

Breath of Fresh Air

Volume 11, No. 2

Information, news and advice for improving asthma well-being

Winter 2009

In Case of Emergency ...

Have a plan. A plan to deal with an asthma attack is the best defense against the severe, sometimes frightening, and potentially dangerous flare-ups of asthma that can, unfortunately, be part of living with asthma. Severe asthmatic attacks can occur in persons with mild as well as severe asthma, well-controlled as well as poorly-controlled asthma. Having a plan of action for dealing with an asthmatic attack is good practice for everyone with asthma.

In the last issue of *Breath of Fresh Air*, the goals of well-controlled asthma were identified and the step-care approach to achieving good control, according to the Guidelines issued by the National Asthma Education and Prevention Program, were defined. In this article we review what the Expert Panel that wrote these Guidelines had to say about “Home Management of Asthma Exacerbations.”

Step 1: You can use your quick-relief bronchodilator more frequently than usual during an asthma exacerbation. You may be familiar with the general recommendation that, *under usual circumstances*, quick-acting bronchodilators are meant to exert their effect for 4–6 hours and so to be used no more than 4–5 times per day. However, during an asthma attack, this “rule” no longer applies. During an asthma flare, you can repeat a treatment with your quick-relief bronchodilator after just 20 minutes. To review, the quick-acting bronchodilators are albuterol (ProAir, Proventil, Ventolin), levalbuterol (Xopenex), and pirbuterol (Maxair). And you can use more than your usual dose of 2 puffs. If you are having great difficulty breathing, carefully (one deep breath for each puff) take 4 or even 6 puffs from your metered-dose inhaler. Using a spacer with the metered-dose inhaler helps you get the most from your metered-dose inhaler.

Some people have a compressor with nebulizer at



home to deliver inhaled medications. Perhaps you use this system to give inhaled medications to your child with asthma, or you find it convenient for your own aerosol medications. If you are suffering an asthma attack, you may find it desirable to use your quick-acting bronchodilator via the nebulizer system at home (albuterol, levalbuterol, or metaproterenol [Alupent]).

As with the metered-dose inhaler, you can repeat the dose after 20 minutes. The two systems (4–6 puffs by metered-dose inhaler vs. one nebulizer treatment) are equally effective in an asthma crisis.

Step 2: If, despite this treatment with your quick-relief bronchodilator, you still find yourself short of breath and wheezing, the next step is, in most instances, steroid tablets or liquid (e.g., prednisone, Medrol, Prelone, and others). Given the frequent side effects that one experiences from steroids taken in tablet or liquid form (“oral steroids”), this feels to many like a big step. But remember, breathing is a priority! Many asthma attacks will not get better with medicines (bronchodilators) that only relax the muscles that are constricting the breathing tubes. They require a medicine (anti-inflammatory steroids) that reduces the swelling and excess mucus production that are also frequently part of asthma attacks. A well-timed and brief course of oral steroids can often prevent the severe asthma flare-ups that result in emergency room visits and hospitalizations, with their longer courses of oral steroids given at higher doses.

Virtually every person with asthma has available or access to a quick-acting bronchodilator. Most people do *not* have a bottle of oral steroids at home. This is an excellent subject to raise with your doctor at your next visit. Should you have oral steroids available at home? Or at least a prescription on hand? What dose of oral steroids would be appropriate to take in an asthma crisis? Does your doctor prefer to have you begin the oral steroid at home and then call his/her office to report that you have done so; or is it better to call first before beginning an oral steroid at home? These are questions that require some thought, based on the severity of your asthma, your past experiences with oral steroids, and your relationship with your

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physician. They deserve discussion at a time when you or your child is not in crisis.

Many people take an inhaled steroid as a regular controller medication for their asthma. Brand names include Aerobid, Alvesco, Asmanex, Azmacort, Flovent, Pulmicort, and Qvar. Inhaled steroids are also contained in the combination inhalers, Advair and Symbicort. Might it be possible to increase the dose of inhaled steroid to treat an asthma attack rather than take the steroid in tablet or liquid form? For a relatively mild asthma attack, this strategy may work. For a severe attack, the inhaled route of delivery is insufficient treatment; oral steroids are the best option.

For a mild asthma attack in someone not already taking an inhaled steroid, starting one twice daily is reasonable. Continue to use it for 1–2 weeks after the attack has abated. If you are already taking an inhaled steroid, studies have shown that doubling your usual dose is inadequate. You need to increase the amount 4-fold for this strategy to work. To do so, you may need a prescription from your physician for a stronger dose of an inhaled steroid. If you use an inhaled steroid combined with a long-acting bronchodilator (Advair or Symbicort), do *not* take 2 or 4 times the usual dose. To do so will give you too much of the

long-acting bronchodilator contained in your inhaler. You will need a separate steroid inhaler to increase the dose of inhaled steroids in an asthma attack.

