Volume 91 No. 6 June 2008

Medicine & Health
RHODE ISLAND
PUBLICATION OF THE RHODE ISLAND MEDICAL SOCIETY

Asthma & Allergy

What's in a Name???

GOOD - authentic, honest, just, kind, pleasant, skillful, valid

NEIGHBOR - friend, near

ALLIANCE - affiliation, association, marriage, relationship

CORPORATION - company, business establishment

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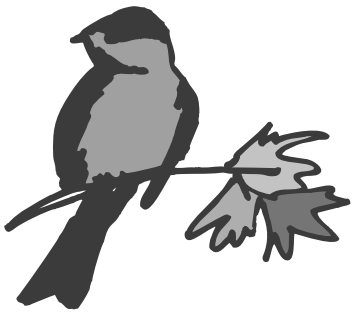
Commentaries



Neuroprotective Trials: No Longer a Cautious Optimism

You can't win a race if you can't find the starting line. Yet that is exactly where we are in the development of drugs to slow down **Parkinson's disease (PD)**. The drive to find these drugs has produced trials that assess an intervention despite not knowing what the disease process is. Let's take the case of PD. In the 1950s there were debates about where the pathological process was. That was definitively answered that decade, until the 1990s when it changed, and continues to change. In the 1980s there were debates about the importance of the Lewy body. That was settled when the Lewy body became a requirement for diagnosis. Ten years ago we figured out what the Lewy body is composed of, but we still don't know whether it's "good" or "bad." Either this ball of condensed protein is gumming up the cells, or, by forming a glob, is taking bad proteins out of circulation, keeping the cells from gumming up. Not only that, but after the 30-year debate, and after the Lewy body was finally accepted as a requirement for the pathological definition of PD, we are now probably about to classify two types of idiopathic PD, one with and one without the Lewy body although no one knows what other differences there are.

For many years we've focused on the dopamine deficiency in PD, but, as a recent editorial in *Neurology* ["The dopamine hypothesis, beating a dead horse,"] pointed out, the dopamine deficiency contributes to many, but not all, of the motor deficits in PD, but has little to do with some motor problems such as dysarthria or freezing, and has nothing to do with the dementia, depression, anxiety, apathy, sleep disorders, fatigue, or sympathetic dysfunction of PD. These are problems that are not understood. What parts of the brain are malfunctioning have not all been identified, let alone their biochemical causes.

Clinical trialists and pharmaceutical companies, realizing the financial risks of funding neuroprotective trials based on the obvious design of treating one group with active drug and the other with placebo and following both, has seized on a clever idea: the "delayed treatment" paradigm. One group is treated at entry, and the other arm is treated initially with a placebo, then after a predetermined period both groups are treated equally with the active drug. If the treatment produces only a symptomatic benefit then the two groups should end up looking the same, whereas if the group treated early does better than the group treated late, one might hypothesize that early treatment either produces increasing benefits, or that the treatment may slow disease progression. Either interpretation still implies that treating early produces a better outcome. Pain treatment, for example, is more effective if begun early and maintained, so that pain patients can be treated with less medicine if they are started early and given doses on a regular basis, whether needed or not. This doesn't alter disease progression (e.g., cancer pain) but does result in better outcomes. In PD one will derive the plausible conclusion that the drug slows the progression, and it will not be disprovable. However, it will not be proof and, at the least, we will know that early treatment, as with pain, results in better outcomes (not including side effects).

The federal government has sponsored expensive trials looking at a variety of drugs to slow disease progression in PD. These trials are based on theories of disease progression having to do with apoptosis (programmed cell death), biochemical death from oxidation and "free radical scavengers," abnormal cell protein folding, abnormal ubiquitination, and possibly inflammation. One trial proposed years ago, but not yet begun, is based on the oxidation hypothesis, no longer the theory of the day. The trial's Principal Investigator worried, as he defended his proposal, that the project, in taking so long to get through the NIH maze, woud have lost its panache by the time it was reviewed. The committee supported the project because it found the "old" theory just as persuasive as the newer ones, and wasn't persuaded that newer meant better. We all thought that it was worth a shot, even if the odds of success were slim. I don't think that any longer.

There's a problem basing large trials on theories, when the theories, unsupported by much data, wax and wane with the season. Theories are tremendously important so long as the hypotheses generate research, but not so good when the research has to be a lengthy, expensive, difficult clinical trial that may siphon off money from better uses.

Like my colleagues, I have thought for many years that it's better to do something than nothing and either put the theory to rest, or show that it works. I have come to see things differently. I think that $10,000,000 is better spent on the basics and not on a single trial that is unlikely to produce benefit. Ten million spent on a poorly supported clinical trial is ten million stolen from basic research. But the problem, of course, is less simple. It is unlikely that the $10,000,000 saved would go to PD basic research. More likely it would go to something unrelated, probably not even to medical research.

Is the PD community better served by a large clinical trial or nothing? For this question I don't have an answer. We can talk about how to spend money better, but too often when government money isn't spent on one unrewarding thing, it's spent on something less useful.

– Joseph H. Friedman, MD

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An Alien Legend With a Bite

Three members of the Brown family of Exeter, Rhode Island, succumbed to consumption [tuberculosis] within a span of four years; and then their only son, Edwin, also became ill. In 1892, little was known of the causes of tuberculosis nor whether supernatural forces underlay such tragedies.

Edwin's condition worsened. In desperation, George Brown, his father, sought the counsel of his neighbors, who concluded that the cluster of deaths must have been caused by some family member, already dead, exacting revenge. The group trekked to the Chestnut Hill Cemetery, behind the Baptist Church, and dug up the three Brown coffins, seeking a body that showed little significant deterioration. The exhumed body of Mercy Lena Brown, the younger daughter to die of consumption, looked intact. Furthermore, her heart contained liquid blood, sure evidence that she had recently consumed human blood and hence was a vampire. Her heart was extracted, cremated and its ashes fed to Edwin. Sadly, though, he died within weeks.

The *Providence Journal* reported the Mercy Brown incident in detail, accompanied by much discussion on the characteristics of vampires [the undead]. Most agreed on their existence since vampires had been part of European folklore for millennia. Dr. Michael Bell, a skeptical authority, declared that "A vampire is a corpse that comes to the attention of the community during a time of crisis, and is taken for the cause of that crisis." Thus, in his judgment, vampires were scapegoats "absorbing the ignorance, the fears, and in some cases the guilt that people have because their neighbors, friends and family are dying."

Somewhere in ancient southeastern Europe, pagan mythology concerning vengeful creatures returning from the dead had evolved into a structured folklore; and by the 13th Century the threat of revenant vampires tainted the legends of every village. The folkloric vampire was typically male, gaunt but with a ruddy and bloated face, red eyes, perilously long fingernails and often was a heretic or one who had been excommunicated. Some vampire tales, particularly from Romania, claimed they could transform themselves readily into wolves or rabid dogs.

Today, when most people believe that the earth is spherical and that skeptics need not be burned alive, it is strange how persistent the vampire legends have become. Ask an average American teenager to describe a vampire: he will render a precise description down to the black cape, the tuxedo, the high collar, an insistent hypersexuality, an east European accent, an aversion to garlic, sharp enlarged fangs – and the capacity to transform himself readily into a bat. Awareness of vampires is now universal. Even Sesame Street contains a vampire puppet, Count Count.

Why the historic association of vampires with bats? Rewording the question, what behavioral or visible characteristics – apocryphal, contrived or natural - may bats and vampires share? They both are said to be strictly nocturnal while dreading sunlight, are predatory, are fearsome in appearance, often endowed with fangs and red eyes, are mysterious in behavior and satanic in heritage, are cave or coffin-dwelling, and while not carnivorous, both are blood-sucking.

The overwhelming majority of bats, however, are benevolent creatures, exclusively insectivorous and not blood-sucking. Indeed, only three bat species are known to consume blood, and all three are confined to the Western Hemisphere. Thus, while bats had been part of the pre-columbian mythology in South America for millennia, the bat as a surrogate for a vampire did not enter European legendry until the Spanish conquerors of Latin America brought these myths back to Europe, along with maize, tobacco and syphilis.

The bat had then been gradually transformed from a timorous rodent adapted to night flying to a terrorizing wraith, and a palpable threat to humanity. By the 18th Century, the bat had become firmly entrenched in the spells of necromancy and vampirism.

The last decade of the 18th Century and the early decades of the 19th Century witnessed the formalization of the vampire image in the genre novels of Goethe, Polidori, Rhymer and much later, in Bram Stoker's *Dracula*.

The 20th Century added a new dimension to the spreading malevolence of the vampire bat. Western Hemisphere bats were threatening range cattle: one Department of Agriculture document estimated that over a half million cattle died annually because of rabies encephalitis transmitted from cow to cow by the biting, blood-sucking feral bats. Rabies vaccines are available but represent an expensive intervention; and most ranchers leave their cattle immunologically unprotected. Thus, rabies in cattle was now added to the burdens initiated by vampire bats. But do bats play any substantive role in human rabies?

There have been 47 verified, documented cases of indigenous rabies in Canada and the United States since 1990, and 43 of these instances were attributable to bat bites. It should be remembered that untreated rabies is a uniformly fatal form of brain inflammation.

Legend and reality, the two companion pillars of human credulity, have always served in man's struggles to understand the world around him; and the imagery of howling wolves, rabid dogs, Transylvanian winters, nocturnal bats and unexplained deaths from rabies or other ills all have coalesced to solidify the vampire myth—whether in Romania or Exeter, Rhode Island.

– Stanley M. Aronson, MD

Disclosure of Financial Interests
Stanley M. Aronson, MD, has no financial interests to disclose.

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Special Focus: Allergy & Asthma – Introduction

Russell A. Settipane, MD, FAAAAI

In the 35 years since the publication of the last allergy update in this journal,[1] significant advances have occurred, both in the understanding of the immunology which underlies allergic disease pathophysiology as well as in the development of new therapeutic strategies. In 1973, when Guy A. Settipane, MD, reviewed pathogenic mechanisms in allergy, IgE had been discovered only six years earlier; arachadonic acid metabolism was just beginning to be elucidated and interleukins and inflammatory cytokines had yet to be described. Most of the therapeutic practices for allergic diseases were employed empirically with little scientific support.

In the past three decades, research on the epidemiology, etiology, diagnosis, treatment and prevention of many allergic diseases has advanced to the point that it is on par with or exceeds that of other specialties. Evidence-based treatment guidelines and practice parameters have been published for a multitude of allergic diseases. Additionally, board certification in the specialty of allergy/immunology has become rigorous, requiring board certification in internal medicine or pediatrics and a minimum of 2 years of fellowship training. Allergy/immunology remains one of the few specialties where Fellows receive both pediatric and adult medicine training; certification is by a conjoint board of Pediatrics and Internal Medicine.

The members of the RI Society of Allergy welcome this issue of Medicine & Health/Rhode Island.

We hope that in disseminating the latest research on allergy and asthma, the care of Rhode Island patients will be enhanced.

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For this issue of *Medicine & Health / Rhode Island*, academic contributions have been provided by members of the Rhode Island Society of Allergy as well as the Division of Pulmonary and Allergy of the Warren Alpert Medical School at Brown University. Subjects range from new research information to reviews of specific topics. Robert Klein and Sheryl Kopel report on the association of obesity and asthma. Stanley Block reviews challenges in the treatment of inner city asthma. Sidney Braman addresses the question as to whether the 2007 "Guidelines for the Diagnosis & Management of Asthma," published by the National Asthma Education and Prevention Program, will improve the quality of care in America. Alan Gaines reviews the stinging insect venom immunotherapy and prevention of anaphylactic deaths. In juxtaposition to the importance of indoor allergens discussed by Dr Block, Henry Freye reviews outdoor aero-allergens, specifically pollen and mold. Anthony Ricci discusses latex allergy and its clinical repercussions. Finally, Russell Settipane reviews advances in therapeutic immunomodulation of IgE mediated diseases.

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Childhood Asthma and Obesity

Sheryl J. Kopel, MSc, and Robert B. Klein, MD

Parallel increases in the prevalence of asthma and obesity have prompted researchers to examine relationships between the two conditions. We highlight the literature and present preliminary pilot data on asthma and obesity collected on a small sample of Rhode Island children attending a 1-week asthma summer camp.

Prevalence Rates of Asthma and Obesity

Asthma, the most common chronic illness in children, affects approximately 6.2 million children under the age of 18.[1] Its prevalence has been steadily increasing (Figure 1), and despite the rates leveling off, it remains a critical concern. Twelve percent of US children have a lifetime history of asthma, and 8.8% report currently having the condition.[2] Rhode Island has an 11% prevalence rate of current asthma in children 0-17 years old—the 5th highest in the US.[3]

Children from racial and ethnic minorities experience a disproportionate asthma burden.[4] From 2001-2005 rates of hospitalizations for asthma among African American children in Rhode Island were nearly triple the rates of their white counterparts; and Hispanic children were hospitalized more than twice as often as white children.[3] Non-Hispanic black and Hispanic children, particularly those of Puerto Rican descent, experience higher prevalence rates and morbidity than white children.[5]

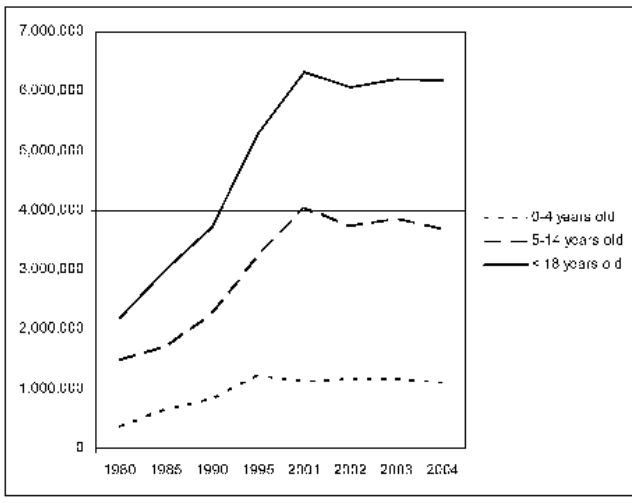
Overweight in children has become a major concern. Since the 1970s, rates have more than quadrupled in US children between 6-11 years old and have sharply increased in preschool-aged children and adolescents. (Figure 2) In adults 20 years of age and older, raw **Body Mass Index (BMI)** values are used to classify weight into categories ranging from underweight to obese. (Table 1) In children, BMI is often converted to percentiles by age and sex utilizing **Centers for Disease Control and Prevention (CDC)**[6] growth charts before cutoff values are applied. In the 2003 National Survey of Children's Health, 31% of Rhode Island children ages 6-17 were overweight (15%) or obese (16%).[7] Between 2001-2005, one in five children entering kindergarten in RI was obese.[3] As with asthma, racial/ethnic disparities are present: non-Hispanic blacks and Hispanics, most notably Mexican-Americans, have higher prevalence rates than whites.[8]

The rise in obesity is attributed to multiple factors: decreases in physical activities, increases in sedentary activities, larger food portions, and a proliferation of calorie-dense convenience foods.[9] Overweight and obese children are at increased risk for detrimental short- and long-term outcomes, including early development of cardiovascular disease risk factors,[10] early onset Type 2 diabetes,[11] psychosocial maladjustment[12] and the persistence of obesity into adulthood.[13] Additionally, research studies implicate obesity in the development and course of asthma.

The Asthma-Obesity Relationship

Schaub and von Mutius[14] cite prospective studies that demonstrate higher rates of incident asthma in children and adolescents with excess weight, some showing the effect only in females, while others also found the effect in boys. High weight is associated with increases in days wheezing,[15] cough/wheeze with exercise,[16] missed school days,[17] and emergency department visits.[18] Obese children may be subject to longer and more intensive treatments than their normal weight peers. In a sample of children admitted to the ICU for status asthmaticus, Carroll and colleagues[19] found that obese patients required longer courses of supplemental oxygen, continuous albuterol and intravenous ste-

Figure 1. Estimated number of children with self reported 12 month (1980-1995) or current (2001-2004) asthma*



* Data from the National Health Interview Survey, United States, 1980-2004 (35)

Figure 2. Increases of Obesity* in Children and Adolescents 1971-2004*

* Percentage of youth with sex- and age-specific BMI >= 95th percentile.

† Data from the National Health and Nutrition Surveys (NHANES) and reported by Ogden and colleagues (34, 36)

Table 1. Body Mass Index categories for adults and children*

Adults (20 years and older)	
Underweight	BMI < 18.5
Normal weight	BMI >= 18.5 - 24.9
Overweight	BMI >= 25 – 29.9
Obese	BMI > 30
Children (2 to 19 years old)	
Underweight	BMI < 5th percentile
Normal weight	BMI >= 5th - < 85th percentile
Overweight	BMI > 85th - < 95th percentile
Obese	BMI > 95th percentile

* Terminology for BMI categories follows recent expert guidelines (37)

roids, and had longer ICU and hospital lengths of stay than normal-weight patients. High weight also appears to be related to the persistence of asthma after the onset of puberty.[20]

Although the majority of research points to excess weight's impact on asthma, the relationship may be bi-directional. **Exercise induced bronchospasm (EIB)** occurs in the majority of pediatric asthma cases,[21] leading many children to eschew physical activity, often prompted by their parents.[17] Maladaptive efforts to prevent EIB may encourage a sedentary lifestyle. Moreover, lack of regular physical exertion is implicated in cardiopulmonary deconditioning, which exacerbates EIB and increases the risk of weight gain.[22] Pulmonary compromise resulting from poorly controlled asthma presents an additional barrier.[22] Several studies have found that youth with asthma take less than half of their prescribed controller medications: this shortfall accounts for increases in morbidity, including more frequent symptoms and activity limitations.[23] A reduction in the use of safer controller medications in persistent asthma leads to more asthma exacerbations and the subsequent use of systemic steroid "bursts". There are quantitatively more potential side effects, including weight gain, from even a short course of a prednisone-type medication than a full year of an inhaled corticosteroid used daily to prevent symptoms.

The literature on the asthma-obesity relationship suggests that each condition can exacerbate the other. Research is under way to understand the physiological mechanisms driving this relationship. Areas of study include lung mechanics, immunity and inflammation, genetics, hormones, and gene-by-environment interactions.[16]

A complementary line of inquiry focuses on behavioral and psychosocial mechanisms influencing weight control. Firm evidence documents that weight loss improves asthma outcomes,[24] and weight gain worsens them.[25] The majority of weight loss studies in obese adults with asthma have employed radical surgical or dietary weight loss methods.[24,26] In children, physical exercise is seen as the more appropriate focus,[9] though healthy eating habits are also emphasized. Exercise also can improve pulmonary function as evidenced by an increased Forced Vital Capacity measure.

Table 2. Demographic and BMI information for children at camp

Sample size = 26 (42% female)

Mean age – 11.3 years, range – 9.0 - 13.8

Race/ethnicity:

Caucasian: 30%

Hispanic: 27%

African American: 23%

Other: 17%

	Mean	SD	Minimum	Maximum
Age (years)	11.3	1.3	9	13.8
Household income	$20,651	$16,400	$4,999	$50,000
Body Mass Index (percentile)	78th	23rd	15th	99th
Asthma Control Test Scores^:	18.9	3.5	12	25

^ Possible scores range from 0-25, higher scores indicate better control.

Physical Activity

With a rate approaching 61%, Rhode Island ranks worst in the US in the percentage of children and teens who fail to exercise regularly.[27] Nationally, about half of all US children get insufficient amounts of daily exercise.[28] Older children, females and ethnic minorities have the lowest activity levels.[29] Barriers to exercise include limited access to appropriate environments and equipment, decreases in school physical education programs, and preference for sedentary pastimes. Children with asthma may experience relatively lower activity levels than their healthy peers due to the severity of their asthma and their parents' doubts about the appropriateness of exercise. The real or perceived risk of EIB may also discourage exercise.

Pilot Data from the Childhood Asthma Research Program

A number of areas merit further research, including the physiological mechanisms driving the relationship between asthma and obesity, the role of race/ethnicity, and the interventions that promote physical activity in this population. Through the partnership of the Childhood Asthma Research Program at the Bradley-Hasbro Research Center, and Hasbro Children's Hospital's **Community Asthma Programs (CAP)**, we have an opportunity to study some of these issues locally, at the CAP asthma summer camp. Last year we began collecting descriptive data on obesity and asthma as a first step.

