

Artigo original**Fundamentals of Asthma Treatment**

Os Fundamentos do Tratamento da Asma

Timothy Scialla, Adam Wanner¹**RESUMO**

A asma é uma doença complexa. Sua característica cardinal é a inflamação crônica que leva a hiper-responsividade brônquica. Como nenhum tratamento é capaz de modificar a história natural da asma, todas as abordagens terapêuticas disponíveis devem ser consideradas com a finalidade de se atingir o controle da asma e não sua cura.

O principal objetivo do controle é o tratamento efetivo da inflamação da via aérea. Na maior parte dos casos, são necessários agentes farmacológicos para obter o controle. Os β_2 -agonistas de curta duração são os medicamentos preferidos para o alívio, graças a seu início rápido de ação. Os corticosteroides inalatórios são o tratamento mais efetivo para o controle dos sintomas asmáticos em longo prazo. Entretanto, em pacientes com asma persistente moderada a grave, é necessária terapia coadjuvante. Adicionar um β_2 -agonista de longa duração é mais efetivo na melhora dos sintomas do que agregar um antagonista dos receptores de leucotrienos. A teofilina continua a ter um papel específico em pacientes com pouca resposta aos corticosteroides inalatórios. O papel dos anticolinérgicos está evoluindo.

Aproximadamente 10% dos asmáticos têm sintomas refratários mesmo com a combinação de tratamentos de controle. A imunoterapia surge como uma alternativa potencial no tratamento desse grupo heterogêneo de alto risco.

Descritores: Asma/tratamento; Asma/prevenção & controle; Asma/imunologia.

ABSTRACT

Asthma is a complex disease. Its cardinal feature is chronic airway inflammation that leads to bronchial hyperresponsiveness. Because no therapies have been shown to influence the natural history of asthma, all currently available treatments must be viewed in the context of achieving asthma control and not as disease-modifying therapies.

The major target of control remains the effective treatment of airway inflammation. In most cases, pharmacological agents are needed in order to obtain control. Short-acting β_2 agonists are the preferred agents for quick relief because of their rapid onset of action, and inhaled corticosteroids are the most effective therapy for long-term control of asthma symptoms. However, for patients with moderate-to-severe persistent asthma, adjuvant therapy is needed. Adding a long-acting β_2 agonist is more effective at improving symptoms than is adding a leukotriene modifier. Theophylline continues to have a role, especially in patients who respond poorly to inhaled corticosteroid therapy, and the role of long-acting anticholinergic agents is evolving.

Approximately 10% of all asthma sufferers will have refractory symptoms despite the use of combination controller therapies. Immunotherapy has emerged as a potential alternative in the treatment of this heterogeneous, high-risk population.

Keywords: Asthma/treatment; Asthma/prevention & control; Asthma/immunology.

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INTRODUCTION

Asthma is a complex and heterogeneous disease. Clinically, it is characterized by episodic and reversible symptoms of wheezing, chest tightness, cough, and shortness of breath. Worldwide, it affects approximately 300 million people (1). Despite the many advances in our understanding of this chronic disease at both the genomic and the cellular level, its prevalence continues to increase. In the United States, the proportion of persons with asthma, in relation to the general population, increased from 7.3% (20.3 million persons) to 8.2% (24.6 million persons) between 2001 and 2009 (2). Fortunately, over the past decade, morbidity and mortality related to asthma have been declining because of the use of more effective asthma treatments (3). Nevertheless, there remain substantial challenges in managing patients with asthma. Responses to asthma treatment show high individual variability. While some patients receive substantial benefits from the standard asthma therapies, others seem to derive very little benefit and still have uncontrolled symptoms.

A broad and general understanding of the “fundamentals of asthma” is necessary for clinicians to make informed treatment decisions for their patients. Therefore, this review will begin with an overview of asthma pathophysiology. We will discuss the singular importance of achieving control of asthma. The clinicians’ major arsenal in this regard includes patient education, trigger avoidance, and drug therapy. We will then discuss the agents currently available as treatments and how those agents can be used synergistically. As the title of this article suggest, our goal is to stress the fundamentals of managing asthma sufferers with a range of symptoms. The framework we present is expanded upon in the subsequent chapters.

