
Asthma Therapy from the Practice Perspective: Changes in the Wind

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The management of asthma presents a challenge to practicing primary care physicians, which is about to escalate considerably. First, it is becoming crystal clear that asthma is a heterogeneous condition that continues to be more prevalent in the community. This makes objective data (FEV₁, PEF, etc.) as essential as the care taken to work with patients so that they not only understand their disease but also how to properly use

the medications they have been prescribed. Second, the number of new classes of agents will increase in the next decade far faster than an understanding of the asthmatic process, making it imperative for the physician to return to the basic principles of therapeutics.

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INTRODUCTION

The management of asthma poses a unique challenge to the practicing physician. Part of this challenge is that despite apparently good therapy, the incidence and death rate from asthma are continuously rising.¹ Periodically, consensus conferences come out² but seem to be rarely followed even by those who take the time to read them. One of the most important points common to these reports is that asthma is a name given to a group of patients with a condition differing in cause, severity, and response to treatment.²

Asthma is defined as a chronic inflammatory disorder with intermittent narrowing of the airways or as a condition characterized by wide variations, over short periods of time, in resistance to the flow in intrapulmonary airways. This resistance to flow or impedance or obstruction is due to a reversible bronchial hypersensitivity that is produced by a combination of bronchiolar smooth muscle hypertrophy and contraction, excessive secretion of a viscous mucous, and inflammation.³⁻⁷

However we define *asthma*, it must be remembered that it is most likely not one entity. Rather, the airway obstruction disorders are heterogeneous with respect to cause, severity, predominant mechanism, and response

to therapy. This heterogeneity has become the basis for the heightened drug development, which has and will change the therapy of the future.⁴ In addition, it is becoming apparent that there are genotypes as well as phenotypes among asthmatic patients.⁸ The latter explain why for some asthmatics, steroids are especially effective, while others respond exceptionally well to anticholinergics or have a major leukotriene involvement, involve IgE, or have one of the many possible triggers.

The common denominator of the pathogenesis of asthma is thought to be an inherited or acquired defect in the homeostatic mechanism that maintains bronchodilation when exposed to bronchoconstrictive stimuli.⁷ Keep in mind that following the induced acute bronchoconstriction, there is usually a secondary, more slowly developing inflammatory phase—the late phase or late asthmatic reaction (LAR).⁷ So prominent is this late phase that it is medically correct to consider asthma an inflammatory disease and to treat it as such.

The stimuli inducing the absolute or relative bronchospasm may be antigens such as pollens, foods, dust, animal dander, fungi, drugs or inhaled environmental irritants, an infection, physical exercise, temperature changes, or emotional stresses. The mechanisms by which bronchospasm takes the upper hand are probably multiple. Currently, considerable evidence points to major differences in the release of a multitude of inflammatory mediators and involvement of many different cells (lymphocytes, macrophages, and eosinophils, just to name a few).^{7,8} Whatever the

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difference, the key to therapy of asthma is to understand the role of the dominant mechanism in a given patient. Clinically and physiologically, the use of two, three, or four different agents is, therefore, appropriate as each agent affects bronchodilation or prevents or reduces inflammation by different mechanisms. Using more than one agent allows one to use each at lower doses, which means a lower incidence of side effects.

As a precise definition of asthma is elusive, so too is its diagnosis unless the physician uses all of the tools he or she has available. Most helpful is the history that may consist only of a persistent cough. The cough may have a pattern (exposure to allergens, cold air, exercise, etc.) or may follow an URI.⁹ The objective evidence of airway obstruction is a low peak flow rate, FEV₁, and FEV₁/FVC ratio that are improved (elevated) by bronchodilators or made worse by methacholine. The physical exam is not usually diagnostic, as “all that wheezes is not asthma” is as true as the flip side that “not all asthma wheezes.” A silent chest is usually far more dangerous than one with high-pitched expiratory wheezes. Once diagnosed, the present thinking translates to immediate anti-inflammatory and bronchodilator therapy either by multiple doses of properly used medications and, if severe, initial short-term oral anti-inflammatory therapy with corticosteroids.