Anti-inflammatory steroids take time to work. You may not notice any benefit for several hours. While waiting for the medication to have its effect, you can continue to use your quick-acting bronchodilator every hour or two to relieve your symptoms.

Step 3: Get help. You are not expected to manage asthma attacks on your own. Begin appropriate therapy, and if you do not get better, seek help. Call your doctor for guidance; or if you are in distress, go to your local urgent care center or emergency department. Get help immediately if your child is breathing very rapidly, drowsy, or blue. Get help quickly if your asthma attack is not getting better and your peak flow is less than half normal. You may need the help of ambulance transport (dial 911) to get to your emergency department safely. Do not try to drive your car and attend to your desperately ill child at the same time. Nor should you drive yourself to the emergency room if your difficult breathing makes it hard to walk to your car. In a crisis, your safety (or your child's safety) is key.



News About Asthma

Review of the Safety of Long-Acting Inhaled Bronchodilators

An Advisory Committee to the Food and Drug Administration (FDA) met in mid-December to discuss the safety of the long-acting inhaled beta-agonist bronchodilators, salmeterol (Serevent) and formoterol (Foradil). They had access to a summary document, 460 pages in length, that reviewed all of the balanced clinical studies of asthma in which some patients received treatment with salmeterol and formoterol while other, comparable patients did not. These long-acting bronchodilators were given either alone or in combination with an inhaled steroid. Two medications, also discussed by the Advisory Committee, combine the long-acting bronchodilator with an inhaled steroid in a single device: Advair (which combines salmeterol and the inhaled steroid, fluticasone) and Symbicort (which combines formoterol and the inhaled steroid, budesonide).

Their conclusion: if you have asthma, you should **not** use one of these two long-acting inhaled bronchodilators without at the same time using an inhaled steroid. In their review, the members of the Advisory Committee found that patients who used salmeterol (Serevent) or formoterol (Foradil) *without* also taking an inhaled steroid were more likely to have a severe asthmatic attack that required hospitalization, that required the help of a breathing machine in an intensive care unit, or that caused death.

Next the FDA will meet to discuss these recommendations and work with the pharmaceutical manufacturers of these drugs to help ensure their safe use. Final decisions are months away.

In the meantime, two important points are worth emphasizing. One is that the Advisory Committee did not find risk associated with the use of long-acting inhaled bronchodilators when used together with inhaled steroids. Thus,

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Breath of Fresh Air

Editor-in-chief

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Frontiers of Knowledge: Focus on Asthma Research

In this new series of articles, called “Frontiers of Knowledge: Focus on Asthma Research,” we will highlight the scientific work being done by members of Partners Asthma Center to unravel the persistent mysteries about asthma: what causes it, what makes it different among different people, how does it affect us, and how can we make it better... and someday cure it?

*We begin with a discussion with **Joshua Boyce, M.D.**, leader of asthma research for the Allergy group at Brigham and Women’s Hospital.*



How did you first get interested in asthma research?

When I was doing primary care pediatrics, I saw that asthma was remarkably common. I became fascinated by the disease and began to ask questions about it: why do people get asthma and exactly what is it. I quickly realized that there wasn’t a lot of information available and that it was pretty poorly understood. A mentor during my residency, Dr. Bob Zwerdling, was the first to tell me that asthma was most likely caused by inflammation of the airways; and if I wanted to understand asthma, I would have to understand mechanisms of inflammation. During my fellowship training in pediatric pulmonary medicine at the Mass General, my program director, Dr. Daniel Shannon, directed me over to the Brigham, to the laboratory of Dr. K. Frank Austen at the Brigham, who was studying the role of leukotrienes in airway inflammation in asthma in collaboration with Dr. Jeffery Drazen. That led me to join the Austen research group in the early 1990s and to a research career that I did not anticipate, but that has turned out to be pretty interesting!

In what direction did the research being done in the Austen laboratory take you?

I started my studies in the area of eosinophil development, but became interested in mast cells, a very important cell type in asthma and in allergic reactions in general.

Most of the research being done at the time—dealing with mast cells and the production of leukotrienes by mast cells—focused on studies done in a test tube on cells grown from mice, and relatively little was known about human mast cells. I decided early on that it made sense to address questions about human mast cells and develop methods to grow human mast cells in a test tube. We discovered some of the key factors in their growth and development and what regulates their function in inflammation—what “makes them tick.” We then started to work on how the chemical production of leukotrienes by mast cells is regulated by factors in the tissue that are associated with inflamma-

tion. We ultimately came to figure out that the leukotriene system—which we think of as causing wheezing in persons with asthma—is important in mast cell development *per se*. Mast cells need to be able to make leukotrienes in order to grow normally, particularly in circumstances that result in inflammation of the respiratory mucous membranes. As it turns out, mast cells are not the only cell type on which leukotriene receptor molecules can act as growth factor receptors. For example, airway smooth muscle cells also multiply when exposed to leukotrienes, a process that may be an important cause of the chronic structural changes in the airways (“airway remodeling”) seen in some people with asthma.