PATHOPHYSIOLOGY

Chronic airway inflammation is the cardinal feature of asthma. It is associated with development of airway obstruction and airway hyperresponsiveness, which lead to recurrent symptoms of wheezing, chest tightness, shortness of breath, and cough. These symptoms are reversible, either spontaneously or with treatment. Airway inflammation involves many different cells and inflammatory mediators. The cells include mast cells, eosinophils, T lymphocytes, neutrophils, macrophages, and epithelial cells, as well as, possibly, autonomic neurons and airway vascular endothelial cells (4). The inflammatory mediators include chemokines, cytokines (IL-4, IL-5, and IL-13), cysteinyl leukotrienes, nitric oxide, growth factors, and IgE (5). In the acute phase of an asthma exacerbation, airway smooth muscle constriction and bronchoconstriction can occur quickly in response to various stimuli. In allergen-induced asthma, this bronchoconstriction develops in response to IgE-dependent release of his-

tamine, leukotrienes and prostaglandins (6). The β_2 agonists, which are the mainstay of “acute/quick relief” of airflow limitation, work by relaxing bronchial smooth muscle and reversing bronchoconstriction.

When the inflammatory signals persist, edema (mucosal and submucosal), mucous cell hyperplasia, hypersecretion of mucus, and infiltration by effector cells ensue, as do changes in the airway smooth muscle (hypertrophy and hyperplasia). In addition, there are pronounced alterations in the tracheobronchial vasculature—proliferation of blood vessels and increased blood flow (7). The effect of this ongoing inflammatory process is bronchial hyperresponsiveness (exaggerated bronchoconstriction to a variety of stimuli). In some patients, airflow limitation becomes resistant to therapy. Airway remodeling (hypersecretion of mucus, subepithelial fibrosis, airway smooth muscle hypertrophy, and angiogenesis) has been associated with progressive loss of lung function, although a causal relationship between the two remains controversial (8). Corticosteroids are our most effective treatment option for this ongoing airway inflammation, because they downregulate these pro-inflammatory proteins through genomic mechanisms (gene transcription). They also have more rapid non-genomic effects, including decreased blood flow in the respiratory mucosa (7).

ACHIEVING ASTHMA CONTROL

Cohort studies of individuals with asthma have suggested that asthma sufferers lose lung function at a faster rate than do individuals without asthma (9-12). Unfortunately, identifying patients most at risk for accelerated loss of lung function has been elusive. In addition, trials that have examined whether inhaled corticosteroids can influence the natural history of asthma have not shown them to modify the disease process (13-15).

All currently available treatments for asthma must be viewed in the context of achieving disease control and not as disease-modifying therapies. The major target of control remains the effective treatment of airway inflammation. Asthma guidelines also stress that control be evaluated in two distinct domains (16): impairment and risk. Impairment describes the current physical limitations of patients attributable to active asthma symptoms and the need for frequent use of quick-relief medications (on > 2 days/week). Risk describes the number and severity of asthma exacerbations in the past year, as well as medication side effects. Assessing risk is meant to emphasize the importance of limiting future exacerbations, with the aim of preventing progressive loss of lung function. However, the two domains are not mutually exclusive. The current level of asthma control has been shown to significantly affect the future risk of exacerbations (17).

COMPONENTS OF EFFECTIVE ASTHMA MANAGEMENT

Treating patients with asthma requires a long-term commitment on the part of patients and providers alike. It requires continual reassessment of symptoms and lung function to ensure that control is maintained. It requires ongoing patient education and control of environmental factors. It requires treatment of comorbid conditions that affect asthma and, in almost all cases, the use of pharmacological agents, the

goal of latter being to achieve asthma control with the fewest adverse effects.

As clinicians, we tend to emphasize medical therapy often at the expense of the other components of asthma management. Chart 1 summarizes the options available for control of environmental factors while Chart 2 lists the comorbid conditions that can make asthma control difficult. The remainder of this review addresses the medications currently prescribed for asthma treatment.

Chart 1 - Inhalant irritants/allergens and avoidance recommendations.