Data collection for this pilot project is ongoing and takes place yearly at the CAP Summer Camp—a 1-week overnight camp for children with asthma, held each summer at Camp Canonicus in Exeter, RI. The Institutional Review Board at Rhode Island Hospital approved the protocol, and families signed informed consent/assent and HIPAA privacy forms. Parent materials were presented in Spanish or English; child forms were presented in English (all campers were fluent).

Table 3. BMI and Selected Study Variables: Preliminary Findings

BMI percentile by demographic information			
	BMI percentile Mean (SD)		
Female:	81.5 (18.7)		
Male:	75.9 (26.1)		
Caucasian	81.1 (11.8)		
Hispanic:	86.1 (18.3)		
African American:	80.7 (25.8)		
Asian:	39.5 (34.6)		
BMI percentile by activity measures*			
	Normal Weight BMI < 85 percentile	Overweight/obese BMI > 85 percentile	
Fels physical activity score (self report)	9.1 (2.1)	9.0 (1.5)	(F (1,24)=.05, ns)
CHSA activity limitation score (parent report)	90.5 (8.2)	76.9 (22.6)	(F (1,20)=3.47, p .08)
BMI percentile and asthma control:	Pearson's r -.43, p<.05		

* On both activity measures, higher scores signify more physical activity

During the camp session children completed several questionnaires including the Fels Physical Activity Questionnaire,[31] which assesses activity level at school and during leisure time during a typical week. Height and weight are measured for the BMI calculation. During camp drop-off parents complete the Child Health Survey for Asthma (CHSA) Child Activity scale,[32] which assesses children's asthma-related physical limitations and the **Asthma Control Test** (**ACT**),[33] which utilizes information about symptom frequency and severity and use of quick relief medications to derive a control score.

Table 2 contains demographic and physiological data for the 26 campers who took part in research during the first wave of data collection. Over half (53%) of the children were overweight or obese, similar to the proportion of overweight children in a large national sample (22% vs. 31%, respectively).[34] However, the proportion of obese children at camp was markedly higher than the reference sample (31% vs 15%, respectively). Selection criteria for camp attendance could partially account for the higher proportion of obese children, as preference for enrollment is given to those with more severe asthma and challenges to control, as indicated by medical history and prescribed amedications, and these asthma indicators are related to overweight status.

Table 3 shows other trends in this preliminary data set. Though our small sample size limited statistical power, our results echo findings in the literature. For instance, the girls tended to weigh more than the boys, and Hispanic children weighed more, on average, than children from other racial/ethnic backgrounds. Heavier children had more problems with control than their slimmer peers (r = -.43, p<.05). Parent report of children's asthma-related activity limitations was marginally related to child weight. Specifically, children above the 85th percentile for BMI experienced more activity limitation than the normal weight campers (F (1,20) = 3.47, p = .08).

Weight was not related to children's self-report of their physical activity. This measure was assessed on the last day of camp; and children's responses about typical activity levels may have been influenced by their immediate experience of a very active week at camp. Subsequently, we will administer the physical activity questionnaire at the beginning of the week. Additionally we intend to include pedometer measurement of physical activity level.

This review of the asthma-obesity relationship and our preliminary findings from a small sample of children attending summer camp indicate that practitioners should promote exercise and provide dietary advice in overweight asthmatic patients. For their heaviest patients, referral for weight loss treatment may be indicated. The use of controller medications can help children maintain healthy physical activity as well as avoid the use of systemic steroids and their potential side effects.

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Inner City Asthma

Stanley Hoyt Block, MD, FAAAAI

Inner-city residents with asthma often have particularly severe disease. Asthma prevalence is as high as 14.3%[1] in children from poor families compared to 6%[2] overall prevalence for children A large survey of Connecticut families showed an 18.4% prevalence of asthma in Hispanic (mainly Puerto Rican) children, compared to 7.4% in non-Hispanic whites.[3] For African Americans, hospitalization rates for asthma are almost three times as high as the rates for whites.[4] Fatalities from asthma, though unusual, are two to six times more common among African Americans and Latinos than among whites.[5]

Why the disparity? The multi-factorial answers include genetic predisposition, barriers to medical care and medication, environmental exposures, financial limitations, language limitations, and cultural beliefs.

The clinician must address these barriers.

Cultural Beliefs

Many inner-city asthmatics traditionally visit the emergency room when their asthma flares, but do not embark on a preventive program through their primary care physicians or allergy or pulmonary specialists. Many believe that asthma is "absent" or "cured" when the asthma is asymptomatic, and that asthma medications are necessary only for acute episodes.[6] In a group of high-risk, low-income, mainly Hispanic and African-American people, over half of those who had asthma thought that they had asthma only when they were symptomatic; this "no symptoms, no asthma" belief was associated with lower use of inhaled steroids.[7] Much education is needed on an individual and group basis to explain the function and use of inhaled steroids, the importance of therapy, and the fact that asthma is a chronic disease with continued inflammation of the airways, requiring preventive (controller) treatment for those with mild-persistent, moderate-persistent and severe-persistent asthma. Many ethnic groups utilize "home" remedies, which may have little or no efficacy in asthma. Sensitive discussions, tolerance and education can help patients understand that Western medicine has much to add and that controller medications, like inhaled steroids, can greatly improve the well being of patients with persistent asthma.

Language barriers

We will need good interpreters or bilingual providers, if we want to lower the high morbidity of this disease among our growing Latino population. Illiteracy is a major problem among inner-city patients, even among those who speak English well. Written plans may work well for more sophisticated suburban populations, but among patients with limited literacy, written documents may be meaningless—especially if written in a language other than the patient's "language of comfort".

Financial barriers

Many patients in the inner city are uninsured. They cannot easily obtain long-term medications. However, providers can help steer these patients to the pharmaceutical companies' free medication programs. If the patient can control his/her asthma and find a job, s/he may be able to get health insurance.

Environmental barriers

Inner-city asthmatics are often exposed to roaches, mice, mold and dust mites and have little ability to control their environment. A study showed that the combination of cockroach sensitization and exposure to high levels of this allergen in the home seemed to increase asthma hospitalization, unscheduled medical visits for asthma, days of wheezing, missed school days, and lost sleep.[8] Thus, persistence with a variety of methods of roach and rodent avoidance is warranted despite the challenges. Since poor patients usually rent their homes, they sometimes cannot follow the usual instructions to reduce allergen exposures. For example, they may be able to purchase allergy proof encasings for their box springs, mattress and pillows for dust-mite control, but may not be able to pull up carpeting (a good method of dust mite reduction). Furthermore, if they complain to the landlord about roaches or rodents, they may fear eviction. Nevertheless, many inner-city patients can reduce the roach bur-

den by using professional exterminators, or by buying "roach baits." The importance of careful cleaning and avoidance of food or garbage around the house must be emphasized. Despite these measures, roach control in multifamily dwellings is often difficult if not impossible. Avoidance of smoking (active and passive) in the home is another important and cost-saving effort. In the inner-city, families who keep dogs primarily for safety may be reluctant to abandon their large canine "pets". Nevertheless, if an asthmatic has a large positive skin test to "dog" (cat, birds, or other animals), the family should be urged to remove the pet from the home.

Treatment plans

In the inner-city, certain limitations may require changes in management. For example, there is a high "no-show" rate for appointments: some patients only "show" when their asthma is exacerbating. Therefore, immunotherapy, (also called "allergy shots") may not be ideal in an inner-city population, as several missed appointments may require starting over in the build-up or maintenance phase. Similarly, the more simple the medical regimen, the more likely the patient is to follow instructions. However, with culturally and linguistically sensitive education, many inner-city patients can be encouraged to follow even a complicated medical regimen. All asthmatics receive a prescription for a short-acting bronchodilator (e.g. Albuterol) by inhaler (and often by nebulizer) to be used on an as needed (not regular) basis. Patients with mild-persistent, moderate-persistent and severe-persistent asthma usually are started on an inhaled steroid (with dose dependent on severity, risk and control). Patients with more severe asthma often require additional medications, such as long-acting beta agonists in addition to inhaled steroids, and may also require leukotriene receptor antagonists (e.g. Montelukast). The most severe allergic asthmatics may also require every two to four week subcutaneous injections of Omalizumab (Xolair), but this medicine's potential side effects require significant office waits (due to reports of anaphylaxis) that make it more difficult to use in the inner-city. Oral steroids are often used in short bursts to achieve control during flares. Chronic oral steroids, while effective, can cause multiple problems. Of course, the more complex the regimen, the more education is required to encourage adherence. For non-English speaking families, this is a particular challenge.

Our Experience

As Medical Director and board-certified Allergist at **The Providence Community Health Centers (PCHC)**, the author has staffed an Asthma/Allergy Clinic at one of PCHC's nine sites for thirty years. PCHC provides primary care (Pediatrics, Ob/Gyn, Internal Medicine and Family Medicine) to 35,000 patients (one out of six Providence residents) who make over 120,000 visits each year. PCHC started an Asthma/Allergy specialty clinic at its Captiol Hill Health Center site thirty years ago, serving mainly inner-city and minority Rhode Islanders (of whom almost 2/3 are Spanish speaking).

Since asthma runs in families, the PCHC's Asthma/Allergy Clinic now cares for asthma among children and even grandchildren of its original patients. The PCHC Asthma/Allergy Clinic sees asthmatics of all ages (about 40% children and 60% adults). Most of the patients served at the Capitol Hill Health Center's Asthma/Allergy Clinic are poor; many are uninsured or underinsured. They speak eight languages:

Spanish (58%)
Khmer (Cambodians) – 5%
Lao – 3%
Portuguese – 2%
Hmong – 1%
Creole 0.5%
Haitian/French – 0.5%
English 30%
Sign language (deaf patients/parents) – occasional.

Regardless of insurance status, the Capitol Hill Health Center's Asthma/Allergy Clinic provides the following to patients:

a) Evaluation by the board-certified Allergist
b) Spirometry
c) Allergy skin tests to determine allergens and asthma "triggers"
d) Translation services
e) Educational material in various languages—at very low literacy levels
f) Nurse Education—about medications, spacers, nebulizers, peak flow meters, metered dose inhalers, dry powder delivery systems, preventive medicines, use of rapid-relief medications, emergency plans, etc.
g) Home visits, when needed, to encourage compliance and to reduce triggers such as dust mites, mold, tobacco smoke, roaches, rodents, pet dander, etc.
h) Smoking cessation assistance
i) Help in getting free medications for the uninsured or underinsured through Patient Assistance Programs and samples. About a third of our patients at the Asthma/Allergy Clinic are uninsured or under-insured for medicines.

Through support of a Rhode Island legislative grant and a research grant with Hasbro Children's Hospital, our Certified Asthma Educator (a Nurse) and her Spanish-speaking assistant teach patients about the importance of controller-medicines and how to use the inhalers, nebulizers, dry-powder delivery systems, peak flow meters etc. Low-literacy educational materials are available for patients who cannot read English (or Spanish) well. The Asthma Educators go over the entire plan with the patient or parents, after they are seen by the physician, so that asthma attacks are minimized, expensive emergency room visits become rare, and hospitalizations are avoided. Many patients who previously missed much work or school can work or attend school faithfully.

Even our most severe asthmatics are usually controlled on a comprehensive program including inhaled steroids (with higher doses required for particularly severe patients), long acting beta agonists, leukotriene receptor antagonists and environmental control. Co-morbidities such as gastroesophageal reflux, sinusitis and allergic rhinitis, all of which can worsen asthma, must be addressed. Only a few require long-term oral steroids, omalizumab or zileuton. Among the most difficult asthmatics to control are those whose asthma is complicated by long-term smoking with the onset of a COPD

component. Similarly, even in non-smokers, some immigrants have had severe asthma for decades with little or no effective treatment in their country of origin and now have much "remodeling" of their airways, making their asthma and fixed-airway obstruction almost impossible to completely control. Even in such patients, an educational program and medicine can improve their quality of life.

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The National Asthma Education and Prevention Program (NAEPP) Guidelines: Will They Improve the Quality of Care in America?

Sidney S. Braman MD, FCCP, and Arul Vigg, MBBS

Asthma affects 300 million people globally.[1] Its prevalence has risen over the last several decades; recent data show that 22 million Americans are affected. Six million of these patients are children. Worldwide, the prevalence has increased by 50% every decade.

In response, the **National Asthma Education and Prevention Program (NAEPP),** in an effort coordinated by the **National Heart, Lung, and Blood Institute (NHLBI)** of the National Institutes of Health, commissioned an expert panel to develop guidelines that would raise public awareness, improve physician recognition of asthma as a growing health problem and improve asthma control. The first expert panel report was offered in 1991, with updates in 1997, 2002, and 2007: The Expert Panel Report 3, "Guidelines for the Diagnosis and Management of Asthma." www.nhlbi.nih.gov/guidelines/asthma.

This paper will highlight the lessons offered by the guidelines and review the changes made to the Expert Panel Report 3.[2]

Definition of Asthma

In 1991, the NAEPP guidelines established asthma as an inflammatory disease, thereby providing the basis for anti-inflammatory therapy. This has been the foundation of treatment over the last two decades.[3] In fact, strong evidence links anti-inflammatory therapy with inhaled corticosteroids to a reduction in asthma mortality.[4] The NAEPP guidelines define asthma as: " a chronic inflammatory disease of the airways in which many cells and cellular elements play a role: in particular mast cells, neutrophils, eosinophils, T lymphocytes, macrophages, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness. The episodes are usually associated with widespread but variable airflow obstruction that is reversible either spontaneously or as a result of treatment."

The Asthma Guidelines: Four Components of Effective Management

1) Environmental control measures to avoid or eliminate factors that precipitate asthma symptoms or exacerbations

The NAEPP definition stresses the episodic nature of asthma. Symptoms may be minimal or nonexistent and can appear suddenly with no apparent cause. More commonly symptoms are the result of specific (aeroallergens) or nonspecific (dust, cigarette smoke, fumes, cold air, exercise, etc.) exposures. For patients who have persistent asthma symptoms, the clinician should evaluate for environmental causes, particularly indoor inhalant allergens (e.g., house-dust mites, indoor pets and cockroaches) as well as exposure to tobacco smoke. Sometimes allergies can be determined by the medical history. If not, skin or *in vitro* testing are useful in identifying causative agents.[5] Once this is determined, a multifaceted comprehensive allergen avoidance plan can be advised.

2) Use of objective measures of lung function to assess the severity of asthma and to monitor the course of therapy

The 2007 and previous guidelines stressed the need for objective measures of asthma because the medical history and physical examination are not reliable tools to determine the level of lung impairment and exclude other diagnoses. Since symptoms result from widespread airflow obstruction, spirometry is extremely useful in making a proper diagnosis.[6] Spirometry measures the amount of air that is forcefully exhaled after a maximal expiration. It is recommended to monitor lung function before and after treatment to insure adequate response. The amount exhaled after 1 second, the FEV_1, is recorded and considered the most reliable number to follow the course of disease. If airflow

Table 1.
Goals of Asthma Therapy NAEPP 2007

Reduce Impairment

1. Prevent chronic and troublesome symptoms, daytime or night
2. Infrequent use of inhaled short-acting beta agonist (rescue) therapy. (<2 days a week)
3. Maintain normal activity levels including exercise, physical activities, work and school.
4. Meet patient and family's expectations of satisfaction with asthma care
5. Maintain normal or near-normal pulmonary function

Reduce Risk

1. Prevent exacerbations of asthma and need for emergency care and hospitalization
2. Prevent loss of lung function and for children, avoid reduction in lung growth
3. Provide optimal pharmacotherapy with minimal or no side effects

obstruction is detected using spirometry, a short-acting beta agonist (also used for rescue therapy during an attack) is given to the patient in the pulmonary function testing laboratory to look for reversibility. Asthmatics will usually show partial or complete resolution of airflow obstruction after a short-acting bronchodilator (such as albuterol) is given. Since reversible airflow obstruction is the hallmark of asthma, this test is useful in making a diagnosis.[7]

Also, the degree of reversibility correlates with airway inflammation;[8] and patients with a high degree of reversibility have a greater chance of developing irreversible airflow obstruction in subsequent years.[9] The test can therefore be useful in identifying high risk patients who need close monitoring, although research has suggested that current asthma therapies do not prevent progression of the underlying disease severity.

3) Comprehensive pharmacologic therapy for long-term management designed to reverse and prevent airway inflammation

The NAEPP guidelines have set obtainable goals for care. (Table 1) Previously, treatment decisions were based on an assessment of disease severity, determined by patient symptoms, need for short-acting beta agonist rescue therapy and spirometry or peak flow assessment. A severity classification of mild intermittent, mild persistent, moderate persistent and severe persistent disease encouraged a step care approach. Mild intermittent disease with symptoms and beta agonist use two or less times a week requires only as needed short-acting beta agonist rescue medication.

When the disease becomes persistent (symptoms occur more than two times a week), anti-inflammatory therapy is essential.[10] Additional pharmacotherapy with long-acting beta agonists, leukotriene pathway modifiers, anti-IgE therapy and prednisone is offered in a stepwise manner the more severe the disease.

4) Patient education that fosters a partnership among the patient, his or her family, and clinicians

Asthma self-management education can provide patients with the skills to control asthma. The patient and all members of the health care team should agree upon the goals; and sites for self- management education outside the usual office setting should be explored. The actions of the medications should be discussed and their potential complications understood. Written plans should guide daily care. An action plan for the acute exacerbation of asthma will specify when to use oral corticosteroids, when to call the physician and when to use emergency services. For asthmatics who have frequent symptoms and exacerbations or those who poorly perceive their symptoms, hand-held peak flow meters may be useful to monitor daily lung function. An action plan for worsening lung function may help avoid emergency room visits and near-fatal attacks.

Key Differences In the 2007 NAEPP Guidelines

The 2007 NAEPP guidelines still advocate the severity scale, but only during the initial assessment, prior to initiating therapy. The 2007 guidelines focus on the assessment of control rather than severity. Control is defined as the degree to which the manifestations of asthma are minimized by therapeutic interventions and the goals of therapy are adequately met. In the 2007 Guidelines, instead of severity driving therapeutic decisions, an assessment of asthma control will determine how the step up therapy algorithm is applied. If the patient has been asymptomatic and does not require rescue therapy, step down therapy (a reduction in medication) may be considered.A number of measures of control have been offered. Some are more suited for research. Others, such as the **Asthma Control (ACT)**, are more suited for clinical use.[11,12] The ACT, endorsed by be **American Lung Association (ALA)**, does not use lung function testing and is a questionnaire that can be quickly scored. The test asks the patient:

1) Has your asthma prevented normal activities at home or at work?
2) Have you had shortness of breath in the past four weeks?
3) Has your asthma kept you awake at night?
4) How often have used your asthma inhaler in the last four weeks? And,
5) Overall, how have you made your asthma control in the last four weeks?

The final score can be used to assess control. The 2007 NAEPP Guidelines also encourage the doctor to ask the patient how satisfied she/ is with his/her asthma care: very satisfied, somewhat satisfied, not satisfied.

The new guidelines broadly classify treatment options by age: 0-4, 5-11 and >12 years. There is new emphasis on patient education and control of environmental factors. The guidelines stress the identification of co-morbid conditions. The approach to exacerbations of asthma has been modified, with a simplified classification of severity.