WHY THE INTEREST IN ASTHMA

The major and understandable reasons why there is so much interest and research into the causes and therapy of asthma can be gleaned from the following statistical and epidemiological information:^{1,10}

- In the United States, asthma is the sixth-ranked chronic condition (14.6 million Americans) and leading serious chronic illness in children (4.8 million children younger than age 18), with an estimated annual economic cost (direct and indirect) to the nation of more than \$12.4 billion.
- Nationally, 10 million days of school are missed because of asthma, making it the number one reason for missed school days in the United States.
- In the decade from 1982 to 1994, the prevalence of asthma increased more than 60%, with that of pediatric asthma increasing by more than 70%.
- The difference in prevalence between African Americans and Caucasian Americans rose from 7% in 1985 to 21% in 1991. This was paralleled by a disproportionately higher (three times as high) death rate, with the result that whereas African Americans represent 12% of the population, they account for more than 20% of the deaths from asthma.

- From 1979 to 1991, the death rates from asthma have increased significantly, with African American males leading the pack with an 84% increase in death rate compared to a 25% increase in Caucasian Americans.

ASTHMA THERAPY IN EVOLUTION

The therapy of asthma has changed over the years. In the 1960s, the most common medication was a combination of ephedrine, a barbiturate, and a theophylline called Tedral®. The medication we all had to know how to use was i.v. aminophylline, and the beta agonists had considerable β_1 activity in addition to the desired β_2 action. In the 1970s, long-acting theophyllines and improved beta agonists were the drugs of choice until the first inhaled corticosteroid came out in the mid-1970s. The additive side effects of the beta agonists and theophylline made this an unlikely combination, but it was the best we had. In that same decade, the availability of agents to prevent bronchoconstriction (cromolyn, nedocromil) and the first synthetic anticholinergic agent (ipratropium) became available. Inhaled corticosteroids changed our approach, and in the 1980s, these and the newer beta agonists were the mainstay of therapy. The 1990s has seen not only the resurgence of the use of the theophyllines (for an anti-inflammatory effect)¹¹ but the development of the first new class of mediator-specific therapies—the leukotriene modifiers.^{12,13} The therapy of the first decade in the new millennium can be summarized by “hang on to your hats.”

CURRENT THERAPY

The drugs presently available to manage asthma fall into two broad categories. The first group is the bronchodilators (relievers), of which there are four general types (see Table I):

1. *Beta agonists.* Stimulation of the β_2 receptor dilates bronchi. The first agents (isoproterenol and epinephrine) were nonspecific beta agonists (stimulating β_1 and β_2) with a short duration of action. Molecular modification has led to considerably more β_2 selectivity and a longer action. Beta agonists are effective but are presently recommended for “rescue” therapy only.¹⁴
2. *Anticholinergics.* These are the oldest group. The development of analogues that lack major systemic effects are now used clinically. These agents are especially useful for the irritative sensitivity in some patients. They are good bronchodilators and, in addition, reduce secretions (cholinergic hyperactivity) of

some asthmatics.^{15,16} Ipratropium (Atrovent®) is useful and has an excellent side effect profile.¹⁵

3. *Methylxanthines*. The “theophyllines” were once used only for their ability to dilate bronchi. The bronchodilator doses, however, were close to that associated with side effects so they became little used until it was found that they are also anti-inflammatory at a lower dose, thereby leading to much less worry of toxicity.^{11,17} Using these agents is increasing as they work well, especially for nighttime symptoms.¹⁸ Isoenzyme-specific phosphodiesterase inhibitors are being developed that will expand theophylline use.
4. *Corticosteroids*. These are effective in reversing the inflammatory or late-phase component of an allergen-induced airway flow obstruction. They are also, indirectly, bronchodilators. Steroids modify the symptoms of bronchial asthma in several ways, including the following:
 - interfere with production and/or release of histamine;
 - lead to or facilitate vasoconstriction;
 - enhance beta-adrenergic responsiveness (catecholamine potentiation);
 - relax bronchiole smooth muscle, either directly or indirectly;
 - decrease the quantity and viscosity of secretions.

They are used alone or in combination with others and are considered, by some, to be essential in the management of asthma.¹⁹ Corticosteroids are often required to break an “attack” (oral use as a “reliever”) and are very useful in preventing future bouts by many topical delivery systems. Using these agents topically (i.e., by inhalation of microparticles from an metered dose inhaler (MDI) or other delivery system), they are quite safe and effective.¹⁹

The second group is the anti-inflammatory (controllers) group, which is also a heterogeneous group with anti-inflammatory, and thereby antibronchoconstrictor, activity. This group includes the following:

1. *Corticosteroids*. These agents, which are often incorrectly maligned, presently form the mainstay of anti-asthma therapy as they directly inhibit the inflammatory process believed to be the major cause of chronicity and progression.¹⁹ One of the newest agents, fluticasone (Flovent®, Flixotide®), has 18 times the glucocorticoid activity of dexamethasone—one of the standards.²⁰
2. *Cromolyn*. Disodium cromoglycate (Intal®, Fivent®) has no bronchodilator activity and no effect on chemical mediators once released but has prophylactic ac-

tivity against asthma and other histamine-induced allergic conditions. They are used to prevent exercise-, cold-, or allergen-induced bronchoconstriction.^{21,22}

3. *Pyranoquinoline*. Nedodromil (Tilade®), a nonsteroidal anti-inflammatory agent, has been shown to inhibit the release of the mediators of inflammation such as histamine, leukotriene C₄, and prostaglandin D₂.²² Combined with other anti-asthmatic drugs, control of asthmatics is surprisingly symptom free. Nedocromil is more potent than cromolyn.²²
4. *Leukotriene modifiers*. This group is the first new approach to the management of asthma in 30 some years. Named from their original source (leukocytes) and chemical configuration (conjugated trienes), these agents modify, by different means, the actions of a major cause of the inflammatory response in asthma.^{4,23-25} The selective leukotriene D₄ antagonist zafirlukast (Accolate®) and its newer and more potent cousin montelukast (Singulair®) are the first in the West.^{24,25} In Japan, pranlukast (Onon®, Ultair®) and ibudilast (Ketas®) act similarly.²⁶ Montelukast, at once a day and with an excellent safety profile, will be hard to beat.²⁴ Leukotrienes can also be inhibited by blocking one of the enzymes (5-lipoxygenase) as in zileuton (Zyflo®, Leutrol®).³ Other inhibitors of the inflammatory process involving the leukotriene pathways will follow as work is ongoing.^{4,13,25} As asthma is proving to be a heterogeneous disease, a trial on these agents is warranted early in therapy.
5. *H₁-selective antihistamines*. Ketotifen (Zaditen®) is the first one developed. This agent also inhibits the action of some of the mediators of inflammation and their secretion by mast cells and also reduces eosinophil infiltration.²⁷ Watch for more to be developed.

DRUGS OF THE FUTURE

Among the candidates for the medications we will see in the future are a group of improvements in existing classes of drugs.

Even the beta agonists are being modified and studied. One agent, with some anti-inflammatory activity in addition to beta agonist activity, is formoterol (Foradil®). Others include the terbutaline pro-drug bambuterol and sepracor, which is D-albuterol (salbutamol) and seems to have far fewer side effects than either the S form or the racemic form.^{28,29}

In the theophylline group, there are isoenzyme selective phosphodiesterase (PDE) inhibitors that should be available in the near future. These xanthine-like drugs that are specific for individual phosphodiesterase isoenzymes should improve the

Table I Drugs Presently Used in the Management of Asthma

Adrenalin-like (active beta agonist bronchodilators)	
Epinephrine (Adrenalin, Bronkaid, Primatene)	i.v., subq, MDI
Metaproterenol/orceprenaline (Alupent, Metaprel)	MDI, soln, tablets
Albuterol/salbutamol (Ventolin, Proventil, Volmax)	MDI, Diskhaler, solution, tablets
Eformoterol (Oxis Turbohaler)	Powder MDI
Terbutaline (Bricanyl Turbohaler, Brethine, Brethaire)	MDI, soln, tablets
Fenoterol (Berotec)	MDI
Salmeterol (Serevent)	MDI
Procaterol (Pro-Air)	MDI
Pibuterol (Maxair)	MDI
Isoetharine (Bronkometer, Bronkosol)	MDI
Bitolterol (Tornalate)	MDI
Atropine-like (cholinergic system inhibitors [®] bronchodilation)	
Ipratropium Br. (Atrovent)	MDI, soln.
Also available with albuterol as Combivent	MDI
Methylatropine nitrate	
Methylxanthines (anti-inflammatory at lower doses)	
Theophylline (Slo-Bid, Theo-Dur, Uniphyll)	oral
Oxtriphylline (Choledyl)	oral
Dyphyllin (Lufyllin, Neothylline, etc.)	oral
Corticosteroids (anti-inflammatory and aid in bronchodilation)	
Prednisone (many trade names)	i.v., oral
Prednisolone (Pediapred, etc.)	oral
Methylprednisolone (Medrol, etc.)	i.v., oral
Beclomethasone (Beclovent, Becloforte, Vanceryl)	MDI
Flunisolide (Aerobid, Aerobid-M, Bronalide)	MDI
Triamcinolone (Azmacort—built-in spacer)	MDI
Budesonide (Pulmicort Turbohaler)	Powder MDI, soln.
Fluticasone (Flovent, Flixotide)	MDI
Cromolyn glycate (inhibitor of mediator release)	
Cromolyn sodium (Intal, Aarane, Fivent)	MDI, soln.
Pyranquinoline (inhibitor of many steps in the inflammatory process)	
Nedocromil (Tilade)	MDI
Luekotriene modifiers (specific inflammatory mediator inhibitors)	
Montelukast (Singulair)	oral qd
Zafirlukast (Accolate)	oral bid
Zileutin (Zyflo, Leutrol)	MDI, oral
Antihistamine plus (Inhibits histamine-1, etc.)	
Ketotifen (Zaditen)	oral