Type of irritant	Avoidance recommendations and considerations
Indoor inhalant allergens*	
Animal allergens (including pet and rodent allergens)	Treatment of choice is removal of exposure If removal of pet not acceptable, then: - Keep pet out of patient's bedroom - Keep bedroom door closed - Remove upholstered furniture and carpets Consider weekly bathing of pet to remove large quantities of dander and dried saliva, although role in allergen avoidance is not established
House dust mite allergen	Encase mattress in an allergen-impermeable cover Encase pillow in an allergen-impermeable cover or wash weekly Wash sheets and blankets on patient's bed weekly in hot water
Cockroach allergen	Avoid leaving food or garbage exposed Consider use of poison baits, boric acid, and traps in houses with cockroach infestation Professional extermination with chemical agents not preferred as can be irritating to some patients
Indoor fungi (molds)	Controlling dampness and fungal growth in home can be beneficial
Outdoor inhalant allergens	
Trees, grass, weeds, and seasonal mold	Consider staying indoors during peak pollen times; particularly midday and afternoon Keep windows closed in an air-conditioned environment Outside activity shortly after sunrise results in less pollen exposure
Indoor/outdoor irritants	
Environmental tobacco smoke	Avoid smoking and exposure to environmental tobacco smoke
Air pollutants (particulate matter, nitrogen dioxide, ozone)	Avoid exertion or outdoor exercise when levels of air pollution are high
Formaldehyde and volatile organic compounds (sources include new linoleum flooring, synthetic carpeting, particle board, furniture, and recent painting)	Patient education on the potential irritating affects of newly installed furnishings and finishes
Gas stoves, wood-burning appliances, and fireplaces	Avoid exposure or make sure appliances vented to the outside
Occupational irritants	Avoidance of exposure recommended Referral to an occupational specialist

*Vacuuming carpets once or twice weekly can reduce house dust. Patients known to be sensitive to house dust should avoid rooms that are being or have just been vacuumed. If patients vacuum, they should wear a dust mask, use a cleaner fitted with a high-efficiency particulate air filter, or use a cleaner fitted with a double bag.

Source: U.S. Department of Health and Human Services (16).

Chart 2 - Comorbid conditions that can worsen asthma symptoms, with treatment recommendations.

Comorbid condition	Recommended treatment
Allergic bronchopulmonary aspergillosis	Prednisone 0.5 mg/kg with gradual tapering Evaluate progress by repeat chest imaging and determination of serum IgE
Gastroesophageal reflux disease*	Avoid heavy meals, fried food, caffeine, alcohol intake Avoid food or drink within 3 hours before bedtime Elevate the head of bed on 6- to 8-inch blocks Institute appropriate pharmacotherapy
Obesity	Weight loss has been shown to reduce asthma exacerbations and improve pulmonary function and quality of life
Obstructive sleep apnea	Expert panels have recommended screening patients with poorly controlled asthma for obstructive sleep apnea, especially if they are overweight or obese.
Rhinitis/sinusitis	Intranasal corticosteroids First- and second-generation antihistamines Immunotherapy can be considered in refractory cases
Stress and depression	Clinical trials still needed to determine role of stress reduction and asthma symptoms Observational studies show an association between chronic stress and worsening of asthma symptoms

*Asthma sufferers with asymptomatic reflux do not appear to benefit from acid suppression therapy.

Source: U.S. Department of Health and Human Services (16).

DRUG THERAPY

In a recent excellent review of drug therapy in asthma (3), Fanta stressed the importance of categorizing medical therapy on the basis of its role in treatment (quick relief versus long-term control), rather than on the basis of its specific molecular action (bronchodilation versus anti-inflammation). We will build on this concept by discussing the use of monotherapy and combination therapy in regards to long-term control. We will also discuss the challenge of severe asthma that is refractory to treatment.

For quick relief of asthma symptoms, the preferred agents are short-acting β_2 agonists (SABAs). They offer the fastest onset of action for bronchodilation and do not lose their potency with an increased number of daily treatments (18). Recent studies have shown that the use of an inhaled corticosteroid-SABA combination is clinically efficacious as rescue medication (19,20). This is appealing because it combines an acute bronchodilator with an anti-inflammatory agent at a time when inflammation is most active and control is not being achieved with the standard dose of the corticosteroid. However, the use of the inhaled corticosteroid-SABA combination has not been universally recommended (16). Although the combined use of a long-acting β_2 agonist (LABA) with a rapid onset of action and an inhaled corticosteroid (specifically the formoterol-budesonide combination) has shown favorable results as quick-relief therapy, its safety has not been extensively studied (3,21,22).

SINGLE-AGENT CONTROLLER THERAPY

Inhaled corticosteroids

Inhaled corticosteroids are the most effective therapy for long-term control of asthma symptoms. They consistently reduce asthma symptoms and airway

hyperresponsiveness, improve peak expiratory flow, and prevent exacerbations (23-25). Their mechanisms of action (genomic and non-genomic) have broad effects on asthma inflammation. They are effective as monotherapy in patients with mild-to-moderate persistent asthma. In low-to-moderate doses, they tend to have very few systemic effects. However, at higher doses, their therapeutic efficacy tends to flatten, while the systemic absorption and side effects continue to increase. Therefore, the goal of effective treatment is to find the lowest dose possible to achieve control. This is done either by adding a second agent or by reducing the dose once control has been achieved and sustained for 3 to 6 months.