The NIH-sponsored NAEPP clinical practice guidelines have shifted the focus from the treatment of acute symptoms to the prevention of symptoms with anti-inflammatory therapy. However, despite these guidelines, many patients are undertreated and, as a result, morbidity and mortality from asthma remain high.[13] The 2007 NAEPP asthma guidelines suggest improvements that are more patient-focused and useful to the clinician.[14]

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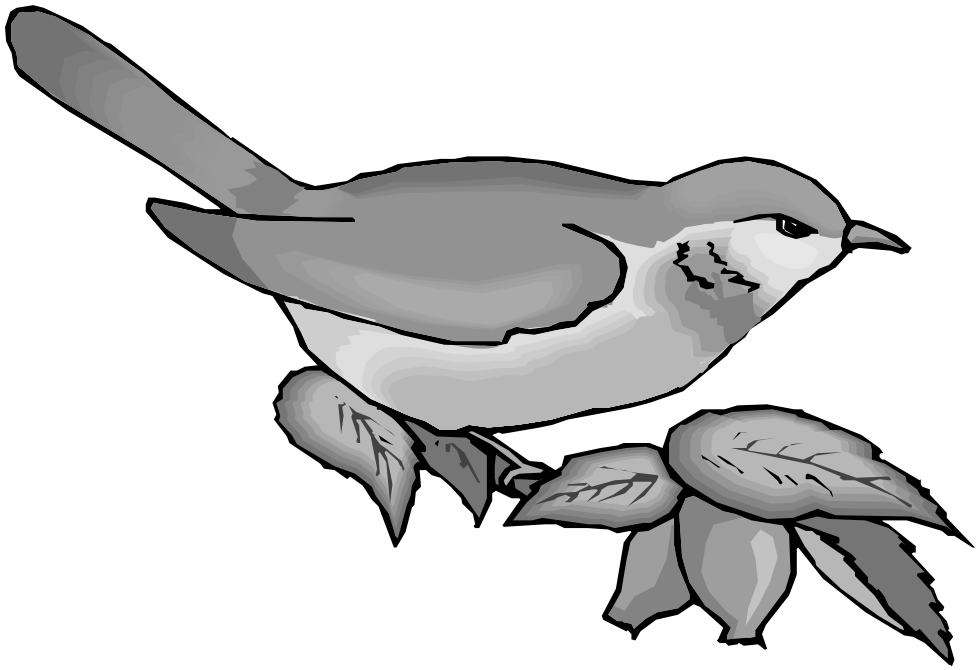

5 mg tablets Rx only

(levocetirizine dihydrochloride)

Brief Summary of Prescribing Information

INDICATIONS AND USAGE: Allergic Rhinitis: XYZAL® is indicated for the relief of symptoms associated with allergic rhinitis (seasonal and perennial) in adults and children 6 years of age and older.

Chronic Idiopathic Urticaria: XYZAL is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 years of age and older.

DOSAGE AND ADMINISTRATION: XYZAL is available as 2.5 mg/5 mL (0.5 mg/mL) oral solution and as 5 mg breakable (scored) tablets, allowing for the administration of 2.5 mg, if needed. XYZAL can be taken without regard to food consumption.

Adults and Children 12 Years of Age and Older: The recommended dose of XYZAL is 5 mg (1 tablet or 2 teaspoons [10 mL] oral solution) once daily in the evening. Some patients may be adequately controlled by 2.5 mg (1/2 tablet or 1 teaspoon [5 mL] oral solution) once daily in the evening.

Children 6 to 11 Years of Age: The recommended dose of XYZAL is 2.5 mg (1/2 tablet or 1 teaspoon [5 mL] oral solution) once daily in the evening. The 2.5 mg dose should not be exceeded because the systemic exposure with 5 mg is approximately twice that of adults (see *Clinical Pharmacology* in Full Prescribing Information).

XYZAL is not indicated for children under 6 years of age.

Dose Adjustment for Renal and Hepatic Impairment: In patients ≥12 years of age with: Mild renal impairment (CL_{CR} = 50-80 mL/min) - 2.5 mg once daily is recommended; moderate renal impairment (CL_{CR} = 30-50 mL/min) - 2.5 mg once every other day; severe renal impairment (CL_{CR} = 10-30 mL/min) - 2.5 mg twice weekly (once every 3-4 days). Patients with end-stage renal disease (CL_{CR} < 10 mL/min) and patients undergoing hemodialysis should not receive XYZAL.

No dose adjustment is needed in patients with solely hepatic impairment. In patients with both hepatic and renal impairment, adjustment of the dose is recommended.

CONTRAINDICATIONS

The use of XYZAL is contraindicated in:

- Patients with known hypersensitivity to levocetirizine or any of the ingredients of XYZAL, or to cetirizine. Observed reactions range from urticaria to anaphylaxis (see *ADVERSE REACTIONS, Post-Marketing Experience*).
- Patients with end-stage renal disease (CL_{CR} < 10 mL/min) and patients undergoing hemodialysis.
- Pediatric patients 6 to 11 years of age with impaired renal function (see *USE IN SPECIFIC POPULATIONS, Pediatric Use*).

WARNINGS AND PRECAUTIONS: Activities Requiring Mental Alertness: In clinical trials the occurrence of somnolence, fatigue, and asthenia has been reported in some patients under therapy with XYZAL. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness, and motor coordination such as operating machinery or driving a motor vehicle after ingestion of XYZAL. Concurrent use of XYZAL with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur.

ADVERSE REACTIONS: Use of XYZAL has been associated with somnolence, fatigue, and asthenia (see *WARNINGS AND PRECAUTIONS, Activities Requiring Mental Alertness*).

Clinical Trials Experience: The safety data described below reflect exposure to XYZAL in 2549 patients with seasonal or perennial allergic rhinitis and chronic idiopathic urticaria in 12 controlled clinical trials of 1 week to 6 months duration. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in practice.

Adults and Adolescents 12 years of Age and Older: In studies up to 6 weeks in duration, the mean age of the adult and adolescent patients was 32 years, 44% of the patients were men and 56% were women, and the large majority (more than 90%) was Caucasian.

In these trials 43% and 42% of the subjects in the XYZAL 2.5 mg and 5 mg groups, respectively, had at least one adverse event compared to 43% in the placebo group.

In placebo-controlled trials of 1-6 weeks in duration, the most common adverse reactions were somnolence, nasopharyngitis, fatigue, dry mouth, and pharyngitis, and most were mild to moderate in intensity. Somnolence with XYZAL showed dose ordering between tested doses of 2.5, 5 and 10 mg and was the most common adverse reaction leading to discontinuation (0.5%).

In clinical trials, the most common adverse reactions in ≥ 2% of adult and adolescent patients (12 years of age and older) taking XYZAL 2.5 mg, XYZAL 5 mg, or placebo were somnolence (5%, 6%, 2%), nasopharyngitis (6%, 4%, 3%), fatigue (1%, 4%, 2%), dry mouth (3%, 2%, 1%), and pharyngitis (2%, 1%, 1%), respectively.

Additional adverse reactions of medical significance observed at a higher incidence than in placebo in adults and adolescents aged 12 years and older exposed to XYZAL are syncope (0.2%) and weight increased (0.5%).

Pediatric Patients 6 to 12 Years of Age: A total of 243 pediatric patients 6 to 12 years of age received XYZAL 5 mg once daily in two short-term placebo controlled double-blind trials. The mean age of the patients was 9.8 years, 79 (32%) were between 6-8 years of age, and 50% were Caucasian.

The safety of XYZAL in children under 6 years of age has not been established [see *Use in Specific Populations (8.4)*].

In clinical trials, the most common adverse reactions in ≥ 2% of pediatric patients (6 to 12 years of age) taking XYZAL 5 mg or placebo, and were more common with XYZAL than placebo were pyrexia (4%, 2%), cough (3%, <1%), somnolence (3%, <1%), epistaxis (2%, <1%), respectively.

Long-Term Clinical Trials Experience: In two controlled clinical trials, 428 patients (190 males and 238 females) aged 12 years and older were treated with XYZAL 5 mg once daily for 4 or 6 months. The patient characteristics and the safety profile were similar to that seen in the short-term studies. Ten (2.3%) patients treated with XYZAL discontinued because of somnolence, fatigue or asthenia compared to 2 (<1%) in the placebo group.

Laboratory Test Abnormalities: Elevations of blood bilirubin and transaminases were reported in <1% of patients in the clinical trials. The elevations were transient and did not lead to discontinuation in any patient.

Post-Marketing Experience: In addition to the adverse reactions reported during clinical trials and listed above, adverse events have also been identified during post-approval use of XYZAL in other countries. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Adverse events of hypersensitivity and anaphylaxis, angioneurotic edema, fixed drug eruption, pruritus, rash, and urticaria, convulsion, aggression and agitation, visual disturbances, palpitations, dyspnea, nausea, hepatitis, and myalgia have been reported.

Besides these events reported under treatment with XYZAL, other potentially severe adverse events have been reported from the post-marketing experience with cetirizine. Since levocetirizine is the principal pharmacologically active component of cetirizine, one should take into account the fact that the following adverse events could also potentially occur under treatment with XYZAL: hallucinations, suicidal ideation, orofacial dyskinesia, severe hypotension, cholestasis, glomerulonephritis, and still birth.

DRUG INTERACTIONS: *In vitro* data indicate that levocetirizine is unlikely to produce pharmacokinetic interactions through inhibition or induction of liver drug-metabolizing enzymes. No *in vivo* drug-drug interaction studies have been performed with levocetirizine. Drug interaction studies have been performed with racemic cetirizine.

Antipyrine, Azithromycin, Cimetidine, Erythromycin, Ketoconazole, Theophylline, and Pseudoephedrine: Pharmacokinetic interaction studies performed with racemic cetirizine demonstrated that cetirizine did not interact with antipyrine, pseudoephedrine, erythromycin, azithromycin, ketoconazole, and cimetidine. There was a small decrease (~16%) in the clearance of cetirizine caused by a 400 mg dose of theophylline. It is possible that higher theophylline doses could have a greater effect.

Ritonavir: Ritonavir increased the plasma AUC of cetirizine by about 42% accompanied by an increase in half-life (53%) and a decrease in clearance (29%) of cetirizine. The disposition of ritonavir was not altered by concomitant cetirizine administration.

USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects: Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, XYZAL should be used during pregnancy only if clearly needed.

Nursing Mothers: No peri- and post-natal animal studies have been conducted with levocetirizine. Cetirizine has been reported to be excreted in human breast milk. Because levocetirizine is also expected to be excreted in human milk, use of XYZAL in nursing mothers is not recommended.

Pediatric Use: The safety and effectiveness of XYZAL in pediatric patients under 6 years of age have not been established.

The recommended dose of XYZAL for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in patients 12 to 17 years of age is based on extrapolation of efficacy from adults 18 years of age and older (see *CLINICAL STUDIES* in Full Prescribing Information).

The recommended dose of XYZAL in patients 6 to 11 years of age for the treatment of the symptoms of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria is based on cross-study comparison of the systemic exposure of XYZAL in adults and pediatric patients and on the safety profile of XYZAL in both adult and pediatric patients at doses equal to or higher than the recommended dose for patients 6 to 11 years of age.

The safety of XYZAL 5 mg once daily was evaluated in 243 pediatric patients 6 to 12 years of age in two placebo-controlled clinical trials lasting 4 and 6 weeks (see *ADVERSE REACTIONS, Clinical Trials Experience*). The effectiveness of XYZAL 2.5 mg once daily for the treatment of the symptoms of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria in children 6 to 11 years of age is supported by the extrapolation of demonstrated efficacy of XYZAL 5 mg once daily in patients 12 years of age and older and by the pharmacokinetic comparison in adults and children.

Cross-study comparisons indicate that administration of a 5 mg dose of XYZAL to 6 - 12 year old pediatric seasonal allergic rhinitis patients resulted in about 2-fold the systemic exposure (AUC) observed when 5 mg of XYZAL was administered to healthy adults. Therefore, in children 6 to 11 years of age the recommended dose of 2.5 mg once daily should not be exceeded (see *DOSAGE AND ADMINISTRATION, Children 6 to 11 Years of Age; CLINICAL STUDIES* in Full Prescribing Information and *CLINICAL PHARMACOLOGY, Pharmacokinetics* in Full Prescribing Information).

Geriatric Use: Clinical studies of XYZAL for each approved indication did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Renal Impairment: XYZAL is known to be substantially excreted by the kidneys and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function (see *DOSAGE AND ADMINISTRATION* and *Clinical Pharmacology, Pharmacokinetics* in Full Prescribing Information).

Hepatic Impairment: As levocetirizine is mainly excreted unchanged by the kidneys, it is unlikely that the clearance of levocetirizine is significantly decreased in patients with solely hepatic impairment (see *CLINICAL PHARMACOLOGY, Pharmacokinetics* in Full Prescribing Information).

OVERDOSAGE: Overdosage has been reported with XYZAL.

Symptoms of overdose may include drowsiness in adults and initially agitation and restlessness, followed by drowsiness in children. There is no known specific antidote to XYZAL. Should overdose occur, symptomatic or supportive treatment is recommended. XYZAL is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested.

The acute maximal non-lethal oral dose of levocetirizine was 240 mg/kg in mice (approximately 200 times the maximum recommended daily oral dose in adults and approximately 230 times the maximum recommended daily oral dose in children) on a mg/m² basis. In rats the maximal non-lethal oral dose was 240 mg/kg (approximately 390 times the maximum recommended daily oral dose in adults and approximately 460 times the maximum recommended daily oral dose in children on a mg/m² basis).

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Update On Stinging Insect Allergy

Alan Gaines, MD, FAAAAI

Ancient texts record deaths from insect stings. Hieroglyphics on the wall of the tomb of Egyptian King Menes reportedly describe his death from a wasp or hornet sting c. 2641 BC,[1] although this is not universally accepted.[2] The Babylonian Talmud, c. second century BC to third century AD, refers to a fatal wasp sting.[1]

In this country, documented deaths from insect sting anaphylaxis occur at the rate of about 40 people per year, although it is likely that additional unrecognized cases are reported as "sudden deaths."[3]

The stinging insects implicated in anaphylactic reactions are in the Hymenoptera order, and in this region consist primarily of the Vespids (wasps, yellow jackets and hornets) and the Apidae (bees). The fire ant, found in the Formidae family, has been implicated in anaphylactic reactions and is a problem in the Southern United States, but not in New England.

Types of reactions

The most common, "normal," reaction to a sting consists of pain, erythema and swelling at the sting site.[3] This usually starts to subside after a couple of hours, and requires only cool compresses and analgesics.

In some cases, a "large local" reaction will develop with fairly massive local swelling, increasing over 24-48 hours and lasting up to a week.[3] These are erythematous and warm to the touch, and can be confused with cellulitis, which is much less common after a sting. Antihistamines and analgesics can reduce the discomfort, and for severe reactions that are disabling or extensive, a short course of prednisone can reduce the swelling. While these large local reactions will frequently recur on future stings, and discussion of stinging insect avoidance is warranted, very few (<5%) will have anaphylaxis on future stings and venom testing and desensitization is not generally indicated in these patients.

Of most concern are the generalized reactions, especially anaphylaxis, estimated, in retrospective studies, to occur in 0.3%-3% of stings.[3] Relatively mild systemic reactions that are limited to the dermis with hives, flushing and angioedema don't strictly meet the criteria for anaphylaxis;[4] these occur more commonly in children. However, many people of any age will react with significant respiratory, cardiovascular, and/or gastrointestinal symptoms as well. The respiratory symptoms can include swelling of the throat or larynx with hoarseness, coughing or choking, difficulty breathing or talking, and stridor or bronchospasm. Nasal congestion and rhinorrhea and watery eyes can be present. The cardiovascular symptoms can include hypotension and circulatory collapse with shock. Nausea, vomiting, and loss of bowel control can occur. These symptoms generally appear within minutes, but can occasionally present several hours after a sting. Most of the fatalities from insect stings have been in adults, perhaps because of coexisting cardiovascular disease. (Figure 1)

While most people who have anaphylactic reactions to stings do not have a history of prior reaction, once someone has had one anaphylactic reaction to a sting they are at greatly increased risk for future systemic reactions: from 30% to 60% of untreated skin-test positive patients with prior reactions will have another systemic reaction on intentional challenge sting.[3, 5] These subsequent reactions are frequently of similar intensity to the original reaction, but may be either milder or more severe. Retrospective studies of "field" stings in previous stinging insect reactors have also shown subsequent reaction rates in the 60% range,[6] although these studies have indefinite insect identification and possible recall bias.

Immediate treatment

While "normal" or large local reactions require little treatment, systemic reactions can be life threatening and require immediate treatment. If there is no history of severe reaction and the only systemic symptom is mild urticaria, use of H1 and H2 antihistamines may be sufficient if there is a quick response. However, generalized urticaria or appearance of any respiratory or cardiovascular symptoms or other signs of systemic anaphylaxis should be promptly treated with intramuscular epinephrine, which is the drug of choice for acute systemic allergic reactions.[7, 8] In adults, the dosage is 0.3 to 0.5 mg; in children the dosage is 0.01mg/kg up to 0.3 mg. It may be necessary to repeat the dose for persistent or recurrent symptoms. There is no con-

Fig 1: Age Distribution of Deaths from Insect Stings, 1980-1999. from: Graft, DF. Venom immunotherapy: Indications, selection of venom, techniques, and efficacy. In: Levine MI and Lockey RF, eds, *Monograph on Insect Allergy*, 4th ed. Pittsburgh: Dave Lambert Assoc., 2003;103-112

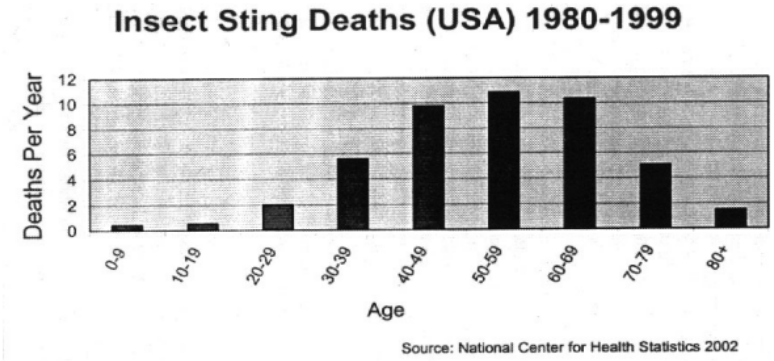

Fig 2: Indications for Venom Immunotherapy

Indications for Venom Immunotherapy (VIT)			
Reaction Type	**Age**	**Results of skin test and/or specific IgE**	**VIT Indicated**
Normal (<2 inches or <24 hours)	Any	Any	No
Large Local (>2 inches and >24 hours)	Any	Any	No
Systemic Reaction, mild, limited to flushing, hives, pruritus, non-life-threatening angioedema	16 and under	Any	Not generally, but may be considered in special circumstances
	Over 16	Either one positive	Yes
Systemic Reaction, moderate or severe, with respiratory or cardiovascular symptoms, with or without cutaneous symptoms as well	Any	Either one positive	Yes
Systemic Reaction, any	Any	Both negative	No, but strongly consider repeat testing in 3-6 months

traindication to the use of epinephrine in a life-threatening situation, such as anaphylaxis.[8]

Additional acute treatment depends on the symptoms and the response to epinephrine. If there is continued hypotension, consideration should be given to intravenous fluids to treat a functional hypovolemia.[7] Use of slow administration of a diluted epinephrine or a vasopressor intravenously may be indicated in some situations. Supine position and elevation of legs can also be helpful in maintaining central perfusion. Bronchospasm should be treated with inhaled beta agonists if it does not respond to the initial epinephrine treatment. Oxygen should also be administered for respiratory or circulatory compromise.

Beta-blockers, commonly prescribed for cardiovascular indications and migraine headaches, can lead to a blunted response to epinephrine in many patients while others may have a paradoxical response and develop acute hypertension when given epinephrine. If a patient on beta-blockade has continued hypotension despite epinephrine, glucagon may be helpful in restoring blood pressure. In patients at significant risk for future reactions or for whom immunotherapy may be prescribed, consideration should be given to switching from the beta-blocker to an alternative class of medication if possible.[7]

Administration of corticosteroids is frequently part of the treatment of anaphylaxis. Although this has minimal if any immediate effect, it may help reduce the late phase of acute reactions or shorten the length of symptoms in prolonged reactions.

As for biphasic reactions, in 1 to 20% of cases of anaphylaxis, including those to insect stings, there can be a biphasic reaction with a recurrence of symptoms several hours after resolution after the initial episode.[9] Some physicians have recommended observation for 8-24 hours after any anaphylactic episode, while others feel this is impractical because the vast majority of such patients will have no further problems. At a minimum, it is imperative that patients be made aware of the possibility of a recurrence and be discharged with a means of self-administering epinephrine.