therapeutic potential and reduce the side effects. These novel PDE inhibitors are specifically targeted to smooth muscle or inflammatory cells.³⁰ A cGMP-specific PDE inhibitor and PDE III and IV inhibitors are coming with the anti-inflammatory activity of corticosteroids without their side effects.^{28,31}

Anticholinergic therapy also will have effective additions. Of the muscarinic receptors, the M₂ and M₃ are related to the control of bronchial smooth muscle.

The long-acting M₃ blocker, oxitropium, is presently in phase III trials.^{16,28}

As effective and potent as currently available corticosteroids are, more agents with narrower spectrums of activity are on the way, including a corticotropin releasing factor (CRF), which is now in trials.²⁸

Newer antihistamines, which seem to block more than histamine, will also surface. Histamine is a potent bronchoconstrictor of the early asthmatic response.

Selective H₁-blockers have been found that reduce pollen-induced and exercise-induced asthma. Examples include ebastine (Ebastel[®]); the phthalazone derivative, azelastine; and a cousin, cetirizine (Zyrtek[®]).²⁸

Single-Mediator Antagonists and Combinations

The new kids on the block, so to speak, are what is making and will make the therapy of asthma change. The physician will have an armamentarium of dozens of classes of agents, each with a subset of patients in which these will be most effective. Research has revised our concept of asthma and its treatment. There are many mediators of the asthmatic process, derived from cells.⁸ Blockers of the eicosanoids (prostaglandins, prostacyclin, thromboxane A₂, and the leukotrienes) or monoclonal antibodies are just a few examples. The list is expanding rapidly.

The first new group are the leukotriene modifiers,^{8,13,23} drugs that modify the response of these mediators of inflammation by one of four ways. The first is the cysteinyl leukotriene inhibitors, of which there are presently almost a dozen agents that antagonize or inhibit a leukotriene (predominantly LTD₄). These agents inhibit phospholipases, prostaglandins, leukotrienes, and IL-1 synthesis.^{4,25,30,32} Iralukast may be the next to surface. The second are the 5-lipoxygenase inhibitors, which prevent the formation of leukotrienes by blocking a pathway in their synthesis. Presently, several agents are in late preclinical or early clinical trials.^{25,30} The third are the five lipoxygenase activating protein (FLAP) inhibitors. Several, such as SB-210661, are in the pipeline and are expected in the next year or so.^{28,32} The last of this group are the leukotriene receptor antagonists. Presently, selective and high-affinity LT₁ antagonists are in the pipeline.^{28,33}

From this point on we enter into a surprising array of specific and general mediator inhibitors and antagonists, with the hope that one or more will be effective in reducing the underlying cause of the chronicity of asthma—inflammation. Enter the many mediators of inflammation.^{3,8} Among those that are being seriously studied and that show early promise include antagonists and/or inhibitors such as: interleukin-5³⁴

PAF,³⁵ which is a mediator of inflammation and bronchoconstriction that, in addition, increases mucous secretion and recruits platelets and eosinophils from the extracellular space into the lungs. Presently, there are at least six compounds under development.^{28,35}

Thromboxane A₂, which is a potent bronchoconstrictor, mucous producer, and blood and vessel permeability inducer and causes airway hyperresponsiveness.³⁶ Serabenas (Bronica[®]), domitroban, and ozagrel are in clinical trials or in some markets. Imitrodast (Logran[®]), which is a thromboxane synthetase inhibitor, will be out soon in Japan.^{28,36}

Neurokinin, in which at least three companies are actively developing antagonists to the NK-1 and NK-2 receptors that show some promise in reducing the inflammatory process.^{28,30}

