asthma (e.g., omalizumab) and LMs are all dosed systemically, either parenterally or orally.

Inhaler drug therapy requires that patients learn specific inhalation techniques for each of the available types of inhaler device. A less than optimal technique can result in decreased drug delivery and potentially reduced efficacy. There are several different types of inhaler devices and each type has its own advantages and disadvantages. Nebulizer/compressor systems require minimal patient cooperation and coordination, but are cumbersome and time-consuming to use. Metered dose inhalers (MDIs) are quicker to use and highly portable, but require the most patient training to ensure coordination for proper use. Up to 70% of patients fail to use them properly. The improper timing of MDI actuation with breath initiation is a common problem. The addition of a spacer/holding chamber allowed the aerosol delivered by the MDI to be contained in the spacer for a finite period of time, thereby circumventing the need for the coordinated actuation of the MDI with inhalation. This system of delivery of aerosolized medications also reduces oropharyngeal deposition (Brown et al. 1993). In the case of IGCs, this can diminish the incidence of oral candidiasis, and in many cases, improve lower airway deposition. Dry powder inhalers (DPIs) are easier to use than MDIs because they are breath-actuated, but require a relatively rapid rate of inhalation in order to provide the energy necessary for drug aerosolization. According to the American College of Chest Physicians and American College of Allergy and Immunology guidelines, there are no differences in pulmonary function response or symptom scores when the same dose of the same GC is used as a DPI or as an MDI with spacer/holding chamber (Dolovich et al. 2005). Delivery of SABAs via different delivery systems has been also studied in different clinical settings. In the ED or inpatient setting, administration of SABAs by nebulizers or MDIs with a spacer/holding chamber is equally effective for improving pulmonary function and reducing symptoms of acute asthma in both adults and pediatric patients (Cates et al. 2002).

Achieving Asthma Control

Periodic monitoring and assessment of patient with asthma through history, physical exam, and measurement of lung function are crucial in optimal asthma care. The physician should determine both the severity and the level of asthma control in relation to current medical treatment in each new or established asthma patient. If the patient is not on any maintenance medications, the severity of asthma is determined by frequency and intensity of symptoms and the level of functional impairment as well as obstruction of lung function measured by spirometry. However, the majority of patients are already on therapy when they present to specialist's office and in these patients the emphasis is changed to assessment of asthma control. This approach presumes that the severity of asthma is related to its responsiveness to treatment (Global Initiative for Asthma (GINA) 2006). Once the level of asthma control is determined, treatment should be adjusted accordingly (Fig. 6.1). If the patient's asthma is not controlled, treatment should be stepped up until full or maximal control is achieved. If asthma has been well controlled for at least 3 months, treatment can be stepped down.

The indicators of full asthma control include no daytime or nighttime symptoms, no asthma exacerbations, no rescue inhaler use, normal lung function, and normal activity levels. Asthma is considered partly