VENOM IMMUNOTHERAPY

While early attempts at desensitizing patients with histories of severe reactions to insect stings using whole body extracts proved ineffective, subsequent studies using actual venoms from the stinging insects proved much more useful. In uncontrolled studies in the 1950s, Dr. Mary Loveless in Connecticut dissected out venom sacs and prepared her own extracts with apparent success.[10] Comprehensive studies using standardized extracts were not performed until the 1970s. These studies confirmed the superiority of purified stinging insect venoms in diagnosing stinging insect allergy and showed the remarkable success of **venom immunotherapy (VIT)** in preventing future reactions. In fact, VIT in history-positive, skin test positive patients appears to reduce the risk of subsequent systemic sting reactions from 60% to less than 5%. Furthermore, when reactions do occur they generally are milder than the original one.[8]

There are several different schedules for building up immunotherapy to effective doses, from 'Rush" 1 or 2 day protocols, which involve more risk, to the more common schedules, increasing doses over several weeks or months. Once the maintenance dose has been reached, usually 100mcg of each venom which had tested positive, the immunotherapy dose is usually given every 4 to 6 weeks, although as duration of therapy increases the interval can sometimes be lengthened to 8 or even 12 weeks.[8]

The risks of systemic reactions to VIT do not appear to be very high, and are not significantly different than those involved in other allergen immunotherapy. It is advisable to have the shots administered by a professional trained in the recognition and treatment of anaphylaxis, with epinephrine and other emergency medications on hand, and for the patient to remain in the office at least 20-30 minutes following each injection. Risk factors for more severe reactions, either to stings in the wild or to VIT, include arrhythmias, hypertension and other conditions with significant cardiopulmonary compromise. The use of beta-blockers in patients with venom hypersensitivity is also complex. While these drugs are normally considered a contra-indication to allergen immunotherapy as they make treatment of anaphylaxis more difficult (especially with regard to successful use of epinephrine), the patients with venom sensitivity who require beta-blockers for other conditions are already at risk of anaphylactic reactions, with likely poor response to treatment, from possible fu-

ture stings. In these patients the administration of the usually well-tolerated VIT is often felt justified to decrease the high risk of reaction in an unmonitored setting.[11]

Selection of Patients and Venoms for VIT

Given the high efficacy and general safety of venom immunotherapy, guidelines suggest that this treatment is indicated for anyone at significant risk for a serious IgE mediated systemic reaction to future stings. (Figure 2) This would include anyone of any age group who reacted to a sting with respiratory or cardiovascular symptoms, including laryngeal edema, dizziness, palpitations, etc, and who has confirmatory skin testing or demonstrable specific IgE. It does appear, however, that children 16 years of age and younger who have had systemic reactions limited to the dermis (urticaria, flushing, and/or non-life threatening angioedema) represent a special case with little chance of recurrent systemic reaction if re-stung, and in whom future reactions, if they do occur, are rarely worse than the original reaction.[12] Many allergists, therefore, feel that this group need not necessarily be treated with venom immunotherapy on a routine basis, and this is reflected in current guidelines.[8]

Although some patients may feel they can identify the insect that triggered their reaction, these identifications are not usually reliable; and current practice is to initiate immunotherapy with all of the hymenoptera for which specific IgE is demonstrated by either skin or blood test.[5]

Duration of Venom Immunotherapy

A body of evidence indicates that 3-5 years of venom immunotherapy will result in long-lasting protection for most patients, even if skin tests remain positive. After such a course, no more than 10-20% of patients will have systemic reactions after subsequent stings, and most of those will be milder or similar to their previous reaction. Some patients, mainly those with history of a particularly severe reaction such as shock or loss of consciousness, or who had honeybee allergy or had reactions to immunotherapy, still seem to be at fairly high risk for systemic reactions to stings if venom immunotherapy is stopped even after 5 years, and some experts recommend indefinite continuation of shots in those patients.[8, 13] The potential risks and benefits of either stopping or continuing the shots needs to be discussed with each patient on an individual basis.

Preventive Management

Any patient who has had more than a local reaction to a Hymenoptera sting requires preventive measures. For those with systemic reactions, referral to an allergist-immunologist for specific IgE testing and consideration of venom immunotherapy is generally indicated.[8] All such patients should also be prescribed self-injectable epinephrine and advised to have this always available, and consideration should be given to having 2 doses available (either an Epipen Twin-pack or a single Twinject) given the possibility of prolonged or biphasic reactions. Patients should be advised to always seek immediate emergency care if they needed to use the epinephrine as well. Patients should consider wearing a medical identification bracelet or necklace. A fast-acting oral antihistamine, such as liquid, dissolvable or chewable diphenhydramine, may be kept available but should not be used in place of epinephrine if a systemic reaction is taking place.

Education regarding avoidance should be offered to these patients. Trained professionals can exterminate any known or suspected nests in the immediate vicinity of the patient's home. Patients should avoid brightly colored clothing or floral prints, and avoid strongly scented perfumes that might attract insects. These patients should not walk outside without shoes, and should wear long pants, long-sleeved shirts, socks, head coverings and gloves if working outdoors (such as gardening). They need to be cautious when eating or drinking outdoors, as stinging insects are attracted to food and beverages and have even been known to be inside open soda cans and to sting people in the lips or mouth.

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The Role of Pollens In Allergy

Henry B. Freye, MD, FAAAAI

One foundation of allergy practice is the physician's knowledge of regional aeroallergens.[1] The periodicity of symptoms in asthma, allergic rhinitis, and conjunctivitis in a patient with pollenosis can be readily explained on the basis of exposure to specific types and quantities of inhaled pollen to which he or she is sensitized. A physician should know the common "hay fever" plants and be familiar with the regional calendar of tree, grass and weed seasons is fundamental.

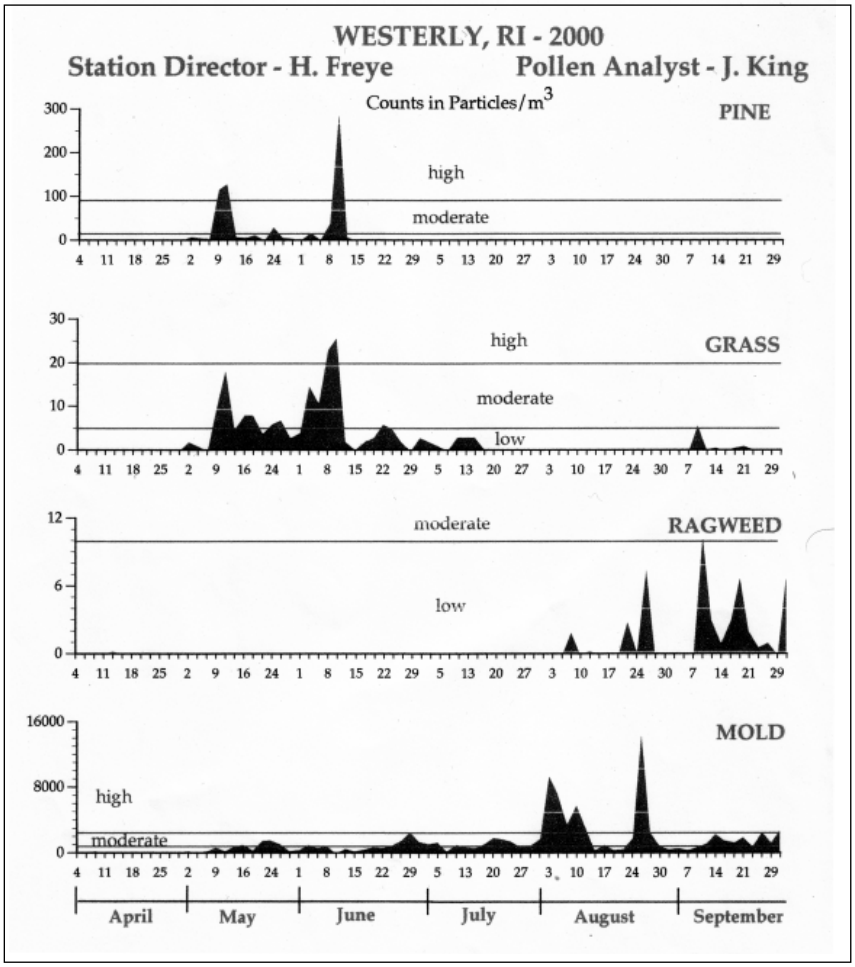
While historic, local and general pollen data are valuable in interpreting skin test reactions and choosing antigens for treatment, unpredictable meteorological factors can cause variations in pollen production, as happened during El Ni¤o in 1997- 1998.[2]

Historical Perspectives

Over 130 years ago, Blackley[3] first popularized the collection and study of grass and weed pollen using gravity-collecting slides. This method continued over the next hundred years in many parts of the world, including the studies in Providence, RI, by Frances Chafee and Guy Settipane.[4] In 1981 Jack Farnham[5] used a roto-rod collecting system, which utilized a volumetric technique to relate particle recoveries to unit volumes of sampled air. Ongoing studies continue through a network of stations throughout New England.[6,7]

Physical Attributes of Aeroallergens

Airborne pollen allergens are primarily proteins associated with biogenic particles measuring 2 to 60 ìm. This size enables the smaller pollens to be readily impacted onto ocular surfaces, inhaled, and aspirated to trigger symptoms in the sensitized individual. The particulate pollen must therefore contain the specific antigenic groupings, which are capable of eliciting reagenic responses. To provoke symptoms, pollens must be present in sufficient numbers and under favorable transport conditions.



Immunotherapy for Pollenosis

Hyposensitization, or a series of injections of increasing amounts of pollen extract we now call immunotherapy, first became popular early in the 20th century. Allergen content was measured in Noon units (weight/volume) in 1911. Subsequently, more sophisticated purification of pollens and standardization of their potency became feasible.[8,9,10,11] The **Food and Drug Administration (FDA)** approved the first licensed standardized short ragweed pollen extract (AMB a 1) in 1981, and grass pollen in 1998.[8]

As increasing doses of extract are injected, tolerance to the injected aeroallergen develops. Concomitantly, there is an initial increase in serum levels of IgG and IgE antibodies to the specific pollen. Ultimately, a higher plateau of IgG occurs and IgE decreases as immunotherapy progresses. This down-regulation of IgE is felt to be a critical mechanism in the improvement seen in allergic rhinitis, allergic asthma and allergic conjunctivitis.[11,12]

The search for an improved method of immunization has spurred recent research. The goal is a vaccine that requires fewer injections, can be given in larger doses with greater safety, and with longer intervals between injections.

Aqueous immunotherapy is the current standard treatment modality. It has been followed by trials of oil-based repository injections, alum-precipitated pyridine pollen extract[13] and other vaccines. Most notable is a recent attempt to immunize patients allergic to ragweed with ragweed- toll-like receptor 9 agonist vaccine to induce tolerance through the immune system.[14]

Although oral hyposensitization to pollens has been attempted in this country,[15,16] the consensus is that despite its effectiveness in certain individuals, treatment in general is less effective than parenteral therapy.[15] However, recent

studies of **sublingual immunotherapy (SLIT)** may signal a change in the treatment of pollenosis, particularly in children who are less receptive to parenteral treatment.[17]

An adjunct to therapy has been the monoclonal antiIgE antibody omalizumab for asthma, which can be used in highly-allergic individuals who had been difficult to manage with the usual immunotherapy alone.[18]

Conclusion

We have described some historical perspectives, methods of pollen collection, temporal relationship to allergic symptoms, physical attributes of aeroallergens, and the methodology of pollen immunotherapy. Not mentioned has been the allergist's singular important intervention: environmental control to moderate the influence of pollens in the treatment of the allergic individual.[18]

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For allergic asthma patients who remain symptomatic on conventional therapies including ICS*...

Capture IgE

And interrupt signals that may lead to asthma attacks.†

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†XOLAIR on average inhibits >96% of IgE from binding to the high-affinity IgE receptor on the surface of mast cells and basophils.[1]

XOLAIR IS INDICATED FOR: Adults and adolescents (aged ≥12 years) with moderate-to-severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. XOLAIR has been shown to decrease the incidence of asthma exacerbations in these patients. Safety and efficacy have not been established in other allergic conditions.

WARNING: Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of XOLAIR. Anaphylaxis has occurred as early as after the first dose of XOLAIR, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, patients should be closely observed for an appropriate period of time after XOLAIR administration, and health care providers administering XOLAIR should be prepared to manage anaphylaxis that can be life-threatening. Patients should also be informed of the signs and symptoms of anaphylaxis and instructed to seek immediate medical care should symptoms occur (see WARNINGS, and PRECAUTIONS, Information for Patients).

IMPORTANT SAFETY INFORMATION

XOLAIR should only be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. XOLAIR should not be administered to patients who have experienced a severe hypersensitivity reaction to XOLAIR (see Boxed WARNING). XOLAIR should be discontinued in patients who experience a severe hypersensitivity reaction. Malignant neoplasms were observed in 20 of 4127 (0.5%) XOLAIR-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of asthma and other allergic disorders. Patients should be given and instructed to read the accompanying Medication Guide before starting treatment and before each subsequent treatment. Patients receiving XOLAIR should be told not to decrease the dose of, or stop taking, any other asthma medications unless otherwise instructed by their physician. The adverse reactions most commonly observed among patients treated with XOLAIR in clinical studies included injection site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). These events were observed at similar rates in XOLAIR-treated patients and control patients.

Reference: 1. XOLAIR [prescribing information]. South San Francisco, Calif: Genentech, Inc; 2007.

Please see Brief Summary, including Boxed WARNING and Medication Guide, on reverse side for additional important safety information.

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WARNING

Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, patients should be closely observed for an appropriate period of time after Xolair administration, and health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening. Patients should also be informed of the signs and symptoms of anaphylaxis and instructed to seek immediate medical care should symptoms occur *(see WARNINGS, and PRECAUTIONS, Information for Patients)*.

INDICATIONS AND USAGE

Xolair (Omalizumab) is indicated for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients. Safety and efficacy have not been established in other allergic conditions.

CONTRAINDICATIONS

Xolair should not be administered to patients who have experienced a severe hypersensitivity reaction to Xolair *(see WARNINGS: Anaphylaxis)*.

WARNINGS

Anaphylaxis

Anaphylaxis has been reported to occur after administration of Xolair in premarketing clinical trials and in postmarketing spontaneous reports. Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life-threatening. In premarketing clinical trials the frequency of anaphylaxis attributed to Xolair use was estimated to be 0.1%. In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond one year after beginning regularly scheduled treatment.

Xolair should only be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. Patients should be closely observed for an appropriate period of time after administration of Xolair, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials and postmarketing spontaneous reports *(see ADVERSE REACTIONS)*. Patients should be informed of the signs and symptoms of anaphylaxis, and instructed to seek immediate medical care should signs or symptoms occur *(See PRECAUTIONS, Information for Patients)*.

Xolair should be discontinued in patients who experience a severe hypersensitivity reaction *(see CONTRAINDICATIONS)*.

Malignancy

Malignant neoplasms were observed in 20 of 4127 (0.5%) Xolair-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of asthma and other allergic disorders. The observed malignancies in Xolair-treated patients were a variety of types, with breast, non-melanoma skin, prostate, melanoma, and parotid occurring more than once, and five other types occurring once each. The majority of patients were observed for less than 1 year. The impact of longer exposure to Xolair or use in patients at higher risk for malignancy (e.g., elderly, current smokers) is not known.

PRECAUTIONS

General

Xolair has not been shown to alleviate asthma exacerbations acutely and should not be used for the treatment of acute bronchospasm or status asthmaticus.

Corticosteroid Reduction

Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of Xolair therapy. Decreases in corticosteroids should be performed under the direct supervision of a physician and may need to be performed gradually.

Information for Patients

Patients receiving Xolair should be told not to decrease the dose of, or stop taking any other asthma medications unless otherwise instructed by their physician. Patients should be told that they may not see immediate improvement in their asthma after beginning Xolair therapy.

Parasitic (Helminth) Infection

In a one-year clinical trial conducted in Brazil in patients at high risk for geohelminthic infections (roundworm, hookworm, whipworm, threadworm), 53% (36/68) of Omalizumab-treated patients experienced an infection, as diagnosed by standard stool examination, compared to 42% (29/68) of placebo controls. The point estimate of the odds ratio for infection was 1.96, with a 95% confidence interval (0.88, 4.36) indicating that in this study a patient who had an infection was anywhere from 0.88 to 4.36 times as likely to have received Omalizumab than a patient who did not have an infection. Response to appropriate anti-geohelminth treatment of infection as measured by stool egg counts was not different between treatment groups. Patients at high risk of geohelminth infection should be monitored for such infections while on Xolair therapy. Insufficient data are available to determine the length of monitoring required for geohelminth infections after stopping Xolair treatment.

Laboratory Tests

Serum total IgE levels increase following administration of Xolair due to formation of Xolair:IgE complexes. Elevated serum total IgE levels may persist for up to 1 year following discontinuation of Xolair. Serum total IgE levels obtained less than 1 year following discontinuation may not reflect steady state free IgE levels and should not be used to reassess the dosing regimen.

Drug Interactions

No formal drug interaction studies have been performed with Xolair. The concomitant use of Xolair and allergen immunotherapy has not been evaluated.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed in animals to evaluate the carcinogenic potential of Xolair.

No evidence of mutagenic activity was observed in Ames tests using six different strains of bacteria with and without metabolic activation at Omalizumab concentrations up to 5000 µg/mL.

The effects of Omalizumab on male and female fertility have been assessed in cynomolgus monkey studies. Administration of Omalizumab at doses up to and including 75 mg/kg/week did not elicit reproductive toxicity in male cynomolgus monkeys and did not inhibit reproductive capability, including implantation, in female cynomolgus monkeys. These doses provide a 2- to 16-fold safety factor based on total dose and 2- to 5-fold safety factor based on AUC over the range of adult clinical doses.

Pregnancy (Category B)

Reproduction studies in cynomolgus monkeys have been conducted with Omalizumab. Subcutaneous doses up to 75 mg/kg (12-fold the maximum clinical dose) of Omalizumab did not elicit maternal toxicity, embryotoxicity, or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery, and nursing.

IgG molecules are known to cross the placental barrier. There are no adequate and well-controlled studies of Xolair in pregnant women. Because animal reproduction studies are not always predictive of human response, Xolair should be used during pregnancy only if clearly needed.

Pregnancy Exposure Registry

To monitor outcomes of pregnant women exposed to Xolair, including women who are exposed to at least one dose of Xolair within 8 weeks prior to conception or any time during pregnancy, a pregnancy exposure registry has been established. Healthcare providers should encourage their patients to call 1-866-4XOLAIR (1-866-496-5247) to enroll in the Xolair Pregnancy Exposure Registry. Healthcare providers can call this number to obtain further information about this registry.

Nursing Mothers

The excretion of Omalizumab in milk was evaluated in female cynomolgus monkeys receiving SC doses of 75 mg/kg/week. Neonatal plasma levels of Omalizumab after *in utero* exposure and 28 days of nursing were between 11% and 94% of the maternal plasma level. Milk levels of Omalizumab were 1.5% of maternal blood concentration. While Xolair presence in human milk has not been studied, IgG is excreted in human milk and therefore it is expected that Xolair will be present in human milk. The potential for Xolair absorption or harm to the infant are unknown; caution should be exercised when administering Xolair to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 have not been established.

Geriatric Use

In clinical trials 134 patients 65 years of age or older were treated with Xolair. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

ADVERSE REACTIONS

Clinical Trials Experience

The most serious adverse reactions occurring in clinical trials with Xolair were anaphylaxis and malignancies *(see WARNINGS)*. Anaphylaxis was reported in 3 of 3507 (0.1%) patients in clinical trials. Anaphylaxis occurred with the first dose of Xolair in two patients and with the fourth dose in one patient. The time to onset of anaphylaxis was 90 minutes after administration in two patients and 2 hours after administration in one patient.

In clinical trials the observed incidence of malignancy among Xolair-treated patients (0.5%) was numerically higher than among patients in control groups (0.2%).

The adverse reactions most commonly observed among patients treated with Xolair in clinical studies included injection site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). These events were observed at similar rates in Xolair-treated patients and control patients. These were also the most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Xolair, or the need for concomitant medication to treat an adverse reaction).

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of one drug cannot be directly compared with rates in the clinical studies of another drug and may not reflect the rates observed in medical practice.

The data described above reflect Xolair exposure for 2078 adult and adolescent patients ages 12 and older, including 1687 patients exposed for six months and 555 exposed for one year or more, in either placebo-controlled or other controlled asthma studies. The mean age of patients receiving Xolair was 42 years, with 134 patients 65 years of age or older; 60% were women, and 85% Caucasian. Patients received Xolair 150 to 375 mg every 2 or 4 weeks or, for patients assigned to control groups, standard therapy with or without a placebo.

Table 1 shows adverse events that occurred ≥1% more frequently in patients receiving Xolair than in those receiving placebo in the placebo-controlled asthma studies. Adverse events were classified using preferred terms from the International Medical Nomenclature (IMN) dictionary. Injection site reactions were recorded separately from the reporting of other adverse events and are described following Table 1.