Leukotriene modifiers

Leukotriene modifiers are effective at treating mild persistent asthma. They are considered an alternative therapy in patients who cannot tolerate or do not wish to take inhaled corticosteroids. Because adherence to pills is often better than is adherence to inhalers, pragmatism suggests that these agents should be considered more frequently. In addition, as these agents come off patent, their cost-effectiveness might sway clinicians to use them as single-agent controller therapy in patients with adequate asthma control. Finally, due to their mechanism of action, these agents have salutatory effects on patients with associated allergic rhinitis or aspirin intolerance.

COMBINATION CONTROLLER THERAPY

For patients with moderate-to-severe persistent asthma, achieving symptom control can be very challenging and often requires inhaled corticosteroids plus adjuvant therapy (26).

inhaled corticosteroids/LABAs

For patients in whom asthma is not effectively controlled by inhaled corticosteroid therapy alone, adding a LABA is effective at improving asthma symptoms, decreasing future exacerbations, and lowering the total dose of inhaled corticosteroids (26-29). A LABA should never be used as monotherapy in the treatment of asthma, because they have been associated with an increased risk of fatal and near fatal asthma attacks (30). The use of an inhaled corticosteroid-LABA combination is believed to have synergistic effects by which the inhaled corticosteroid improves the efficacy of the LABA and vice versa (31). The LABAs are thought to facilitate transcription of anti-inflammatory genes, whereas inhaled corticosteroids potentiate the action of the β_2 agonist either by inhibiting its local deposition or by enhancing β_2 receptor signaling in the lung (31-33). Combined with an inhaled corticosteroid, the use of a LABA is considered safe and is recommended as the initial adjuvant for achieving asthma control (34).

Inhaled corticosteroids, LABAs, and leukotriene modifiers

In asthma patients on inhaled corticosteroid therapy, adding a leukotriene modifier is less effective than is adding a LABA (35). Combining a leukotriene modifier with a LABA (without an inhaled corticosteroid) is also less effective (36). Therefore, leukotriene modifiers are often used as a third agent to limit the total dose of inhaled corticosteroid in patients with difficult-to-control asthma.

Theophylline

Theophylline is a weak bronchodilator at the suggested plasma concentration (5-15 mg/L). Its potency is limited by side effects that can develop at a plasma concentration > 20 mg/L. The anti-inflammatory effects of theophylline have recently been re-examined. At a lower concentration (5 mg/L), theophylline activates histone deacetylases, which inhibit the expression of inflammatory genes such as nuclear factor kappa B (37). At lower doses, theophylline might have synergistic effects as an adjuvant to inhaled corticosteroid therapy (activated glucocorticoid receptors recruit histone deacetylases to inflammatory genes). In one study, low-dose theophylline was found to be as effective as are leukotriene modifiers in controlling mild-to-moderate asthma (38). Theophylline might have a role in patients who are poor responders to inhaled corticosteroids (smokers and obese patients).

inhaled corticosteroids and tiotropium

Short-acting anticholinergic agents are not currently recommended in the usual treatment of asthma. The long-acting anticholinergic tiotropium has been shown to be an effective bronchodilator and to reduce

exacerbations in patients with COPD (39). It was only a matter of time before its potential role in asthma was closely examined. In a recent, large, double-blind, randomized control trial, patients already on an inhaled corticosteroid were randomized to the addition of tiotropium, the addition of a LABA, or the doubling of the inhaled corticosteroid dose (40). The primary endpoint was peak expiratory flow. Adding tiotropium was more effective than was doubling the inhaled corticosteroid dose and was equally as effective as was adding a LABA. Although further studies are pending to clarify the future role of tiotropium, its use can now be considered in patients who are intolerant to LABAs and are already on an inhaled corticosteroid.

SEVERE ASTHMA REFRACTORY TO COMBINATION THERAPY

Approximately 10% of asthma sufferers will have refractory symptoms despite a combination of controller therapies (41). This is a heterogeneous group of patients who often require either continuous oral corticosteroids or frequent corticosteroid "bursts" every year. Among such patients, there is greater morbidity and use of health care services. Although managing asthma in this population is challenging, there are now several novel treatment options to help these patients achieve better asthma control (42). In addition, patients with severe asthma display a number of asthma phenotypes that can help clinicians determine which of these therapies to pursue.