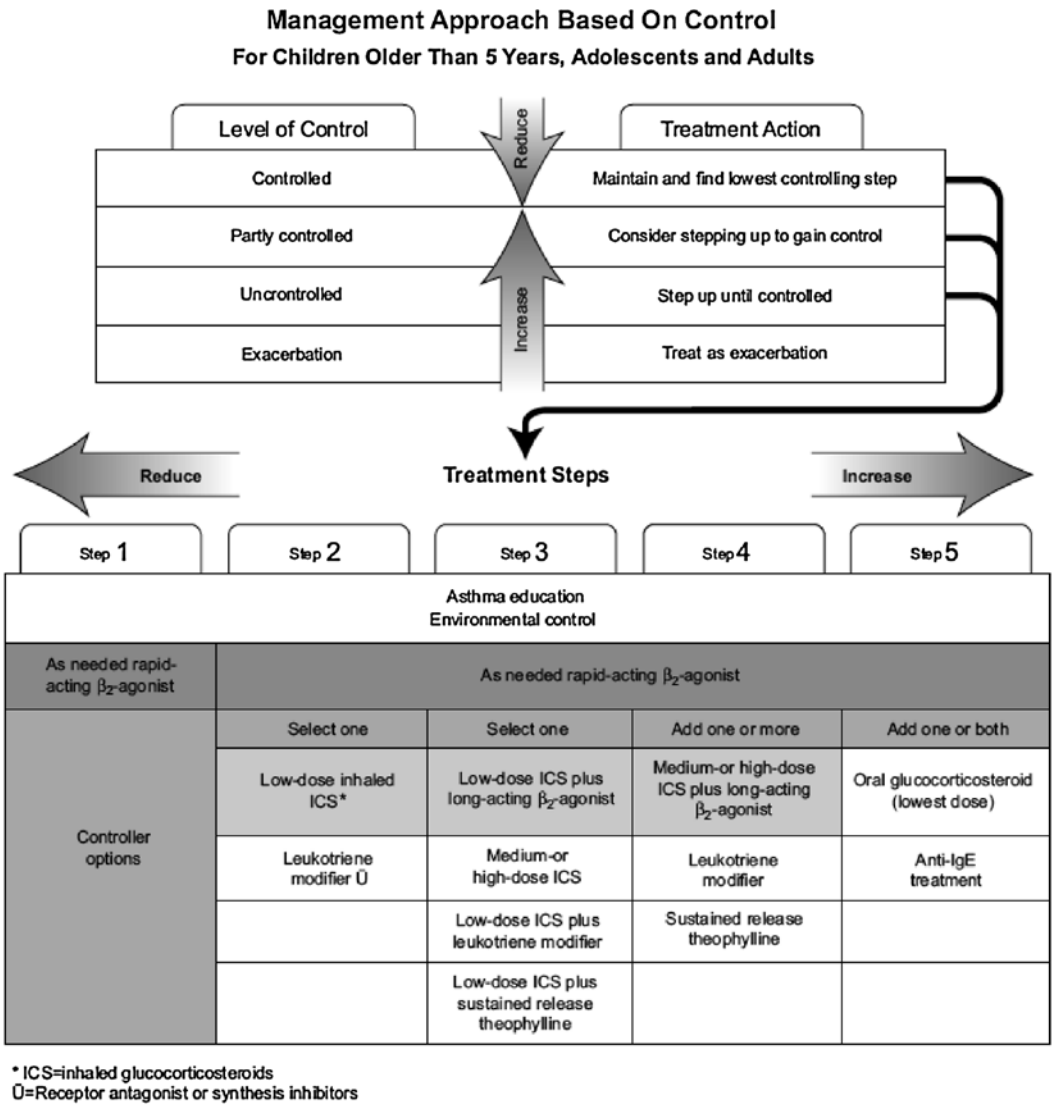

Fig. 6.1 Management approach based on control. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (2006). Available at http://www.ginasthma.org/

controlled if one to two of the indicators of asthma control are not met. Asthma is uncontrolled if three or more indicators of asthma control are not reached.

The approach outlined in the 2006 GINA guidelines recommends a management approach based on control (Table 6.2). This new approach to managing asthma symptoms involves five treatment steps for achieving control of asthma.

STEP 1 treatment is reserved for patients with very mild symptoms that occur less than twice a week and have no exacerbations. These patients should be managed with as needed short acting beta-2 agonists only.

STEP 2 treatment involves adding a single controller therapy to rescue medication. The recommended controller is a low-dose IGC. An alternative approach

is to use an LM. Studies of mild asthma treated with IGC or IGC plus LABA did not demonstrate any added benefit to the combination treatment with an inhaled GC alone (O'Byrne et al. 2001). Once the patient is committed to controller they should be well controlled for at least a year before a decision is made to discontinue controller therapy (Global Initiative for Asthma (GINA) 2006).

At *STEP 3*, the recommended treatment is to add a LABA to low-dose IGC. The alternative approach is to add a LM to low-dose IGC or increase IGC to medium to high dose.

At *STEP 4*, the preferred treatment is to increase the dose of IGC to medium to high dose IGC in combination with LABA. However, data from the GOAL study suggest that this approach further improves only a small percentage of patients (Bateman et al. 2004). If patients reach *STEP 5*, they have likely failed standard therapies. At this point other treatment modalities should be introduced. These include anti-IgE therapy and oral steroids. Difficult to control asthma will be discussed in more detail later.