Table 1
Adverse Events ≥1% More Frequent in Xolair-Treated Patients

Adverse event	Xolair n=738 (%)	Placebo n=717 (%)
Body as a whole		
Pain	7	5
Fatigue	3	2
Musculoskeletal system		
Arthralgia	8	6
Fracture	2	1
Leg pain	4	2
Arm pain	2	1
Nervous system		
Dizziness	3	2
Skin and appendages		
Pruritus	2	1
Dermatitis	2	1
Special senses		
Earache	2	1

Age (among patients under age 65), race, and gender did not appear to affect the between group differences in the rates of adverse events.

Injection Site Reactions

Injection site reactions of any severity occurred at a rate of 45% in Xolair-treated patients compared with 43% in placebo-treated patients. The types of injection site reactions included: bruising, redness, warmth, burning, stinging, itching, hive formation, pain, indurations, mass, and inflammation.

Severe injection-site reactions occurred more frequently in Xolair-treated patients compared with patients in the placebo group (12% versus 9%). The majority of injection site reactions occurred within 1 hour-post injection, lasted less than 8 days, and generally decreased in frequency at subsequent dosing visits.

Immunogenicity

Low titers of antibodies to Xolair were detected in approximately 1/1723 (<0.1%) of patients treated with Xolair. The data reflect the percentage of patients whose test results were considered positive for antibodies to Xolair in an ELISA assay and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to Xolair with the incidence of antibodies to other products may be misleading.

Postmarketing Spontaneous Reports

Anaphylaxis: Based on spontaneous reports and an estimated exposure of about 57,300 patients from June 2003 through December 2006, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients. Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to Xolair administration with no other identifiable cause. Signs and symptoms in these reported cases included bronchospasm, hypotension, syncope, urticaria, angioedema of the throat or tongue, dyspnea, cough, chest tightness, and/or cutaneous angioedema. Pulmonary involvement was reported in 89% of the cases. Hypotension or syncope was reported in 14% of cases. Fifteen percent of the reported cases resulted in hospitalization. A previous history of anaphylaxis unrelated to Xolair was reported in 24% of the cases.

Of the reported cases of anaphylaxis attributed to Xolair, 39% occurred with the first dose,19% occurred with the second dose, 10% occurred with the third dose, and the rest after subsequent doses. One case occurred after 39 doses (after 19 months of continuous therapy, anaphylaxis occurred when treatment was restarted following a 3 month gap). The time to onset of anaphylaxis in these cases was up to 30 minutes in 35%, greater than 30 and up to 60 minutes in 16%, greater than 60 and up to 90 minutes in 2%, greater than 90 and up to 120 minutes in 6%, greater than 2 hours and up to 6 hours in 5%, greater than 6 hours and up to 12 hours in 14%, greater than 12 hours and up to 24 hours in 8%, and greater than 24 hours and up to 4 days in 5%. In 9% of cases the times to onset were unknown. Twenty-three patients who experienced anaphylaxis were rechallenged with Xolair and 18 patients had a recurrence of similar symptoms of anaphylaxis. In addition, anaphylaxis occurred upon rechallenge with Xolair in 4 patients who previously experienced urticaria only.

Hematologic: Severe thrombocytopenia has been reported in postapproval use of Xolair.

Skin: Hair loss has been reported in postapproval use of Xolair.

OVERDOSAGE

The maximum tolerated dose of Xolair has not been determined. Single intravenous doses of up to 4000 mg have been administered to patients without evidence of dose-limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20-week period, which was not associated with toxicities.

MEDICATION GUIDE
XOLAIR®
(OMALIZUMAB)

IMPORTANT: XOLAIR SHOULD ALWAYS BE INJECTED IN YOUR DOCTOR'S OFFICE.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT XOLAIR?

A severe allergic reaction called anaphylaxis has happened in some patients after they received Xolair. Anaphylaxis is a life-threatening condition and can lead to death so get emergency medical treatment right away if symptoms occur.

Signs and Symptoms of anaphylaxis include:

- wheezing, shortness of breath, cough, chest tightness, or trouble breathing
- low blood pressure, dizziness, fainting, rapid or weak heartbeat, anxiety, or feeling of "impending doom"
- flushing, itching, hives, or feeling warm
- swelling of the throat or tongue, throat tightness, hoarse voice, or trouble swallowing

Get emergency medical treatment right away if you have signs or symptoms of anaphylaxis after receiving Xolair.

Anaphylaxis from Xolair can happen:

- right after receiving a Xolair injection or hours later
- after any Xolair injection. Anaphylaxis has occurred after the first Xolair injection or after many Xolair injections.

Your healthcare provider should watch you for some time in the office for signs or symptoms of anaphylaxis after injecting Xolair. If you have signs or symptoms of anaphylaxis, tell your healthcare provider right away.

Your healthcare provider should instruct you about getting emergency medical treatment and further medical care if you have signs or symptoms of anaphylaxis after leaving the doctor's office.

WHAT IS XOLAIR?

Xolair is an injectable medicine for patients ages 12 and older with moderate to severe persistent allergic asthma whose asthma symptoms are not controlled by asthma medicines called inhaled corticosteroids. A skin or blood test is done to see if you have allergic asthma.

WHAT ELSE SHOULD I KNOW ABOUT XOLAIR?

- You should not receive Xolair if you have ever had an allergic reaction to a Xolair injection.
- Do not change or stop taking any of your other asthma medicines unless your healthcare provider tells you to do so.
- There are other possible side effects with Xolair. Talk to your doctor for more information. You can also go to www.xolair.com or call 1-866-4XOLAIR (1-866-496-5247).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Jointly marketed by:
Genentech, Inc.
1 DNA Way
South San Francisco, CA
94080-4990

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Manufactured by:
Genentech, Inc.
1 DNA Way
South San Francisco, CA
94080-4990

(4840201)
Revision Date: July 2007

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8121302/XOL-400057

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PATANASE® Nasal Spray safely and effectively. See full prescribing information for PATANASE Nasal Spray.

PATANASE (olopatadine hydrochloride) Nasal Spray

Initial U.S. Approval: 1996

INDICATIONS AND USAGE
PATANASE Nasal Spray is an H_1 receptor antagonist indicated for the relief of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older. (1)

DOSAGE AND ADMINISTRATION
For intranasal use only.

The recommended dose of PATANASE Nasal Spray in patients 12 years and older is two sprays per nostril twice daily. (2)

Priming Information: Prime PATANASE Nasal Spray before initial use and when PATANASE Nasal Spray has not been used for more than 7 days. (2.2)

DOSAGE FORMS AND STRENGTHS
Nasal spray 0.6%: 665 mcg of olopatadine hydrochloride in each 100-microliter spray. (3) Supplied as a 30.5 g bottle containing 240 sprays.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Epistaxis, nasal ulceration, and nasal septal perforation. Monitor patients periodically for signs of adverse effects on the nasal mucosa. Avoid use in patients with nasal disease other than allergic rhinitis. (5.1)

Avoid engaging in hazardous occupations requiring complete mental alertness such as driving or operating machinery when taking PATANASE Nasal Spray. (5.2)

Avoid concurrent use of alcohol or other central nervous system depressants with PATANASE Nasal Spray. (5.2)

ADVERSE REACTIONS
The most common adverse reactions (>1%) included bitter taste, headache, epistaxis, pharyngolaryngeal pain, post-nasal drip, cough, and urinary tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9195 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Alcon®

Now Available

PATANASE® Nasal Spray is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age or older.

The most common adverse reactions (>1%) included bitter taste, headache, epistaxis, pharyngolaryngeal pain, post-nasal drip, cough, and urinary tract infection. Nasal ulceration and nasal septal perforation occurred at a rate of <1%; patients should be monitored periodically for signs of adverse effects on the nasal mucosa. Avoid use in patients with nasal disease other than allergic rhinitis.

For full prescribing information, please visit www.patanase.com

Alcon

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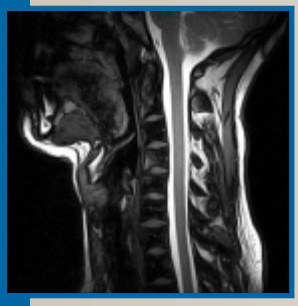

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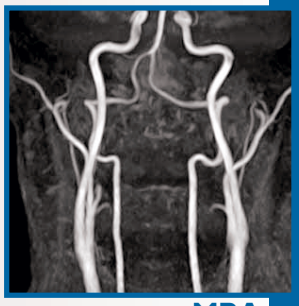
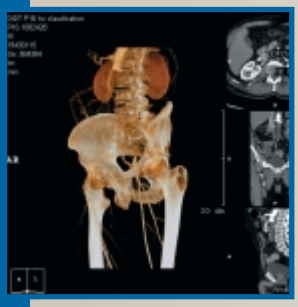
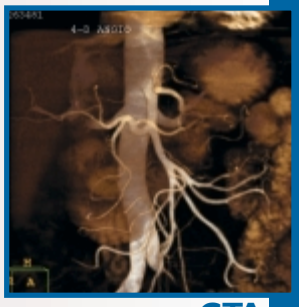


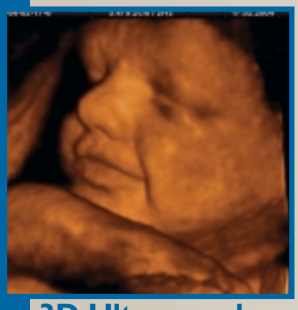
MRA



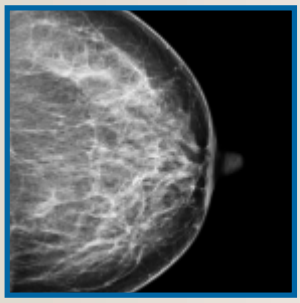
CT • 3D CT



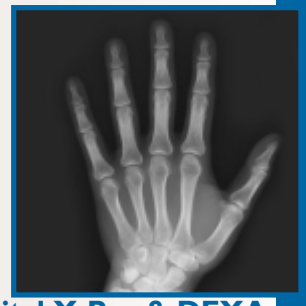
CTA



3D Ultrasound



Digital Mammography



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OMNARIS™
(ciclesonide)
Nasal Spray, 50 mcg
For intranasal use only

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE
Seasonal Allergic Rhinitis
OMNARIS Nasal Spray is indicated for the treatment of nasal symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older.

Perennial Allergic Rhinitis
OMNARIS Nasal Spray is indicated for the treatment of nasal symptoms associated with perennial allergic rhinitis in adults and adolescents 12 years of age and older.

CONTRAINDICATIONS
OMNARIS Nasal Spray is contraindicated in patients with a hypersensitivity to any of its ingredients.

WARNINGS
The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. In addition, some patients may experience symptoms of corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, rapid decreases in systemic corticosteroid dosages may cause a severe exacerbation of their symptoms.

Patients who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in children or adults using corticosteroids. In children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS
General
Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS: Pediatric Use). Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the administration of intranasal corticosteroids. Patients with a known hypersensitivity reaction to other corticosteroid preparations should use caution when using ciclesonide nasal spray since cross reactivity to other corticosteroids including ciclesonide may also occur.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has occurred. In clinical studies with OMNARIS Nasal Spray, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of OMNARIS Nasal Spray. Therefore, patients using OMNARIS Nasal Spray over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa. Intranasal corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; or in patients with untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex.

If recommended doses of intranasal corticosteroids are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, topical corticosteroids should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

The risk of glaucoma was evaluated by assessments of intraocular pressure in 3 studies including 943 patients. Of these, 390 adolescents or adults were treated for up to 52 weeks and 186 children ages 2 to 11 received treatment with OMNARIS Nasal Spray 200 mcg daily for up to 12 weeks. In these trials, no significant differences in intraocular pressure changes were observed between OMNARIS Nasal Spray 200 mcg and placebo-treated patients. Additionally, no significant differences between OMNARIS Nasal Spray 200 mcg and placebo-treated patients were noted during the 52-week study of adults and adolescent patients in whom thorough ophthalmologic assessments were performed including evaluation of cataract formation using slit lamp examinations. Rare instances of wheezing, nasal septum perforation, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal application of corticosteroids. Close follow-up is warranted in patients with a change in vision and with a history of glaucoma and/or cataracts.

Information for Patients
Patients being treated with OMNARIS Nasal Spray should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients who are on immunosuppressive doses of corticosteroids should be warned to avoid exposure to chickenpox or measles, and if exposed, to obtain medical advice. Patients should use OMNARIS Nasal Spray at regular intervals since its effectiveness depends on its regular use (see DOSAGE AND ADMINISTRATION).

In clinical trials, the onset of effect was seen within 24 to 48 hours with further symptomatic improvement observed over 1 to 2 weeks in seasonal allergic rhinitis and 5 weeks in perennial allergic rhinitis. Initial assessment of response should be made during this timeframe and periodically until the patients symptoms are stabilized.

The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve by a reasonable time or if the condition worsens. For the proper use of this unit and to attain maximum improvement, the patients should read and follow the accompanying patient instructions carefully. Spraying OMNARIS Nasal Spray directly into the eyes or onto the nasal septum should be avoided. It is important that the bottle is gently shaken prior to use to ensure that a consistent amount is dispensed per actuation. The bottle should be discarded after 120 actuations following initial priming or after 4 months after the bottle is removed from the foil pouch, whichever occurs first.

Drug Interactions
Based on *in vitro* studies in human liver microsomes, des-ciclesonide appears to have no inhibitory or induction potential on the metabolism of other drugs metabolized by CYP 450 enzymes. The inhibitory potential of ciclesonide on CYP450 isoenzymes has not been studied. *In vitro* studies demonstrated that the plasma protein binding of des-ciclesonide was not affected by warfarin or salicylic acid, indicating no potential for protein binding-based drug interactions.

In a drug interaction study, co-administration of orally inhaled ciclesonide and oral erythromycin, an inhibitor of cytochrome P450 3A4, had no effect on the pharmacokinetics of either des-ciclesonide or erythromycin. In another drug interaction study, co-administration of orally inhaled ciclesonide and oral ketoconazole, a potent inhibitor of cytochrome P450 3A4, increased the exposure (AUC) of des-ciclesonide by approximately 3.6-fold at steady state, while levels of ciclesonide remained unchanged. Therefore, ketoconazole should be administered with caution with intranasal ciclesonide.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Ciclesonide demonstrated no carcinogenic potential in a study of oral doses up to 900 mcg/kg (approximately 20 and 10 times the maximum human daily intranasal dose in adults and children, respectively, based on mcg/m^2) in mice for 104 weeks and in a study of inhalation doses up to 193 mcg/kg (approximately 8 and 5 times the maximum human daily intranasal dose in adults and children, respectively, based on mcg/m^2) in rats for 104 weeks. Ciclesonide was not mutagenic in an Ames test or in a forward mutation assay and was not clastogenic in a human lymphocyte assay or in an *in vitro* micronucleus test. However, ciclesonide was clastogenic in the *in vivo* mouse micronucleus test. The concurrent reference corticosteroid (dexamethasone) in this study showed similar findings. No evidence of impairment of fertility was observed in a reproductive study conducted in male and female rats both dosed orally up to 900 mcg/kg/day (approximately 35 times the maximum human daily intranasal dose in adults based on mcg/m^2).

Pregnancy: Teratogenic Effects
Pregnancy Category C
Oral administration of ciclesonide in rats up to 900 mcg/kg (approximately 35 times the maximum human daily intranasal dose in adults based on mcg/m^2) produced no teratogenicity or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at 5 mcg/kg (less than the maximum human daily intranasal dose in adults based on mcg/m^2) or greater produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at 1 mcg/kg (less than the maximum human daily intranasal dose based on mcg/m^2).

There are no adequate and well-controlled studies in pregnant women. OMNARIS Nasal Spray, like other corticosteroids, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nonteratogenic Effects
Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

Nursing Mothers
It is not known if ciclesonide is excreted in human milk. However, other corticosteroids are excreted in human milk. In a study with lactating rats, minimal but detectable levels of ciclesonide were recovered in milk. Caution should be used when OMNARIS Nasal Spray is administered to nursing women.

Pediatric Use
The safety and effectiveness for seasonal and perennial allergic rhinitis in children 12 years of age and older have been established. The efficacy of OMNARIS Nasal Spray in patients 6 to 11 years of age for treatment of the symptoms of seasonal allergic rhinitis is supported by evidence from four adequate and well-controlled studies in adults and adolescents 12 years of age and older with seasonal and perennial allergic rhinitis, and one study in patients 6 to 11 years of age with seasonal allergic rhinitis. The efficacy of OMNARIS Nasal Spray for the treatment of the symptoms of perennial allergic rhinitis in patients 6 to 11 years of age has not been established (see CLINICAL TRIALS: Pediatric Patients Aged 6 to 11 Years). The efficacy of OMNARIS Nasal Spray in children 2 to 5 years of age has not been established. The safety of OMNARIS Nasal Spray in children 2 to 11 years of age was evaluated in 4 controlled clinical studies of 2 to 12 weeks duration (see CLINICAL PHARMACOLOGY: Pharmacodynamics, CLINICAL TRIALS, ADVERSE REACTIONS: Pediatric Patients).

Clinical studies in children less than two years of age have not been conducted. Studies in children under 2 years of age are waived because of local and systemic safety concerns.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including OMNARIS Nasal Spray, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

Geriatric Use
Clinical studies of OMNARIS Nasal Spray did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS
Adult and Adolescent Patients Aged 12 Years and Older:
In controlled clinical studies conducted in the US and Canada, a total of 1524 patients ages 12 years and older received treatment with ciclesonide administered intranasally. The overall incidence of adverse events for patients treated with OMNARIS Nasal Spray was comparable to that in patients treated with placebo. Adverse events did not differ appreciably based on age, gender, or race. Approximately 2% of patients treated with OMNARIS Nasal Spray 200 mcg in clinical trials discontinued because of adverse events; this rate was similar for patients treated with placebo. Adverse events, irrespective of drug relationship, that occurred with an incidence of 2% or greater and more frequently with OMNARIS Nasal Spray 200 mcg (N = 546) than with placebo (N = 544) in clinical trials of 2 to 6 weeks in duration included headache (6.0% vs 4.6%), epistaxis (4.9% vs 2.9%), nasopharyngitis (3.7% vs 3.3), and ear pain (2.2% vs 0.6%). In a 52-week long-term safety trial that included 663 adults and adolescent patients (441 treated with ciclesonide: 227 males and 436 females) with perennial allergic rhinitis, the adverse event profile over the treatment period was similar to the adverse event profile in trials of shorter duration. Adverse events considered likely or definitely related to OMNARIS Nasal Spray that were reported at an incidence of 1% or greater of patients and more commonly in OMNARIS Nasal Spray versus placebo were epistaxis, nasal discomfort, and headache. No patient experienced a nasal septal perforation or nasal ulcer during long-term use of OMNARIS Nasal Spray. While primarily designed to assess the long-term safety of OMNARIS Nasal Spray 200 mcg once daily, this 52-week trial demonstrated greater decreases in total nasal symptom scores with OMNARIS Nasal Spray versus placebo treated patients over the entire treatment period.

Pediatric Patients Aged 6 to 11 Years:
Two controlled clinical studies 2 and 12 weeks in duration were conducted in the US and Canada and included a total of 1282 patients with allergic rhinitis ages 6 to 11 years, of which 913 were treated with OMNARIS (ciclesonide) Nasal Spray 200 mcg, 100 mcg, or 25 mcg daily. The overall incidence of adverse events for patients treated with OMNARIS Nasal Spray was comparable to that in patients treated with placebo. Adverse events did not differ appreciably based on age, gender, or race. In clinical trials, 1.6% and 2.7% of patients treated with OMNARIS Nasal Spray 200 mcg or 100 mcg, respectively, discontinued because of adverse events; these rates were lower than the rate in patients treated with placebo (2.8%). Adverse events, irrespective of drug relationship, that occurred with an incidence of 3% or greater and more frequently with OMNARIS Nasal Spray 200 mcg (N = 380) than with placebo (N = 369) included headache (6.6% vs 5.7%), nasopharyngitis (6.6% vs 5.4%), and pharyngolaryngeal pain (3.4% vs 3.3%).

Pediatric Patients Aged 2 to 5 Years:
Two controlled clinical studies 6 and 12 weeks in duration were conducted in the US and included a total of 258 patients 2 to 5 years of age with perennial allergic rhinitis, of which 183 were treated with OMNARIS Nasal Spray 200 mcg, 100 mcg or 25 mcg daily. The distribution of adverse events was similar to that seen in the 6 to 11 year old children.