Tryptase^{28,30,37}

Very late antigen (VLA), especially VLA-4, inhibitors of eosinophil involvement.²⁸

A variety of chemokine inhibitors, one of which is the chemo-attractant eotaxin, which is secreted by inflamed lung tissue, thereby attracting eosinophils. Eotaxin receptor blockers that are being investigated as eosinophils are believed to be major contributors to the pulmonary damage seen in asthma.³⁴

In addition to specific mediator inhibitors, there are other classes of agents, including potassium channel openers that appear to have the ability to inhibit histamine- and antigen-induced bronchoconstriction and to have some bronchodilator action.³⁸ Other classes include the following which are on the way: (1) lemakalim, which is in phase II trials;²⁸ (2) monoclonal antibodies, in which studies are under way on Monoclonal Abys to IgE, the CD23 antigen, and to interleukin-5 (TRFK-5);^{28,34} and (3) miscellaneous—auteral (picumast di-HCl) is a multimediator release inhibitor, ibudilast (Ketas[®]) potentiates PGI₂ and antagonizes both LTD₄ and PAF,²⁶ and immunomodulators and antibody-mediated inhibitors are also being studied.²⁸

There are many more agents in early preclinical or clinical studies as the changing understanding of the pathophysiology of asthma opens doors and minds.

PRINCIPLES OF THERAPY

Whether using old established therapy or one of the newer agents, the principles of therapy stand. The first is that the physician must establish not only the diagnosis but also the extent of the disease. The second is that the secret of successful therapy is to use as little medicine as needed, which means that one must follow patients closely with whatever therapy that is used and at whatever dose, so that one uses what is needed and no more. Carefully observed therapeutic trials really do make sense as all asthmatics do not have the same response to a given dose of an agent, plus the fact that different patients have different prominent mechanisms.

It is now clear that using multiple mechanisms to open and keep open the airways makes much more sense than pushing any one to the point of toxicity. The treatment of asthma means proper use of several pharmacological agents plus patient education as to their use. The physician may know the drugs and the principles of their use, but unless the patient also clearly understands the disease and its treatment, the physician can expect only limited success.

For proper management, the use of home peak flow rates to help patients get attuned to their condition and facilitate their control is essential.² Patients must be taught to take their "anti-asthma" medications regularly and not just when they are "tight" and to use their MDIs or other delivery systems correctly. In addition, office spirometry is indispensable in not only making the diagnosis of asthma but also in following the patient during therapy.^{39,40} Nothing beats objective evidence that there is an obstruction to airflow when the patient tells the physician that he or she is breathing just fine.

Once the physician has objective evidence, he or she must ensure that the medicine, if in the aerosolized or metered dose (MDI) form, is delivered to the lungs. Delivery of aerosolized medications is greatly enhanced at present by using one of the many spacer devices^{41,42} and making sure that the patient inhales the mist very slowly. The rate of inspiration should be less than 1 liter per second, which means that it takes 4 to 5 seconds to breathe the mist in. This and the timing of the inspiration help. Newer systems make this easier, and there are many new and innovative delivery systems in clinical trials at this time.⁴²

With the advent of more potent inhaled steroids,^{19,20} inhaled anticholinergics,^{15,16} oral leukotrienes modifiers,^{12,13,43} the nonsteroidal anti-inflammatory agents,²² and a demonstrated anti-inflammatory effect of theophylline,^{11,17} our "first line" is not clearly established. The only clear recommendation is that the beta agonists are to be used as rescue therapy only.¹⁴

The initial therapy for a severe attack of bronchospasm is a nonpressurized aerosol therapy (for adults, 2.5 mg of salbutamol/albuterol—or equivalent—added to 20 mg [which is 1 amp] Intal nebulizer solution and 1 nebulizer of Atrovent). To ensure resolution of the bronchoconstrictive episode, a short pulse of prednisone or methylprednisolone is required. Usually a 6- to 8-day course, starting with at least 40 mg and working down to 10 mg (for prednisone), is effective.

The advent of a new class of agents, the leukotriene inhibitors/antagonists, offers the clinician a new

opportunity to better define his or her patient, as there will be instances when these agents alone will offer a previously refractory patient considerable relief.⁴³ As new drugs become available, it is essential that physicians keep up and not be resistant to change.

The bottom line is that physicians can no longer treat all asthmatics with the same therapy and expect good results. It is expected that in the next decade, the physician must be equipped to tailor the "cocktail" of therapy to the needs of each individual patient.

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