Immunotherapy

Omalizumab is an anti-IgE monoclonal antibody that is used in asthma sufferers whose symptoms are uncontrolled on triple therapy (an inhaled corticosteroid-LABA-leukotriene modifier combination). Omalizumab has been proven to decrease asthma exacerbations and emergency room visits, as well as improving quality of life in patients with moderate-to-severe allergic asthma (43). The prototypical patient in whom such treatment is considered has an asthma phenotype that includes a documented sensitization to a perennial aeroallergen (dust mite, animal dander, mold, or cockroach) as well as a serum IgE level of 30-700 IU/mL. Unfortunately, even with these parameters in place, it is difficult to predict which patients will respond to omalizumab therapy. In one study, the prescribing physician's overall assessment of the benefit of treatment after 16 weeks was found to predict who did best with this treatment in the long run (44). Finally, in those patients already requiring oral corticosteroids on a daily basis, omalizumab neither allows reduction in the dose of oral corticosteroids nor significantly decreases asthma exacerbations (43).

Two other biologics have received additional attention more recently. Mepolizumab is an anti-IL-5 monoclonal antibody. It is effective in reducing the

number of eosinophils in the airway and blood. In earlier trials, its effects on patients with mild-to-moderate asthma were disappointing (45,46). However, two small randomized trials recently showed that mepolizumab can reduce asthma exacerbations while reducing oral corticosteroid doses in a highly selected group of patients (47,48). Their phenotype included refractory asthma with persistent airway eosinophilia (> 3% eosinophils in induced sputum), despite treatment with oral corticosteroids or high-dose inhaled corticosteroids. The responders tended to have late-onset asthma (symptom onset in their late 20s) and less atopy than expected for the observed degree of eosinophilia. Despite reducing the frequency/severity of exacerbations, the addition of intravenous mepolizumab did not improve lung function.

Lebrikizumab is anti IL-13 monoclonal antibody. IL-13 is elevated in some patients with refractory asthma despite the use of inhaled and systemic corticosteroids. It has been proposed that IL-13 induces periostin secretion from bronchial epithelial cells with subsequent fibroblast activation and airway remodeling (49). In a recent trial, asthma patients treated with lebrikizumab had greater improvements in lung function than did those receiving a placebo, at 12 weeks but not at 24 weeks (50). Rates of exacerbations were not improved with treatment. In that study, the patients designated as having "high periostin levels" (above the median for the 212 patients studied) seemed to derive the most benefit from lebrikizumab, suggesting the existence of another asthma phenotype for specific therapy in the future.

Bronchial thermoplasty (BT)

Bronchial thermoplasty (BT) has recently been approved for the treatment of severe asthma. It involves performing three bronchoscopies in which thermal energy is delivered to the airway wall with the goal of reducing smooth muscle mass. The largest trial to date, which included a control sham bronchoscopy group, showed statistical improvement in a quality of life score in the intervention group, although the control

group also showed greater than expected improvement (51). Secondary outcomes did note a benefit to BT in regards to severe exacerbation, emergency room visits, and days missed from work or school. Although the results were not uniform in those who underwent BT, no specific responder phenotype was evident. Some have suggested that patients with more prominent proximal airway inflammation and obstruction gain greater benefit from BT (52). In addition, its use was found to be safe in patients with an FEV1 as low as 60% of predicted, which might also constitute a target group. However, the long-term side effects of BT and the durability of its clinical benefits remain unknown.

Macrolide therapy

The phenotype of non-eosinophilic (neutrophilic) asthma has emerged as a challenging form to manage (41). Patients with neutrophilic asthma are more likely to be smokers and do not respond as well to inhaled corticosteroid therapy. Evidence of the benefits of macrolide therapy in chronic asthma is not conclusive, although macrolides do decrease neutrophil numbers and levels of associated cytokines in the airways (53,54).

FINAL CONSIDERATIONS

The key goal of asthma treatment is to achieve control. Mechanistically, this is achieved by combating ongoing airway inflammation. The approach to poorly controlled asthma is multifaceted. It involves patient education on allergen avoidance, as well as treatment of any comorbid conditions that can exacerbate asthma symptoms. Medical therapy in poorly controlled asthma begins with the use of inhaled corticosteroids. The most frequent adjuvant treatment associated with the best patient outcomes is the addition of a LABA. In patients who cannot tolerate the inhaled corticosteroid-LABA combination or in who asthma remains uncontrolled, there are additional roles for leukotriene modifiers, theophylline, and even long-acting anticholinergic bronchodilators. For patients with severe asthma that is refractory to treatment, a heterogeneous, high-risk group, novel therapies continue to emerge.

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