Manufactured for:
Sepracor Inc.
Marlborough, MA 01752 USA
Made in Germany
November 2007

NEW

Medication delivered where it's needed.

Nasal symptoms get the message.

Introducing OMNARIS— a new intranasal corticosteroid spray

- Provided 24-hour relief of nasal symptoms in seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR)[1-3]
  - Based on average of AM and PM reflective TNSS*
  - Onset of action was seen within 24 to 48 hours, with further symptomatic improvement observed over 1 to 2 weeks in SAR and 5 weeks in PAR[2]
- Well-tolerated[2,4]
- Low-volume, alcohol-free, and scent-free[2,5]
- Novel hypotonic formulation delivers medication to the site[2,5,6]

INDICATIONS

OMNARIS Nasal Spray is indicated for the treatment of nasal symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older and with perennial allergic rhinitis in adults and adolescents 12 years of age and older.

IMPORTANT SAFETY INFORMATION

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. The growth of pediatric patients receiving intranasal corticosteroids, including OMNARIS Nasal Spray, should be monitored routinely.

Patients using drugs that suppress the immune system are more susceptible to infection and should avoid exposure to chickenpox or measles. Rare instances of wheezing, nasal septum perforation, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal application of corticosteroids. Close follow-up is warranted in patients with a change in vision and with a history of glaucoma and/or cataracts. The development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred with OMNARIS. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of OMNARIS. Ketoconazole should be administered with caution with intranasal ciclesonide due to potential for increased exposure to des-ciclesonide.

In clinical trials, adverse events that occurred with an incidence of 2% or greater and more frequently with OMNARIS than placebo were headache (6.0%), epistaxis (4.9%), nasopharyngitis (3.7%), and ear pain (2.2%).

*TNSS (Total Nasal Symptom Score) was measured by symptoms of runny nose, itchy nose, sneezing, and nasal congestion.

Please see Brief Summary of Prescribing Information on the following page.

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NEW

omnaris™

(ciclesonide) Nasal Spray, 50 mcg

Relief With Staying Power.

Latex Allergy

Anthony R. Ricci, MD

When Christopher Columbus visited Hispaniola in 1496, he observed people playing games with bouncing balls. Returning to Spain with the rubber balls, Columbus related how people of the New World made balls from the liquid of a tree.[1] For three centuries, rubber remained an unstable product until, in 1839, it was discovered that the elastic properties of rubber could be made more permanent through treatment with sulfur and heat. [2] Most of the world's rubber comes from the tree *Hevea brasiliensis*. When its bark is cut, liquid latex is released.

The rubber trade began in the Amazon basin, but Southeast Asia is the predominant manufacturer of the latex used in most of the world's 44,000 rubber latex products (e.g., tires, footwear, belts and hoses, medical devices, wire cables, balloons, condoms, diaphragms, rubber gloves, nipples for baby bottles and pacifiers).

Latex balloons, gloves, and condoms are made by a dipping process. Very soft products maunfactured by dipping have the highest amount of latex proteins and, therefore, are the most allergenic. Cornstarch powder is applied to the molds during manufacturing to prevent stickiness. Water soluble latex proteins, which adhere to the cornstarch particles, can be aerosolized upon removal of the latex glove.[3] These particles can sensitize nearby persons or evoke symptoms in previously sensitized people.[4]

Respirable particles can also be shed from powder-free latex gloves.[5] High exposure areas include operating rooms and labor and delivery suites. Sensitized individuals can become symptomatic after exposure. Some manufacturers of surgical and household gloves also compound casein into the glove. This may cause skin reactions in milk-sensitive persons.[6]

Latex allergy is a hypersensitivity to the substance obtained from the milky sap of the rubber tree. The sensitized person reacts in an exaggerated manner to a harmless substance (an allergen or antigen). A latex allergic person can have a reaction to the chemical additives used in manufacturing the products or to the latex plant proteins themselves. IgE antibody is produced when the immune system detects an allergen. Histamine and other chemical mediators are released, causing erythema, pruritis, rhinorrhea, hives, rash, and watery, edematous eyes. This can swiftly progress to anaphylaxis with labored breathing, a precipitous drop in blood pressure, rapid pulse, tissue edema and death.

The AIDS epidemic and subsequent universal precautions have spurred the use of latex products. The incidence of latex allergy, as with most allergies, increases with chronic exposure.

In 1987, 1 billion gloves were imported into the United States; the following year, the number burgeoned to 8 billion![7] Occupations outside of health care also expose workers to the latex protein. One glove manufacturing plant reported a 3.7% prevalence of occupational asthma caused by latex allergy.[8] Workers in latex doll manufacturing plants have higher prevalence of latex sensitization.[9]

Persons who have had repeated or extended surgeries, particularly those beginning in early life, are especially vulnerable. Patients with spina bifida (myelomeningocele), urogenital abnormalities or intestinal surgery with exposed mucous membrane colostomy have an increased prevalence of latex allergy if latex has been used in their care.

Prevalence of Latex Sensitization

Of 326 atopic children seen at a university hospital,3% had a positive latex skin test;[10] and 9.5% of 325 consecutive adult inpatients awaiting surgical or urological procedures had positive latex skin tests.[11] Of 1000 volunteer blood donors, 6.5% had latex-specific immunoglobulin E (IgE) antibodies (men were twice as likely to be sensitized as women, but the prevalence was not associated with race or age).[12] Of health care workers responding to a self-reported questionnaire, 53% described a reaction to rubber gloves.[13]

Symptoms of Latex Allergy

There are three types of latex allergy symptoms

1. Irritant contact dermatitis.

This nonimmune dermatitis evolves gradually over several days and is not caused by the latex protein, but by glove compression, antiseptic hand washing, numerous glove chemicals, and latex accelerators. Patients present with erythema, scales, and fissures. Avoidance of latex gloves, use of cotton liners, and hand care which minimizes skin pressure can diminish symptoms.

LATEX ALLERGY AND CROSS REACTIVE FOODS

Avocado	Chestnut
Kiwi Fruit	Papaya
Potato	Passion Fruit
Banana	Melon

SOURCES OF LATEX EXPOSURE

MEDICAL

Gloves	Urinary catheters
Tourniquets	Face masks
Wound drains	Adhesive tape
Injection ports	Electrode pads
Bulb syringes	Matresses
Stethoscope	Ambu bags

HOUSEHOLD

Balloons	Condoms and diaphragms
Rubber bands	Toys
Shoe soles	Erasers

Sports equipment
Clothing, including elastic on underwear
Feeding nipples and pacifiers
Powdered latex gloves used in food handling
Diapers, incontinence and sanitary pads
Computer mouse pads
Carpet backing
Handles on racquets and tools

NOTE: For more information see the American Academy of Allergy Asthma & Immunology www.AAAAI.org

2. Delayed type IV allergic contact dermatitis.

The onset of the rash occurs between 6 to 48 hours after contact with the glove chemicals. Symptoms include erythema, blisters, papules, vesicles, pruritis, and crusting.

3. Immediate type 1 hypersensitivity.

Symptoms usually occur within minutes to several hours after contact with the latex protein. They include: local and generalized urticaria, angioedema, nausea, vomiting, feelings of impending doom, and abdominal cramps. Aerosolized latex particles are frequently the causative factor.

Anaphylactic reactions to latex have been reported in patients with a history of allergic or irritant contact dermatitis. It is believed that the disruption in the skin's natural protective barrier increases latex protein absorption.[14] A patient can suddenly develop life-threatening systemic symptoms after using latex gloves for many years.

More than 50% of people with latex sensitivity have a history of atopy.[15] One in four atopic health care workers has a positive skin prick test to latex. Only 50% of these persons, however, are clinically symptomatic.[16]

Latex and Food Allergy

Bananas, kiwi fruit, chestnuts, avocado, and tomato may cross-react with the latex protein[17] and cause anaphylactic reactions in latex sensitive persons. Apples, figs, melons, celery, potatoes, papayas, cherries, and peaches have caused oral pruritis, which can progress to more serious symptoms.[18] A person who has reactions to any of these foods may have an increased risk of developing latex allergy. Latex sensitive people should avoid only the food which causes allergic symptoms. It is not recommended that these patients eliminate all the potentially cross-reacting foods: this could result in unhealthy dietary restrictions.

Latex has been called the "hidden food allergy." Particles can be introduced into food products by preparers' gloves. Rhode Island was the first state to ban natural rubber latex glove use in food service. United States Senator Sheldon Whitehouse, State Representative Elizabeth Dennigan, and this writer worked together to pass the Rhode Island Latex Gloves Safety Act in July, 2001. The law bans latex glove use by any food handler.

Diagnosis

A medical and occupational history which includes questions related to prior latex reactions, in addition to immunologic testing, usually diagnoses latex allergy. Latex allergy risk factors and the nature of past reactions should be thoroughly investigated. Frequently, patients will not attribute their nasal or bronchial symptoms to latex allergy, but confuse the symptoms with those of allergic rhinitis. None of the patients who succumbed to fatal latex anaphylaxis during barium enema examinations, however, had any of the known risk factors other than atopy. [19] Risk factors, unfortunately, may not always predict potential latex allergy reactions.

FDA-approved *in vitro* tests which measure latex-specific IgE are the only methods available in the United States to help diagnose latex allergy.[20,21] Because these tests have a false-negative rate of approximately 20%, their clinical usefulness is limited.

Rhode Island was the first state to ban natural rubber latex glove use in food service.

Management

The primary treatment of latex allergy, as with most allergies, is avoidance. Reducing exposure to latex in the workplace by using nonlatex, vinyl, or nitrile gloves and nonpowdered, low-protein, latex gloves, will eliminate or reduce the allergen.

Health care workers must be protected from airborne latex antigen, to decrease the risk of future latex sensitization. In 1999, the administration decided to transform the 350-bed Kent County Memorial Hospital into a latex safe hospital. This transition occurred over one year at an approximate cost of $250,000. All duct vents and surfaces were cleaned or changed; all latex was removed. Latex balloons from florists and latex gloves worn by rescue workers were banned. The hospital has had no new cases of Workers Compensation related to latex since the transition. In fact, several latex allergic health care workers have returned to their former jobs without consequent symptoms.

Latex allergic patients who must undergo surgery in a non latex-safe hospital should be scheduled as the first case of the day when the likelihood of contact with aerosolized latex particles is low. All latex rubber tubing and blood pressure cuffs must be wrapped to prevent contact with the patient. These patients must be visibly and prominently labeled as latex allergic at the bedside and on wristbands. Occasionally, latex allergic patients are pretreated with steroids, antihistamines, and histamine H2-blockers. Anaphylaxis, however, can occur despite pretreatment.[22]

Latex allergic persons should wear Medic-Alert identification, carry two doses of epinephrine, and carry several pairs of nonlatex gloves for use by emergency medical personnel.

Treatment of Anaphylaxis

Acute latex anaphylactic reactions must be treated with epinephrine, oxygen, fluids, and steroids. Maintaining the airway and circulation is essential. Diphenhydramine (Benadryl) may be used to treat urticaria. Staff wearing latex gloves should not treat a latex allergic patient. Transporting an acutely ill latex-allergic patient to a non-latex safe hospital can be extremely dangerous.

Long-Term Latex Avoidance

Latex-allergic persons benefit by eliminating or reducing their exposure to latex. Asthma and bronchial hyperreactivity has been shown to decrease in latex-sensitive workers who reduced or avoided latex exposure after a median follow-up period of 56 months.[23] Twenty latex-sensitized anesthesiologists who did not use latex gloves for 10 to 15 months all became asymptomatic; 16 of 18 demonstrated a decline in latex-specific IgE. Their latex skin test titration end points did not change appreciably. This suggests that a longer period of avoidance or stricter environmental controls may be necessary to immunologically improve these patients' sensitivities.[24]

Conclusions

Liberia recently announced that it will resume exportation of rubber following its three year civil war. This will lead to sensitization and increased latex allergy in the workers of the restored rubber plantations as well as dissemination of the minute latex protein particle via food preparation and workers' clothing.

Every state should follow Rhode Island's lead and ban the use of latex gloves during the preparation of food in restaurants, institutional kitchens and supermarkets.

There has been a significant increase in latex rubber allergy since the implementation of universal precautions in the late 1980s. People are at a higher risk of developing both immediate, type 1, and delayed type 4 hypersensitivity to rubber latex. Latex gloves are still frequently used during surgery and in food-preparation. Hidden latex protein continues to sensitize unsuspecting, susceptible people. Education on allergen avoidance and cross-reacting allergens can improve management and treatment of latex allergy and, hopefully, one day terminate sensitization.

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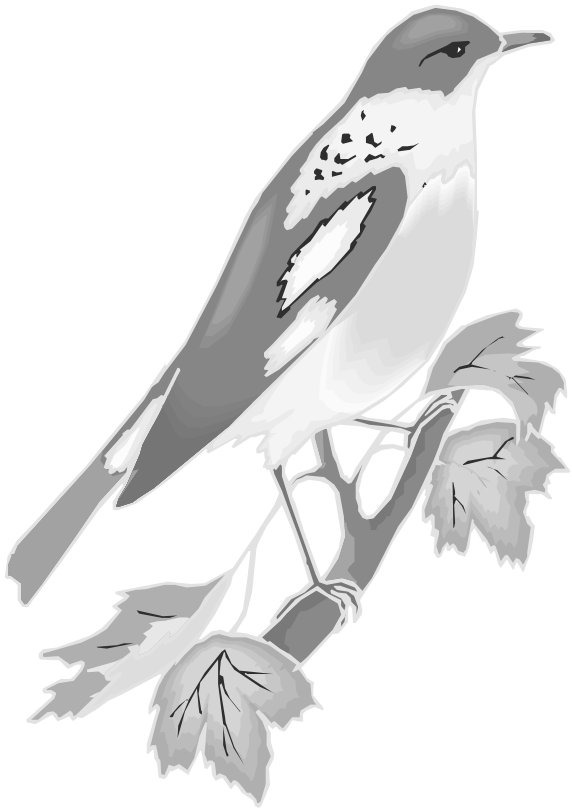

Advances In Therapeutic Immunomodulation of IgE-mediated Respiratory Disease

Russell A. Settipane, MD, FAAAAI

Allergic diseases of the airways impose devastating burdens on individuals, as well as on society.[1,2] Despite treatment advances, pharmacotherapy improvements, and practice parameters[3,4] with diagnosis and management guidelines,[5] the "Allergies in America" survey reported an allergic rhinitis prevalence of 14.2% in the adult US population. The majority of nasal allergy sufferers, moreover, complained that their medications did not provide 24-hour relief, with effectiveness wearing off over time.[6]

The "Asthma in America" survey confirmed previous estimates of prevalence: 5% of Americans, or nearly 15 million people, suffer from asthma.[7] Almost half those persons reported that asthma limited their ability to take part in sports or recreation; more than a third said it limited their normal physical exertion. Over 4000 deaths occur annually from asthma.[5] In Rhode Island, there are approximately 12 asthma-related deaths per year.[8] (Figure 1)

First line therapy in the management of allergic respiratory disease is identification and avoidance of environmental aeroallergens. Second line generally comprises pharmacotherapeutics. "Allergic immunomodulation" encompasses various third line therapies, which attempt to suppress or modify the immune mechanisms responsible for IgE mediated respiratory disease, particularly asthma. Such therapeutic agents include methotrexate, soluble interleukin-4 (IL-4) receptor, anti-IL-5, recombinant IL-12, cyclosporin A, **intravenous immunoglobulin (IVIG)**, allergy immunotherapy, **omalizumab (anti-IgE)**, and others. This review focuses on the status of three agents: subcutaneous immunotherapy, sublingual immunotherapy, and monoclonal anti-IgE therapy.

Background: The role of IgE in the pathogenesis of allergic disease

The discovery of IgE in 1967[9,10] was probably the single most important milestone in the understanding of allergic disease pathogenesis, although its presence had long been suspected.[11] Since then, scientists have recognized the central pathogenic role of IgE in mediating the allergic response that follows exposure to environmental allergens and is important to the development and persistence of inflammation.[12,13] The following observations highlight the role of IgE.

In the preschool years, when coughing or wheezing in association with common respiratory viral infections is common, early sensitization to inhaled allergens is associated with the prognosis for persistent asthma beyond the preschool years.[14,15] Similar observations hold true regarding the association of IgE with adult asthma.[16] At Rhode Island Hospital, atopy was reported in 58% of adult patients with asthma attending a pulmonary clinic, which corresponds to recent national observations.[17] Additionally, the diagnosis of allergic rhinitis has been shown to increase, by 3-fold, the risk for the subsequent development of asthma.[18]

The combination of IgE sensitization to indoor allergens and high levels of allergen in the home is associated with increased asthma severity.[19-21] Notably, patients have improved after their homes' offending allergen(s) is eliminated or reduced.[22-24]

Subcutaneous Immunotherapy

Description

Subcutaneous immunotherapy [often called "conventional immunotherapy" or allergy shots] is the repeated subcutaneous administration of allergens (aeroallergens, hymenoptera venom, drugs, etc) to patients with IgE-mediated conditions, to protect against the allergic symptoms and inflammatory reactions associated with the natural exposure to these allergens.[3] It is the only therapeutic method available to achieve allergen-specific tolerance.

History

Subcutaneous immunotherapy, which emerged as an empiric therapy for ragweed hayfever in 1900, was first described in the literature in 1911.[25] Over the past century, allergen immunotherapy has progressed as a result of improved un-

Table 1. Probable effective dose range for allergen extracts

Antigen	Probable effective dose range
Dust Mites	500-2000 AU
Cat	1000-4000 BAU
Grass	1000-4000 BAU
Ragweed	6-12 µg of Amb a 1
Dog	15 µg of Can f 1
Nonstandardized extract	Highest tolerated dose

Adapted from Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Allergen immunotherapy: a practice parameter second update. J Allergy Clin Immunol. 2007;120:S25-85.[3]

Table 2: Comparison of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT)

	FDA approved	Standardized dosing	Optimal dosing	Magnitude of efficacy	Degree of Safety
SCIT	+	+	Established	++	+
SLIT		-	Unknown	+	++

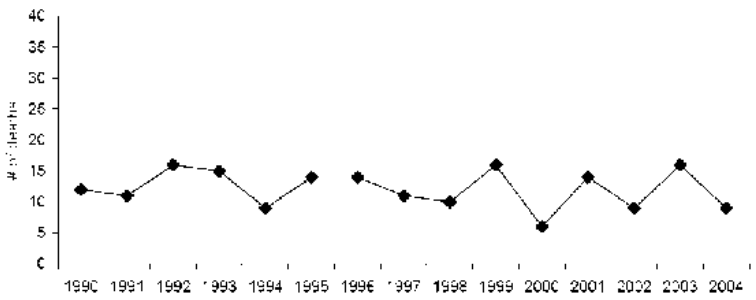

Figure 1. Asthma mortality (absolute numbers) in RI for all ages, 1990-2004

Adapted from the Rhode Island Department of Health. The Burden of Asthma in Rhode Island: The Role of Poverty. Providence, RI: Rhode Island Department of Health, March 2007.

derstanding of IgE-mediated immunologic mechanisms, the characterization of specific antigens and allergens, and the standardization of allergen extracts. Resources which discuss immunotherapy include the **National Asthma Education and Prevention Program's Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma**[5] **(EPR-3 Asthma Guidelines)** and recent practice parameters on rhinitis[4] and immunotherapy.[3]

Indications

Efficacy of allergen immunotherapy has been demonstrated in the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma and stinging insect hypersensitivity. (See article by Gaines.)

The presence of specific IgE to the offending allergen should be documented by skin test or serologically; and there should be clinical correlation with symptoms on exposure.

Allergic rhinitis

The decision to initiate allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms and the adverse effects of medication.

Asthma

The same recommendations apply as for allergic rhinitis. Additionally, the EPR-3 Asthma Guidelines state that allergen immunotherapy be considered for patients with persistent asthma if there is clear evidence of a relationship between symptoms and exposure to an allergen to which the patient is sensitive.[5] Immunotherapy is usually reserved for patients whose symptoms occur all year or during a major portion of the year, and for whom the medication is ineffective, multiple medications are required, or the patient will not tolerate the medication. Special safety precautions apply for administering immunotherapy to patients with asthma.