Special Considerations

In every patient with asthma, the diagnosis of asthma should be confirmed with a compatible history, physical examination, and spirometric testing, generally pre- and post-SABA. Once the diagnosis is confirmed, one should look for potential triggers of asthma. The most common triggers include upper respiratory tract infections, environmental allergens with concomitant allergic rhinitis, gastroesophageal reflux disease, chronic rhinosinusitis, work-related triggers in occupational asthma, aspirin, and beta blockers. These triggers, if eliminated, can improve asthma control and decrease the dose of IGCs needed to maintain control of asthma symptoms (Platts-Mills 2004; Sandrini 2003; Adams 2002; Szczeklik et al. 2001; Covar et al. 2005; Harding et al. 2000; Patterson and Harding 1999).

Seasonal and perennial allergens are significant triggers of asthma symptoms. The indoor allergens are especially targeted as a potentially correctable cause of asthma exacerbations. However, it is very difficult to reduce an allergen load to the level where a significant clinical benefit will be noted (Luczynska et al. 2003; Woodcock et al. 2003; Wood et al. 1989). No large-scale studies have been able to show a sustained effect.

Allergen immunotherapy is based on the principle of inducing tolerance to environmental proteins. It has been used for decades for treatment of allergic asthma as well as for treatment of allergic rhinitis and stinging insect hypersensitivity. The inhaled allergens that trigger patient's asthma are usually identified with history and allergen skin testing.

The efficacy of allergen immunotherapy in allergic rhinitis and stinging insect hypersensitivity has been well established. However, the role of allergic immunotherapy in asthma has been controversial. A Cochrane review that examined 54 randomized trials suggested that allergen immunotherapy is effective in asthma, reducing asthma symptoms, and bronchial hyperresponsiveness (Abramson et al. 2003). Allergy immunotherapy should be reserved for patients with relatively mild allergic asthma, especially those whose triggers can be identified by clinical history and the presence of specific IgE (seasonal and/or perennial allergies). It is administered with subcutaneous injections of allergen vaccines, at weekly to monthly intervals. Due to potential for severe allergic reactions, allergen immunotherapy is contraindicated if the patient's FEV1 is below 70%. It is our opinion that allergen immunotherapy should not be used in moderate and severe persistent asthma because the risk of inducing severe asthma exacerbations outweighs the potential benefit of allergen immunotherapy. Allergen immunotherapy should not replace controller asthma medications and it should be used in addition to patient's maintenance medications.

Another important trigger of asthma symptoms is gastroesophageal reflux disease. Despite the lack of definitive studies to support the link between GERD and asthma symptoms, it is routinely recommended to aggressively treat any patient with GERD and asthma with dietary modifications, proton pump inhibitors or H-2 blockers and surgery for severely symptomatic patients. However, improvement in asthma control is inconsistently observed with this approach (Gibson et al. 2000) and, in fact, GERD may be consequence of poorly controlled asthma, as well as a cause of it. GERD may also contribute to vocal cord dysfunction which may be mistaken for asthma (Powell et al. 2000; Bahrainwala and Simon 2001).

Respiratory tract infections represent the most frequent triggers of asthma exacerbations (Martin 2006).

They enhance underlying airway inflammation and their effect may persist for weeks. Viral infections, such as rhinoviruses, are the most common triggers of asthma exacerbations in children and perhaps adults (Johnston et al. 1995; Nicholson et al. 1993). All patients with asthma should receive annual influenza vaccinations and probably pneumococcal vaccine as well. Supporting this approach, a recent study suggested that the diagnosis of asthma increased the risk for pneumonia (Talbot et al. 2005). Another potentially important cause of asthma worsening could be a chronic infection with *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. However, it is still uncertain whether infection with these bacteria plays a significant role in asthma pathogenesis (Martin 2006).

Exercise-induced asthma is a unique category of asthma since these patients have symptoms only with exercise. Effective strategies for treating exercise-induced asthma should be employed in the following order: two inhalations of SABA 15–20 min prior to exercise. If that fails, one may consider using a LM or a LABA 1–2 h prior to exercise (Edelman et al. 2000b). When exercise-induced symptoms occur more than twice a week, addition of IGC is recommended. Additionally, one may use inhaled cromones prior to exercise (Spooner et al. 2000). It is very important that patients with exercise-induced asthma immediately consult their physician if they develop asthma symptoms unrelated to exercise. In patients where the diagnosis is unclear, spirometry or peak flows pre- and postexercise should be ordered.