What are you working on now in your laboratory?

Most recently we got back to the study of leukotriene E₄, which had been thought of almost as a by-product, the leukotriene at the end of the chemical pathway and the one that is excreted in the urine. Because the precursors, leukotriene C₄ and D₄, are more powerful constrictors of bronchial muscle, leukotriene E₄ got somewhat ignored. But it turns out that leukotriene E₄ is the one that is capable of inducing inflammation and hyperresponsiveness of the airways. We were able to find out that leukotriene E₄ has its own receptor system. One of the leukotriene E₄ receptors that we are working on right now looks like it is a receptor not only for leukotriene E₄ but also for a class of cardiovascular drugs. This finding opens up a whole new potential area of therapy in asthma.

The gratifying part of research focused on basic mechanisms is to get to the point where you are finding things that might be directly applicable to human disease. It’s a circle in that you begin with observations that are made in the clinic and you go into the lab to try to figure out those observations, and that brings you back to the clinic. It may take you 15 years to complete the circle, but ideally, that’s what a physician-scientist tries to do.

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What's the next frontier for your research?

What I would like to do is figure out all of the components of the leukotriene E₄ receptor system. It appears that there is more than one receptor. And I would like to move that area into the clinic and test whether current antagonists or additional antagonists might be developed to target that system. And one wonders whether these drugs might also affect other allergic diseases. As an allergist and particularly as an allergist who treats children, I see lots of children with food allergies and other diseases where the biologic processes are very similar to asthma. When you try to develop a drug for

asthma, you may find a drug that works as well or even better in other allergic diseases. We are also studying related receptors and pathways that are a little further away from the clinic at this point but — who knows? — in 5 to 10 years may be ready for “prime time” as well.

From a practical standpoint, one of the biggest challenges that we face is staying funded. The National Institutes of Health’s freeze on funding increases for the past 7 years has created a real challenge to keep the research going and to foster the next generation of young scientists who want to do the same thing. We are looking for all sorts of ways to do that.

Spotlight



Martin Flax is a successful lawyer (practicing consumer law and juvenile and criminal law as a public defender) in Dedham. He has had asthma since early childhood. Growing up in St. Louis his asthma was unusually severe during his early adolescence. He had frequent asthmatic attacks and spent a lot of time in the local emergency room and hospital. To control his asthma he was treated with oral steroids (prednisone) ... at a time when there were few other options for treatment besides bronchodilators like adrenaline, theophylline, and isoproterenol (Isuprel). In desperation, his parents and pediatrician decided to send him in 1972 to Denver, to the Children’s Asthma Research Institute and Hospital. There he lived in a residential facility for 15 months while his asthma was brought under control. (The Children’s Asthma Research Institute and Hospital came to be known as the National Asthma Center. It was a charitable organization that provided residential care free of charge to children with intractable asthma. In 1978 it merged with National Jewish Hospital, which for a years was known as the National Jewish Medical and Research Center and now is called National Jewish Health.) Martin reflected on his experiences there for this *Breath of Fresh Air* article.



We were assigned to a cottage, with a circle of rooms around a common central area. There were perhaps 20 children living together in each cottage, with a resident dorm leader, perhaps a college student. There were about 5–6 cottages, and a hospital on the grounds. We went to the local public school in Denver; for me the last year of junior high school and the first semester of high school. Every day we would check our peak flow, and we could go over to the hospital if we needed more medications.

They would organize field trips for us. The doctors would go with us on camping trips or skiing in the mountains of Colorado. And they had sports leagues, like a touch football league for the boys. They tried to keep us doing as many regular activities as possible.

Every now and then they would have research studies. I remember listening to meditation tapes with a set of headphones. And at that time the medication, cromolyn, was being newly introduced. It had a capsule of medication and an inhaler device with a propeller [Spinhaler], but I couldn’t take it because it made me cough.

The philosophy was to train you to take care of your asthma yourself. We met with the doctors often, and the “house parents” would help us. I remember taking theophylline capsules and occasional nebulizer treatments. But I gradually got better and was able to reduce my dose of prednisone to a small dose taken every other day. After 15 months I was doing well enough that I could go home. The average stay was about 1 ½ years. One of the other children there, whom I grew up with, went on to become a doctor; and I think that he takes care of asthmatic patients.