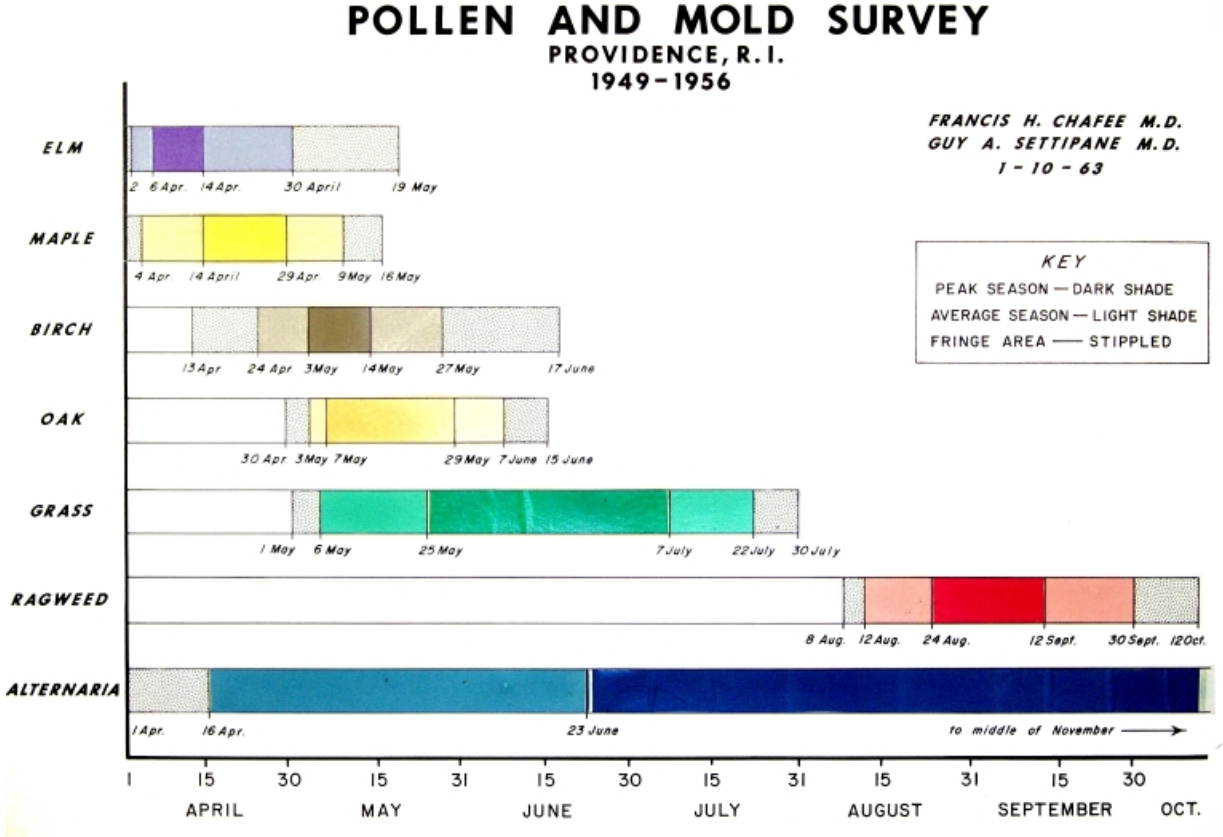

Figure 2. Aeroallergen Survey, Providence RI. Adapted from Chafee FH, Settipane GA. Atmospheric pollen and mold survey. *J Allergy Clin Immunol* 1964 May-June;35:193-200.[48]

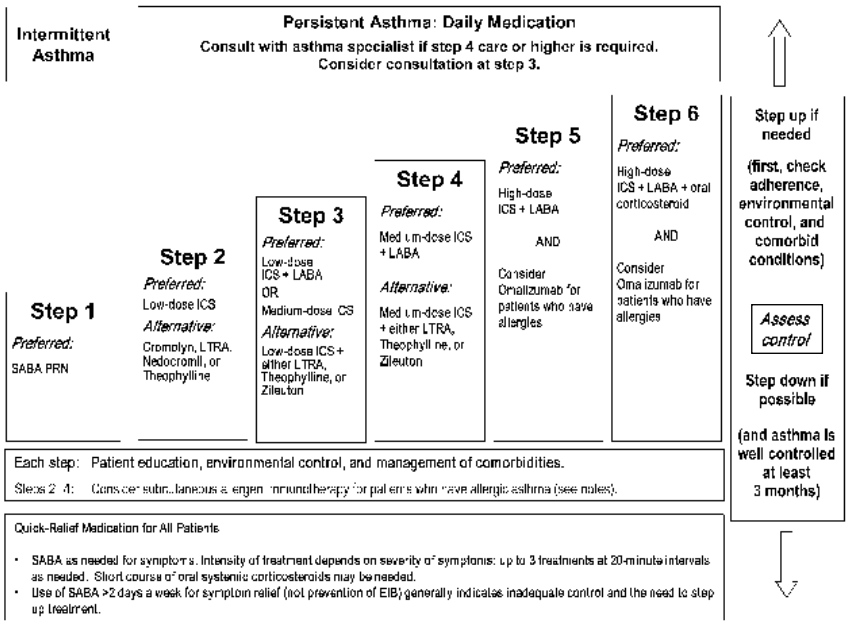

Figure 3. Stepwise approach for managing asthma in youths > 12 years of age and adults

Key: Alphabetical order is used when more than one treatment is listed within either preferred or alternative therapy. EIB, exercise-induced bronchopasm; ICS, inhaled corticosteroid; LABA, long-acting inhaled beta2-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta2-agonist.

Adapted from Expert panel report 3: Guidelines for the diagnosis and management of asthma. Available online at www.nhlbi.nih.gov/guidelines/asthma/epr3/index.htm; last accessed Jan 29, 2008.

Mechanism

Immunologic changes in response to subcutaneous immunotherapy are complex. Although we have no single best marker to explain the efficacy of immunotherapy, numerous antibody and cellular changes have been observed: i.e., the modulation of T- and B-cell responses by the generation of allergen-specific T regulatory cells; increases in allergen-specific IgG4, IgG1, and IgA; decrease in IgE and decreased tissue infiltration by mast cells and eosinophils. Additionally, successful subcutaneous immunotherapy is associated with a change towards a non-allergic TH1 cytokine profile.[26]

Efficacy

Many double-blind, placebo-controlled, randomized clinical trials demonstrate a beneficial effect of subcutaneous immunotherapy,[27-35] for the treatment of allergic rhinitis[30] (including ocular symptoms[35-36]), allergic asthma[27,32,34,37,38] and stinging insect hypersensitivity;[31,39] and the therapy is effective in both adults and children.[41-47]

Allergic rhinitis

The robust research has shown subcutaneous immunotherapy to be effective in a dose dependant manner, with optimal doses determined. (Table 1) The physician should be familiar with the key aeroallergens in the patient's region. In Rhode Island, Chafee & Settipane,[48] in the 1950s, performed landmark pollen count studies characterizing the local pollen seasons. (Figure 2) (See article by Freye).

Asthma

In addition to demonstrating the efficacy of subcutaneous immunotherapy in allergic asthma,[27,32,34,37,38] immunotherapy may prevent the development of asthma in children who have allergic rhinitis.[49] Immunotherapy has also been shown to prevent the development of new allergic sensitivities in monosensitized children and adults.[43,50,51] The EPR-3 Asthma Guidelines suggest that immunotherapy should be considered when there is a significant allergic contribution to the patient's symptoms.

Administration Schedules

Subcutaneous immunotherapy is usually initiated with once to twice weekly injections at a low dose. During the build-up phase, the dose is usually raised 1 to 3 times a week. The duration of the build-up generally ranges from 3 to 6 months, at which point the maintenance phase begins, and the injection schedule interval is slowly increased to a range of every 2 to 4 weeks for inhalant allergens.

Alternative allergen immunotherapy build-up phases include accelerated "cluster" and "rush" schedules, which permit patients to attain therapeutically effective maintenance doses more rapidly than with conventional build-up schedules. These accelerated approaches are associated with an increased risk of anaphylaxis.[52,53]

Approximately 90% of appropriately selected allergic rhinitis patients reaching optimal doses of subcutaneous immunotherapy will experience improvement within one year of therapy.[54] Therapy typically lasts 3–5 years; the majority of patients experience a persisting beneficial effect for at least 3 years after stopping immunotherapy.[55] Less commonly, patients may experience a prompt relapse.

Safety

There is an inherent risk of local allergic reactions (wheal & flare) at the injection site, as well as systemic anaphylaxis. A prospective study has reported the frequency of systemic reactions to be 0.3% of immunotherapy doses, representing 3.7% of patients. Severe systemic reactions can be life-threatening and fatal reactions do occur.[3] Anaphylactic related fatalities are rare (1 in 2.5 million injections).[56]

Given this risk, allergy immunotherapy should be administered only in a setting where procedures that can reduce the risk of anaphylaxis are in place and where the prompt recognition and

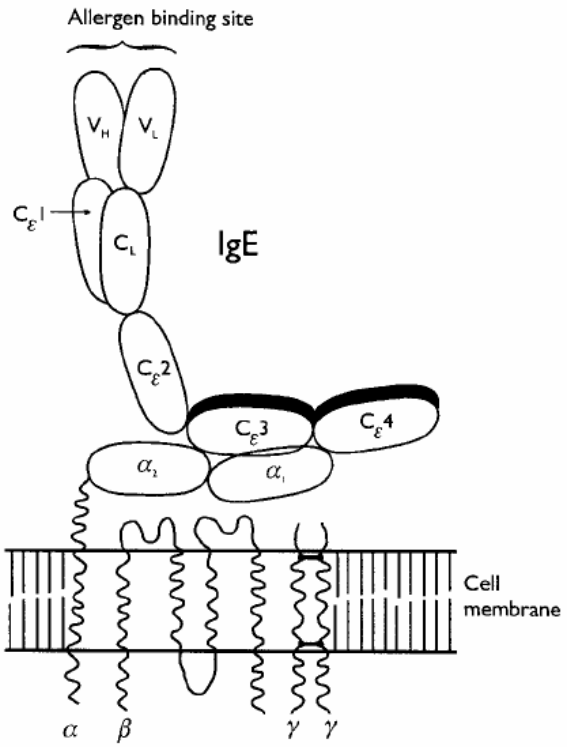

Figure 4. IgE binding to the high affinity IgE receptor *(FcεRI)*. One end of the IgE molecule, the Fab region, binds to specific components (or epitopes) of the allergen, while the other end, the Fc region (C3 domain), binds with high affinity to IgE receptors present on tissue mast cells and circulating basophils. (Adapted from Holgate ST. Asthma and allergy—disorders of civilization? *QJ Med* 1998;91:171-184.[76])

treatment of anaphylaxis is ensured. The preferred location for administration is in the office of the physician who prepared the patient's allergen immunotherapy extract. Because most systemic reactions that result from subcutaneous immunotherapy occur within 30 minutes of an injection, the allergen immunotherapy practice parameters recommend that patients should remain in the physician's office for at least 30 minutes after an injection.[3]

Risk factors for severe reactions include symptomatic asthma and administration of injections during periods of symptom exacerbation. Individual local reactions (wheal & flare) do not appear to predict subsequent systemic reactions. However, patients with greater frequency of large local reactions may be at increased risk for future systemic reactions.[57]

Special precautions are recommended for patients with asthma. Allergen immunotherapy should not be initiated unless the patient's asthma is stable with pharmacotherapy. The EPR-3 Asthma Guidelines highlight that severe and sometimes fatal reactions to immunotherapy, especially severe bronchoconstriction, are more frequent among patients who have asthma, particularly those who have poorly controlled asthma, compared with those who have allergic rhinitis.[56,58]

Sublingual Immunotherapy

Description

A modification of the conventional form of subcutaneous immunotherapy is a form of mucosal immunotherapy where allergen is applied to the oral cavity or more commonly to the sublingual site - **sublingual immunotherapy (SLIT).** SLIT, considered investigational, has generated excitement as a potentially more convenient and safer method of administration.[3,59]

History

The first description of oral mucosal (swallowed) immunotherapy dates back to the early 1900s, but this technique failed to gain popularity then. In the last two decades, after numerous publications, SLIT has virtually replaced the conventional form of immunotherapy in many European countries.[60-63] Some US practitioners use variations of SLIT; however, the FDA has not approved the preparations employed in the US. Additionally, the preparations administered by US physicians are not the same as preparations which are being rigorously studied by FDA-approved protocols. No form of SLIT has been approved by the FDA for use in the US at this time.

The American College of Allergy, Asthma and Immunology and the **American Academy of Allergy, Asthma and Immunology's (AAAAI)** Immunotherapy and Allergy Diagnostics Committees formed a joint task force which recently published an updated report on SLIT for the North American allergy community.[64]

Efficacy

Since the first double-blinded, placebo-controlled studies of SLIT were published in 1986, numerous controlled trials utilizing noninjection routes of allergy immunotherapy have been published; the majority reported favorably on this form of immunotherapy.[64] But many questions remain unanswered, including optimum dosing (which appears to be considerably higher than doses now used), multiple allergen administration, treatment schedules, and duration of treatment. The clinical trials underway in the US are limited to the study of single allergen preparations. Preliminary comparative studies suggest SLIT is less effective than immunotherapy administered by subcutaneous injection. [65,66]

Safety

From the limited data, SLIT appears to have a more favorable safety profile than subcutaneous immunotherapy, which raises the hope that it may allow for home administration, thereby expanding the number of patients who can receive specific allergen immunotherapy (e.g., young children, adults who cannot easily comply with weekly visits). However, the safety of SLIT remains to be rigorously studied, particularly in asthmatic patients, who often are at higher risk for anaphylaxis. (Table 2)

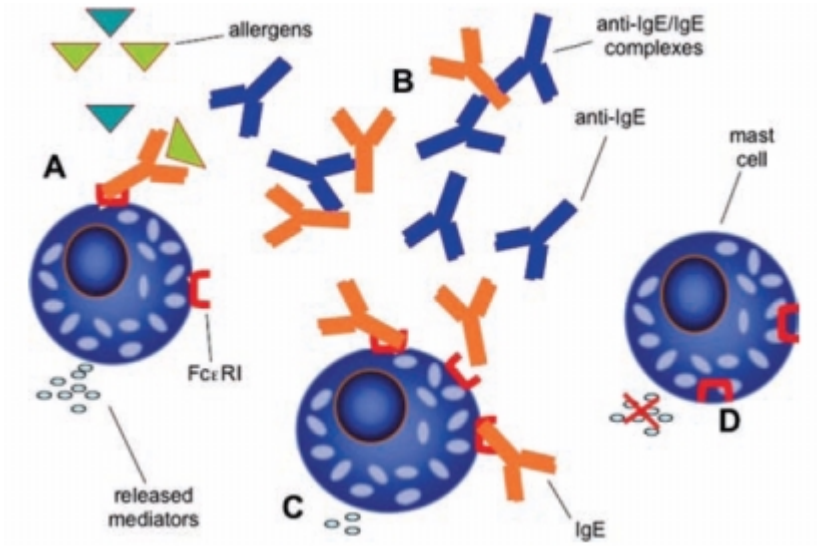

Figure 5. The process of mast cell/basophil "defunctionalization" with anti-IgE treatment. (A) Cells are capable of responding to a particular allergen when they express high-affinity IgE receptors (FcåRI) that are occupied by IgE with specificity for that allergen; as low as 100 molecules of receptor-bound–specific IgE could initiate the cell-triggering process. (B) When anti-IgE is present in the extracellular environment, it binds to free IgE and forms complexes that are eventually removed by the reticuloendothelial system of the liver. (C) Receptor-bound IgE dissociates from FcåRI at a constant rate. Because of the presence of anti-IgE, the cell receptors that are freed are not reoccupied by IgE molecules. (D) Unoccupied FcåRI gets internalized because lack of IgE binding fails to stabilize the receptor on the cell surface. With reduction of cell-bound IgE, mast cells (and basophils) can not respond to allergen and release their inflammatory products.

Adapted from Soresi S, Togias A. Mechanisms of action of anti-immunoglobulin E therapy. *Allergy Asthma Proc* 2006;27:S15–S23.[74]

Monoclonal Anti-IgE

Description

Anti-IgE therapy targets an early point in the allergic inflammatory cascade.[67] Omalizumab (Xolair, Genentech, South San Francisco, California), a recombinant humanized monoclonal anti-IgE antibody, is the first therapeutic agent, specifically targeting IgE, to undergo clinical evaluation for the treatment of allergic diseases of the airway. Omalizumab, which has been rigorously investigated in the treatment of patients with asthma,[68-70] is the sole FDA-approved anti-IgE available in the US.[71] Omalizumab's FDA approved indication is for adults and adolescents (aged ³12 years) with moderate-to-severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen, and whose symptoms are inadequately controlled with inhaled corticosteroids. In studies with asthma patients with IgE levels between 30 and 700 IU/ml, it has been shown to decrease the incidence of asthma exacerbations.

The 2007 EPR-3 Asthma Guidelines define the place of omalizumab in therapeutic paradigms.[5] The Guidelines recommend that omalizumab may be considered adjunctive therapy in step 5 or 6 care for patients who have allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose ICS and LABA. (Figure 3.)[72] All patients with allergic asthma in whom step 4 therapy fails should be evaluated carefully (preferably by an asthma specialist) before initiating omalizumab to (1) confirm the diagnosis of asthma, (2) identify and treat comorbid conditions associated with poor asthma control, (3) evaluate the possibility of incomplete adherence with current therapy, and (4) engage patients in a partnership in which they are trained to use medications and environmental control strategies.

Omalizumab's structure comprises a human IgG framework on to which is grafted the complementarity-determining region from an anti-IgE antibody produced in mice.[10] Less than 5% of the humanized monoclonal anti-IgE antibody comprises residues of murine origin, which minimizes the potential for an immune response toward the non–self protein.[73] Omalizumab is administered by subcutaneous injection every 2 or 4 weeks, with the dose depending on pre-treatment total IgE level and body mass.

Mechanism

Omalizumab selectively targets IgE, thereby (1) helping reduce mast-cell degranulation, limiting the release of inflammatory mediators, and (2) down-regulating high-affinity IgE receptors.[74]

The omalizumab antibody recognizes the C3 domain of human IgE, which is the IgE binding site for the high affinity IgE receptor and which is in the vicinity of the low affinity IgE receptor.[75,76] (Figure 4) By binding to this domain, the IgE antibody is blocked from binding to its receptors. Omalizumab binds to circulating IgE, regardless of IgE specificity; as it does so, the complexes formed are removed by the hepatic reticuloendothelial system. The resulting reduction in free serum IgE is around 95%.[69,77] However, reduction in free serum IgE, per se, has no known therapeutic effect. The subsequent reduction in mast cell and basophil-bound IgE is responsible for the clinical efficacy of anti-IgE therapy. (Figure 5). When mast cells and basophils do not carry IgE on their surfaces, allergic reactions do not occur. After the initiation of omalizumab therapy over a period of weeks the IgE binding to receptors on mast and basophils is reduced. This reduction results in down-regulation of the cell surface IgE receptors, ultimately leading to a decrease in the release of mediators in response to allergen exposure. Inhibiting the immune response to allergen reduces acute allergic reactions and the inflammatory and physiological consequences, such as late reductions in lung function and tissue eosinophilia.[78,79]

Another potential immunomodulatory role of anti-IgE therapy is to affect antigen presentation through the removal of IgE from the surface of dendritic cells.[74,80]

Efficacy

The evidence which supported the incorporation of omalizumab as a therapeutic option by the EPR-3: Asthma Guidelines includes the following. Adding omalizumab to inhaled corticosteroids can reduce exac-

erbations and subsequent use of systemic steroid bursts, reduce daytime allergic asthma symptoms and nighttime awakenings and reduce disruptions of daily routine activities. The vast majority of patients in clinical trials of omalizumab had moderate or severe persistent asthma incompletely controlled with inhaled corticosteroids. [81] In many patients, but not all, adding omalizumab to inhaled corticosteroids therapy produced a significant reduction in asthma exacerbations[68,69,70,82,83] a small but significant improvement in lung function,[68,69] and reduced asthma exacerbations and emergency department visits.[84,85] Omalizumab appears to have a modest steroid-sparing effect, allowing a median reduction of 25% over that of placebo in trials.[68,70,83] Omalizumab is the only adjunctive therapy to demonstrate added efficacy to high-dose ICS plus LABA in patients who have severe persistent allergic asthma.[85] In studies of patients with severe persistent asthma, omalizumab resulted in clinically relevant improvements in quality-of-life scores in more patients than did placebo.[70,85-87]

Safety

The XOLAIR prescribing information includes 2 warnings: anaphylaxis and malignancy.[71] Anaphylactic reactions have occurred after many injections and after many hours.[88] Clinicians are advised to be equipped for the identification and treatment of anaphylaxis, to observe patients following each injection (the optimal length is not established and is left to the clinician's judgement), and to educate patients about anaphylaxis. In regard to malignancy, a team of oncologists concluded that there was no evidence of a causal association.