Anaphylaxis can be an important cause of asthma exacerbation. It is usually seen in the setting of a known trigger in a patient with underlying asthma. Examples of common anaphylactic triggers include foods, insect stings, latex, allergen immunotherapy injections, drugs, etc. The treatment of choice for these patients is intramuscular (IM) epinephrine followed by intravenous (IV) antihistamines and steroids.

Aspirin-induced asthma (AIA), also known as aspirin exacerbated respiratory disease, can affect up to 10% of adults with asthma (Nelson et al. 2003). Upon ingestion of aspirin and other NSAIDs, susceptible individuals will develop bronchoconstriction which may progress to full respiratory arrest. AIA is especially common in patients with nasal polyps and chronic sinusitis (Samter's triad), and it is frequently seen in more severe asthmatics. Aspirin-sensitive patients have an increased production of cysteinyl LTs at baseline and after aspirin challenge. While these patients should be instructed to avoid ASA and other nonsteroidal anti-inflammatory drugs (NSAIDs), the syndrome can persist and remain severe despite the absence of exposure to these medications. These patients can benefit greatly from LMs (Dahlen et al. 1998; 2002), although this is not true in every case. Some aspirin-sensitive patients benefit from aspirin desensitization (Pleskow et al. 1982). This can be particularly important if ASA or other NSAIDs are required for treatment of other conditions. However, the therapeutic effect was more convincing with upper airway disease than with lower airway disease.

Difficult to Treat Asthma

Patients with difficult to treat asthma do not achieve control with standard inhaler therapy. Their asthma can also be referred to as severe or refractory asthma. They appear to represent a minority of the asthma population (20–30%). They are characterized by frequent day and night-time symptoms, an FEV1 below 60% despite daily high doses of IGCs and frequently systemic GCs. While they often have a low FEV1, the ATS workshop definition of refractory asthma does not require the FEV1 to be persistently low, supporting the concept that asthma is a variable disease with different phenotypic presentations (Wenzel et al. 2000).

In all asthmatics, but particularly severe asthmatics, it is important to identify and treat potential triggers and co-morbidities. One should always review carefully the list of medications that the patient is taking for those which could potentially worsen underlying asthma, such as aspirin/NSAIDs and beta blockers. Additionally, the presence of GERD, chronic rhinosinusitis, bronchiectasis, obstructive sleep apnea, pulmonary hypertension, and other conditions should be determined and aggressive therapy instituted as needed. Asthma mimickers should be recognized since they can present as severe asthma and cause unnecessary treatments with steroids. Paradoxical vocal cord dysfunction is a common asthma mimicker, which is treated by addressing exacerbating factors, such as GERD, sinusitis, anxiety, and retraining breathing techniques (Bahrainwala and Simon 2001). Eosinophilic conditions can complicate severe asthma. The most common conditions are

Churg-Strauss vasculitis, allergic bronchopulmonary aspergillosis and chronic eosinophilic pneumonia.

Initial recommended treatment for patients with severe persistent asthma are high dose IGC plus LABA. However, nearly 40% of patients severe enough to require this combination of medications will not achieve adequate control of their asthma symptoms on this regimen and will continue to have frequent breakthrough asthma exacerbations (Bateman et al. 2004). Additional therapy should be offered to these patients, but there are very little data to support these additions. Adding LMs, specifically Zileuton, may be of some benefit when an aspirin-sensitive component is present (Dahlen et al. 1998). The monoclonal anti-IgE antibody omalizumab can be effective in patients with moderate to severe persistent asthma on combination therapy with high dose IGC and LABA, who have elevated total IgE and documented year-round environmental allergies (Humbert et al. 2005). When these approaches fail, consideration should be given to daily systemic GC. Once asthma control is established with systemic GCs, the dose should be reduced to the lowest dose at which asthma symptoms remain controlled. Unfortunately, some patients on higher doses of systemic steroids remain symptomatic and difficult to control. Because these patients are often complicated and difficult to treat, patients with severe persistent asthma often benefit from referral to an asthma specialist for further management.