Despite having to leave home and see his parents only once or twice during his residential stay in Denver, Martin feels that it was a good learning experience for him. He learned greater self reliance.

I think sometimes it’s scarier for a parent to watch their child wheeze than it is for the child. I got to know how to take care of my asthma better — not let it get to the point when you needed to go to the hospital.

Now, 37 years later, Mr. Flax uses a combination inhaler containing a corticosteroid and long-acting bronchodilator during his allergy season. He uses one inhalation once or twice daily during the summer months,

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none during the winter. He has not needed any prednisone for years, has been free of serious asthma attacks, and has not needed emergency or hospital care for a very long time.



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they did not find risk with Advair and Symbicort. The other is that their concerns about the safety of use of long-acting inhaled bronchodilators without an inhaled steroid did not extend to patients who use these drugs to treat their emphysema and chronic bronchitis (chronic obstructive pulmonary diseases, or COPD).

New Medications.

Ciclesonide. A new steroid medication has become available to treat allergic rhinitis (as a nasal spray, called Omnaris) and asthma (as an inhaler, called Alvesco). The medication is ciclesonide, and it has a unique feature. The medication itself is not active until it has been acted on by chemicals along the nasal and bronchial membranes. There it becomes an active steroid, used to reduce inflammation and prevent asthmatic symptoms.

There are obvious advantages to having an inhaled steroid that does not exert its action in the mouth, where some of the medicine deposits on its way down to the bronchial tubes. It makes the risk of developing a yeast infection in the mouth and back of the throat (oral candidiasis or “thrush”) less likely; and it means that not as much active medicine will be swallowed and absorbed into the bloodstream, where it can affect the bones, eyes, and skin.

Inhaled ciclesonide (Alvesco) is delivered by metered-dose inhaler, 60 puffs per canister, and comes in two strengths (80 micrograms per puff and 160 micrograms per puff). It has been approved for use in adults and children 12 years and older. It can be taken once daily in asthma.

Olopatadine nasal spray. If your allergies include itchy, watery eyes (“allergic conjunctivitis”), you may already know of an ophthalmic antihistamine, olopatadine eyedrops, called Patanol. Now the makers of this medication have made available a spray to treat nasal allergies, including sneezing and itchy, watery or stuffy nose. Olopatadine nasal spray (Patanase) is a pump spray, to be used two sprays each nostril twice daily in persons aged 12 years and older. It begins to bring relief of symptoms in approximately 30 minutes. Another antihistamine also available to treat allergic rhinitis is azelastine (Astelin). Other approaches to the treatment of allergic rhinitis include nasal steroid sprays, antihistamine tablets/liquid, and decongestant tablets/liquid.

Discontinuation of Alupent Metered-Dose Inhaler. With the availability of an environmentally safe propellant to power metered-dose inhalers, the use of harmful chlorofluorocarbons (CFCs) is fast disappearing. As of January 1, 2009, albuterol metered-dose inhalers with CFCs are no longer being sold. You will need to purchase one of the albuterol-HFA metered-dose inhalers, marketed as ProAir, Proventil, or Ventolin.

Some other metered-dose inhalers containing CFCs will continue to be manufactured until suitable alternatives are available. An example is the quick-acting bronchodilator, pirbuterol (Maxair), delivered from a patented breath-actuated inhaler device called the Autohaler. However, the manufacturer of another quick-acting bronchodilator, metaproterenol (Alupent), has decided to stop production of its CFC-containing metered-dose inhaler. When the current supply runs out, probably as of December, 2008, Alupent metered-dose inhalers will no longer be sold.

Metered-dose inhalers containing the environmentally-safe HFA propellant are listed in the following table:

Category	Generic Name	Brand Name
Quick-acting bronchodilator	Albuterol	ProAir, Proventil, Ventolin
	Levalbuterol	Xopenex
Inhaled steroid	Beclomethasone	Qvar
	Fluticasone	Flovent
	Ciclesonide	Alvesco
Combination long-acting bronchodilator and inhaled steroid	Salmeterol-fluticasone	Advair
	Formoterol-budesonide	Symbicort

Save the Date!

This fall our Asthma Center celebrates its 20th Anniversary. It was in October, 1989 that we began as the Longwood Medical Area Adult Asthma Center. Over the last two decades, we have grown to include specialists in both pediatric and adult asthma care from multiple hospitals throughout the Partners Healthcare system.

Help us celebrate 20 years of excellence in asthma care, research, and patient and provider education. We are planning a gala event for **Thursday, October 1, 2009** and invite you to be part of it. We will provide additional details in upcoming issues of *Breath of Fresh Air*.



Breath of Fresh Air

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