Acute Asthma

Asthma exacerbations represent the most feared complication of this chronic disease. They can range from mild to severe and the patients can present acutely to the emergency room or their lung function can worsen gradually over time. Prompt treatment usually leads to full recovery. It is critical to identify individuals who are at high risk for asthma-related death since these patients will require more aggressive treatment and closer monitoring (Table 6.3). Finally, the poor perception of symptoms can delay care and patients need to be educated on how to recognize the beginning of asthma exacerbations and seek prompt medical care.

The treatment of asthma exacerbations begins by determining the severity of the exacerbation. Mild asthma exacerbations usually can be treated at home.

Table 6.3 Patients at high risk of asthma-related death

- History of near-fatal asthma requiring intubation and mechanical ventilation
- History of hospitalization or emergency care visit for asthma in the past year
- Current or recent use of oral glucocorticosteroids
- Patients are not currently using inhaled glucocorticosteroids
- Patients who are overdependent on rapid-acting inhaled beta-2 agonists, especially those who use more than one canister of salbutamol (or equivalent) monthly
- History of psychiatric disease or psychosocial problems, including the use of sedatives
- History of noncompliance with an asthma medication plan

Patients are frequently prescribed written action plans, which include identification of worsening asthma by symptoms, beta agonist use, and peak flows. These plans include instructions on how to manage their exacerbation. Regardless of whether the action plain is written or not, patients should be educated on how to recognize and treat an asthma exacerbation (Gibson et al. 2002). Of note, doubling the dose of IGC has not been shown to be effective in preventing an acute asthma exacerbation, although a fourfold higher dose may diminish the severity of an exacerbation (Harrison et al. 2004; FitzGerald et al. 2004; Foresi et al. 2000). Moderate to severe exacerbations often require treatment in the hospital or emergency room under close supervision. Early administration of systemic steroids has been show to decrease hospital admissions (Rowe et al. 2001a). Studies have demonstrated that intravenous and oral GC have similar efficacy supporting the dosing of steroids before arrival in the emergency room (Ratto et al. 1988; Harrison et al. 1986). It is still appropriate to administer IV steroid to the patient with severe asthma exacerbation, especially when nausea and vomiting are a concern. All asthma exacerbations should be treated with increasing doses of SABAs. In many cases, these may be the only class of medications required. As previously mentioned, delivery of SABAs in the ED setting by nebulizers or MDIs with holding chambers is equally effective for improving pulmonary function and reducing symptoms of acute asthma in asthma patients (Cates et al. 2002). Additionally, in the inpatient setting, the available evidence suggests that there is no difference in the pulmonary function response between using a nebulizer and using an MDI with a spacer/holding chamber for administering short-acting beta-2 agonist therapy (Dolovich et al. 2005). Continuous nebulization may

be used in patients with severe asthma and may be better than intermittent in children with severe asthma exacerbations (Gibbs et al. 2000). Adding ipratropium to nebulized short acting beta agonist may reduce airway obstruction and hospital admissions, especially in patients with severe asthma (Rodrigo and Castro-Rodriguez 2005). Intravenous magnesium is not recommended for routine use, but it may be helpful in severe exacerbations (Rowe et al. 2001b). Patients who receive GCs in the ED should also receive GCs on discharge, preferably both as an oral GC burst and as an inhaled medication (Rowe et al. 1999).

Conclusion

Asthma is a treatable disease that affects millions of people, irrespective of their age. Patients who suffer from asthma are not identical and each individual patient presents to a physician's office with a unique combination of symptoms. The current guidelines for diagnosis and management of asthma are helpful for a busy physician because they summarize the latest evidence-based recommendations for treatment of asthma. However, the guidelines only represent an ancillary tool designed to foster better care. They are not designed to replace the art of practicing medicine, which still requires learning the "particulars" of every patient's story to devise a specific therapeutic plan for each patient. We are hopeful that this review of current medications and treatment approaches in asthma facilitates the process of determining the most appropriate therapy for patients with asthma.

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