Potential Future Uses

Despite its limited FDA approval, various clinical trials and reports have shown anti-IgE antibodies to be efficacious in treating pediatric patients with severe asthma,[89,90] patients with seasonal and perennial allergic rhinitis, [91-94] peanut sensitivity, [95,96] sensitivity toward latex products, [97] chronic urticaria[98]and as an adjunct to subcutaneous immunotherapy.[99,100]

Use of anti-IgE as an adjunct to allergy immunotherapy deserves attention. Among the potential shortcomings of conventional subcutaneous immunotherapy are the inconvenience of repeated injections, and the risk of anaphylactic reactions. Thus, a potential use of anti-IgE is the application to prime allergic patients for more vigorous and safe subcutaneous immunotherapy. Studies have demonstrated that the combination of omalizumab and subcutaneous immunotherapy confer added efficacy to either treatment alone, and confer added safety to rush immunotherapy.[101-103]

Summary

IgE is responsible for activation of allergic reactions and is important to the pathogenesis of allergic diseases and the development and persistence of airway inflammation. Clinical evidence strongly supports the efficacy and safety of SLIT for the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma and stinging insect hypersensitivity. Practice parameters help to guide the use of immunotherapy in conjunction with other pharmacologic and nonpharmacologic approaches. Allergy immunotherapy should be considered in patients with poor symptom control or adverse effects resulting from medications. In the US, subcutaneous immunotherapy remains the preferred form of immunotherapy. Its major advantages over sublingual immunotherapy appear to be efficacy and FDA approval, whereas SLIT seems to hold the promise of being safer and more convenient. If clinical trials with SLIT prove successful, an FDA-approved formulation will expand treatment choices; but for now, SLIT should be considered investigational.

Whereas immunotherapy was first introduced over one century ago, the monoclonal anti-IgE antibody, omalizumab was introduced in 2004. Omalizumab works by nonspecifically inhibiting the IgE-mediated inflammatory cascade before it starts. FDA approval is currently limited to adults and adolescents (aged ≥ 12 years) with moderate-to-severe persistent allergic asthma. Omalizumab's expense can limit patients' access.

Access to care is critical if the goals of the EPR-3 Asthma Guidelines are to be met. The Rhode Island Department of Health, in collaboration with community programs, the health care community, and policy makers produced The Asthma Control State Plan 2003-2008. With support by the State and other agencies, together with the implementation of the comprehensive management approach outlined in the EPR-3 Asthma Guidelines, there is good reason for hope that in Rhode Island, our most severe asthma patients will achieve control of their disease with reduction in asthma risk, morbidity and mortality.

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Discussion of off-label or investigational usage of products: Omalizumab is being investigated in other disease states; the article does not advocate off-label use of Omalizumab.

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Images In Medicine

MR Imaging of Acute Appendicitis in Pregnancy

Jill A. Steinkeler, MD, and Courtney A. Woodfield, MD

A 23 year old pregnant woman at 14 weeks gestation presented with a one-day history of epigastric pain that gradually localized to the right lower quadrant. At presentation, the patient was afebrile, blood pressure 110/74, and heart rate 85 beats per minute. Physical examination revealed tenderness to palpation in the right lower quadrant without rebound, guarding or peritoneal signs. Laboratory data demonstrated a white blood cell count of 7, hemoglobin 10.4, and platelets 129. Amylase, lipase, liver function tests, renal function and urinalysis were normal.

An initial right upper quadrant and pelvic **ultrasound (US)** on the day of admission revealed no sonographic abnormality in the abdomen or pelvis. The appendix was not visualized. The patient was subsequently admitted for observation. Her right lower quadrant pain persisted, and a **magnetic resonance imaging (MRI)** of the abdomen and pelvis was performed on hospital day 3 for further evaluation of her pain.

MRI of the abdomen and pelvis without gadolinium revealed a high, midline appendix that was dilated distally with intraluminal fluid contents as well as an appendicolith. (Figure 1A) There was associated periappendiceal edema without defined fluid collection or abscess formation. (Figure 1B) MRI findings were diagnostic of acute appendicitis. The patient underwent subsequent emergent appendectomy, and pathology confirmed acute suppurative appendicitis.

Evaluation of pregnant patients with abdominal or pelvic pain can be a diagnostic dilemma. Especially challenging is the differentiation of normal physiologic changes of pregnancy from disease entities. For example, upward displacement of the appendix and physiologic leukocytosis of pregnancy can be confounding factors. Imaging plays an important role in the work-up of these patients. Due to the theoretical potential harmful effects of fetal exposure to ionizing radiation,[1] US and increasingly MRI are the initial modalities of choice for imaging the abdomen and pelvis during pregnancy.

Acute appendicitis is the most common non-obstetric surgical condition in pregnant patients. Early diagnosis prior to rupture confers a fetal loss rate of < 2%, compared to a rate of > 30% after appendiceal rupture.[4] MRI has been reported to have a sensitivity of 100% and specificity of 93.6% for diagnosing appendicitis in the pregnant patient.[2] MR can also often reveal alternative diagnoses for pain, including degenerated fibroids, hemorrhagic ovarian cysts, ovarian vein thrombosis, ovarian torsion, urolithiasis, inflammatory bowel disease, and small bowel obstruction.[3,4] In our pregnant patient with abdominal pain, MRI proved to be diagnostic for acute appendicitis. The role of MRI in imaging pregnant patients with abdominal and pelvic pain will likely increase in the future, especially when US is limited or nondiagnostic.

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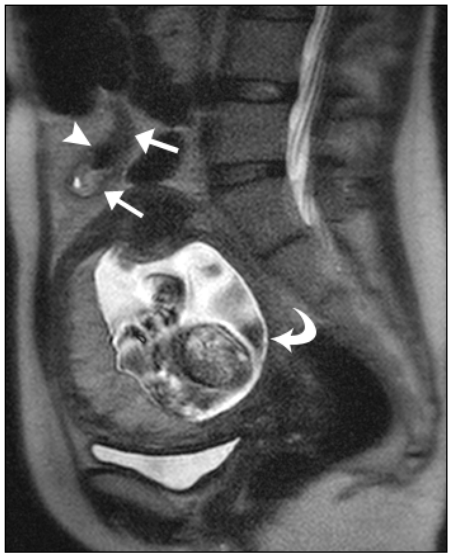

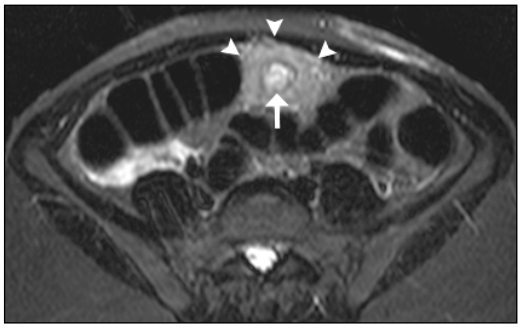

Figure Legends: **Fig 1** - Acute appendicitis in a 23 year old pregnant female at 14 weeks gestation. **(Left)** Sagittal T2 weighted image demonstrates a dilated (1.6 cm in diameter) appendix (arrows) with high T2 signal intensity intraluminal fluid and a low T2 signal intensity appendicolith (arrowhead). Intrauterine gestation (curved arrow). **(Above)** Axial STIR image highlights edema (arrowheads) surrounding the dilated midline appendix (arrow).

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The authors have no financial interests to disclose.

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GERIATRICS FOR THE PRACTICING PHYSICIAN

QUALITY PARTNERS OF RHODE ISLAND
Quality Partners of RI
EDITED BY ANA C. TUYA, MD

Case Presentation: Mr. J, an 88 year-old man found on the floor, complaining of generalized weakness

Rebecca Starr, MD, and Ana Tuya Fulton, MD

Mr. J is 88-years old, with a medical history of bladder cancer, status-post resection with a neo-bladder, right ureteral stent and chronic renal insufficiency. He was brought to a local emergency department after his son found him on the floor. The patient said that earlier in the day, he was getting up from a chair, felt weak, and slid to the ground. He could not get up. Review of systems was positive for having chills during the past few days; decreased appetite, with 6-pound weight loss over the last month; and bloody urostomy output over the past 36 hours and was otherwise negative.

Medical History

He was diagnosed with bladder cancer in January 2006. Cystoscopic pathology showed grade III papillary urothelial carcinoma invading the lamina propria and muscularis. He underwent 6 courses of BCG intravesicular treatment. Repeat pathology in May 2006 showed muscle invasive disease. In July 2006, Mr. J underwent radical cysto-prostatectomy and ileal loop diversion. He was not treated with chemotherapy or radiation, and subsequent CT scans showed no metastasic disease. Other medical history included chronic renal failure, with a baseline creatinine of approximately 2.5 mg/dl, hypertension; diet-controlled diabetes mellitius II; hypercholesterolemia, bilateral deep venous thromboses diagnosed in April 2007 (on warfarin); right ureteral stent secondary to obstruction caused by the bladder cancer; peripheral vascular disease; and Gleason 3 Prostate cancer.

Medications

Warfarin 3 mg daily, amlodipine 10 mg daily, atorvastatin 10 mg daily, mirtazepine 30 mg at bedtime, pantoprazole 40 mg daily and pentoxyfylline 400 mg twice daily. He had no known drug allergies.

Social History

Mr. J was a retired engineer. He was in the military approximately 60 years ago, but had no known exposure to harmful substances. He smoked a pipe for several years, but quit 10-15 years ago. He drank alcohol rarely, and never used illicit substances. Prior to his diagnosis of bladder cancer, he had been active and lived alone. Subsequently, he lived with his son. His health and functional status had gradually declined over the last year, with several hospitalizations and short stays in **skilled nursing facilities (SNF)s** for rehabilitation.

Physical Exam

The patient was thin, slightly diaphoretic, tired-appearing, but pleasant with a gentle smile. His temperature was 100.9F, blood pressure was 148/64 (not orthostatic), heart rate was 64, respirations were 16, and his pulse oximetry was 97% on room air. Head and neck exam was significant for temporal wasting and dense *arcus senilis*. Lung and cardiac exams were normal. His abdomen was soft, non-tender, non-distended, and there were no palpable organs. He had a left lower quadrant ostomy, with a pink stoma and blood-tinged urine in the ostomy bag. He had no lower extremity or scrotal edema. He was alert with intact cognition, and neurological examination was normal, although gait was not assessed.

Labs

WBC 13.4; 94% polys, no bands. Hgb 10.3, platelets 279. Chem 7 revealed sodium of 141, potassium 4.8, bicarbonate 23, BUN 0.5, and creatinine of 5.9. CK was 582, troponin <0.15, PT 43.2, INR 4.90, AST 50, ALT 67, alkaline phosphatase (ALP) 507, T Bili 1.3, D Bili 0.5, Albumin 2.5, Protein 7.4, Lactate 1.3. U/A showed 2+ blood, 600 protein, 3+ LE, 13RBC, 2WBC. EKG showed NSR @ 64, 1st degree heart block (unchanged)

Imaging studies: Chest X-ray & CT of the head were normal. CT of the abdomen and pelvis showed an obstructing 6mm stone in the distal left ureter with extensive inflammatory stranding and hydroureter. The liver had a nodular contour.

Hospital Course

Mr. J was admitted with a diagnosis of acute on chronic renal failure secondary to an obstructing stone. He was seen by a urologist, and underwent percutaneous drainage of his left kidney and had nephrostomy tubes placed bilaterally. He received a 7-day course of piperacillin/tazobactam for treatment of pyelonephritis. His liver enzymes continued to rise. ALP 527, AST 91, ALT 97, T Bili 4.4, D Bili 3.9 after several days. An ultrasound showed coarsened echotexture but no focal lesions. There was no evidence of ductal dilatation, no stones and a negative sonographic Murphy's sign.

What is the Differential Diagnosis of Asymptomatic Elevated bilirubin?

Elevation of direct bilirubin is divided into three major categories: extrahepatic cholestasis (or biliary obstruction), intrahepatic cholestasis, and hepatocellular injury.

Table 1. Evidence for and Against Three Major Causes of Elevated Bilirubin

Extrahepatic cholestatsis	Intrahepatic cholestasis	Hepatocellular injury
- No signs of ductal dilatation or stones - US negative for tumors - No evidence of acute or chronic pancreatitis - No recent travel or suspicion for parasitic infection	- Viral hepatitis panel negative - No alcohol use, past or present - Auto-immune panel negative - No evidence of sepsis or hypoperfusion - No use of total parenteral nutrition - No evidence of end-stage liver disease	- Elevated alkaline phosphatase and history of invasive bladder cancer - No evidence of metastatic disease on US or CT of the abdomen - No history of congestive heart failure - Patent vessels with no evidence of Budd-Chiari

US = Ultrasonography

Once the above possibilities were ruled out, drug-induced hepatotoxicity (also known as drug-induced liver injury, or DILI) was raised as a possible etiology for the elevated liver tests. DILI encompasses a spectrum of clinical disease, ranging from mild biochemical abnormalities to acute liver failure. It is a clinical diagnosis based on history, probability of suspected medication as a cause of liver injury, and exclusion of other causes. The incidence is difficult to determine, and thought to be under-diagnosed.[1]

The definition of liver injury is twice the upper limit of normal levels of ALT or conjugated bilirubin, or a combined increase in levels of AST, ALP, and total bilirubin, with at least one being more than twice the upper level of normal. Elevations in serum enzyme levels (ALT, AST, ALP) indicate liver injury. Increases in both total and conjugated bilirubin, decreased platelet count, or abnormal coagulation studies are indicators of overall liver function. Clinical patterns of DILI include hepatocellular, cholestatic, and a mixed pattern. There are also immunoallergic, autoimmune, and steato-hepatitis drug reactions.

The patient's medications were reviewed to identify possible causes of DILI. While in the hospital, he had been on piperacillin/tazobactam, an antibiotic known to cause a cholestatic drug reaction, but he had already completed his 7-day course. He had been taking atorvastatin for over 5 years. He had been taking mirtazapine for the last 6 months.

A literature review revealed 2 reports of patients with hepatic injury secondary to mirtazapine:[2] a 54-year-old woman on mirtazapine for 3 years, and a 49-year-old woman on mirtazapine for 1 year. Both patients developed elevated liver tests and prolonged jaundice. After they stopped mirtazapine, their liver tests returned to normal after a few months. Both atorvastatin, and mirtazapine were stopped. The patient's liver studies began to decline, and he was discharged to a SNF with a plan for ureteral stone removal once his liver studies normalized.

Six days after discharge, the patient was readmitted because of abnormal lab values, weakness and anorexia. He felt some chills, but denied fever, nausea, vomiting or abdominal pain. In the ED, his vital signs were normal. His physical exam was notable for jaundice and scleral icterus, but no abdominal pain or distention. His urostomy bag contained dark urine.

His labs showed WBC 7.9, hgb 104, platelets 265. His chem 7 revealed CO2 19, BUN 40, and a creatinine of 3. His INR was 1.2. U/A showed 1+ bili, 2+ blood, 30 protein, 3+ LE, WBC >180, and RBC 32. AST was 102, ALT 116, ALP 703 (482 on discharge); T Bili was 8.2 (3.4), D Bili 5.2 (2.2), Albumin 2.0 and T Protein 7.3. US/RUQ of the liver indicated coarse echo texture. No biliary dilatation or focal hepatic lesion was seen. The gallbladder was contracted, and the vessels were patent.

The patient was admitted, and the consulting Gastroenterology team recommended an MRI/MRCP. The MRI showed multiple T2 hyper-dense images, suspicious for malignancy. A liver biopsy, performed under ultrasound guidance, showed high-grade transitional cell carcinoma.

Final Diagnosis

Metastatic bladder cancer to the liver with resulting cholestasis

Resolution of case

The patient's oncologist felt that because of the patient's poor performance status, chemotherapy was not an option. The patient was discharged to Steere House, and expired two weeks later under hospice care.

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Hospitalizations and Associated Costs for Principal versus Additional Diagnoses of Asthma: Implications for Monitoring Children's Health

Deborah N. Pearlman, PhD, Nancy Sutton, RD, MS, Sze Liu, MPH, Janice Fontes, MS, and Jay S. Buechner, PhD

Asthma is the most common chronic disease of childhood in the **United States** (US).[1] Much of the health care cost of asthma is for treatment in the hospital. Hospitalizations for pediatric asthma increased in the US over the past decade, but recently plateaued at historically high levels.[2] In 2004, pediatric asthma hospitalizations in the US were responsible for $330 million in incurred charges.[3]

Surveillance of pediatric asthma hospitalization rates is essential to track trends over time, to identify children likely to be hospitalized due to asthma, and to quantify the burden of disease borne by population subgroups, in particular, children residing in poverty areas. Much of our knowledge about hospitalizations for childhood asthma comes from studies that define an asthma hospitalization as one with a principal diagnosis of asthma. A retrospective study of 2003 National Hospital Discharge Survey data found that 75% of all admissions for childhood asthma were assigned a principal discharge diagnosis of asthma.[4] Of the remaining asthma discharges, most were assigned a principal diagnosis of respiratory illness and an additional diagnosis of asthma.[4] This report explores the implications of using different case definitions of asthma-related hospitalizations, focusing on average length of stay and hospital charges in analyses stratified by neighborhood poverty.

Methods

Under licensure regulations, acute-care hospitals in Rhode Island have reported to the Department of Health's Center for Health Data and Analysis a defined set of data (demographic and clinical) on each inpatient discharge beginning January 1, 1989. This analysis covers inpatient discharges ages 0 – 17 years occurring January 1, 2001 – December 31, 2005. Rate estimates were not adjusted for repeated hospital admissions of the same child during this period.

Two mutually exclusive groups of pediatric asthma discharges were established: (1) all discharges with a principal diagnosis of asthma (ICD-9-CM diagnosis code 493), and (2) discharges with a principal diagnosis of a respiratory illness (ICD-9-CM codes 460 through 496) plus an additional (secondary or tertiary) diagnosis of asthma.

Patient characteristics included: age (0 to 4, 5- 11, 12-17), sex (male vs. female), race and ethnicity (black, Hispanic, white, other race), type of health coverage (public, including RIte Care and fee-for-service Medicaid, commercial/other self-pay), and census tract of residence, (poverty or non-poverty). Records of hospital admissions (2001-2005) were matched with census tract level variables from the US Census 2000 Summary File 3 (SF 3) – Sample Data.[5] A poverty census tract was defined as a census tract where 20% or more of the residents live at or below the federal poverty level, as determined in the 2000 US Census.[6]

Rates per 10,000 children aged 0 to 17 years were calculated using Rhode Island population for the years 2001-2005 from the US Census Bureau.[7] Analyses of hospital charges and length of stay were stratified by poverty and non-poverty census tracts. To calculate changes in rates over time, the baseline rate was subtracted from the rate in a subsequent year, and the difference was divided by the baseline rate and expressed as a percentage.

Table 1.
Hospital inpatient discharges with a diagnosis of asthma, by position of asthma diagnosis and selected patient characteristics, ages 0 – 17, Rhode Island, 2001 –2005.

Characteristic		Position of Asthma Diagnosis	
		Principal N (%)	Additional* N (%)
Age	0 to 4 years	1645 (62.5)	769 (78.5)
	5 to 11 years	668 (25.4)	156 (15.9)
	12 to 17 years	320 (12.1)	55 (5.6)
Sex	Male	1616 (61.4)	569 (58.1)
	Female	1017 (38.6)	411 (41.9)
Race	Black	315 (13.1)	95 (10.8)
	Hispanic	534 (22.3)	190 (21.6)
	White	1551 (64.6)	595 (67.6)
Payer type	Medicaid/RIte Care	1363 (51.9)	492 (50.7)
	Commercial/Other	1211 (46.1)	464 (47.8)
	Self-pay	51 (2.0)	14 (1.5)
Census tract of residence	Poverty	954 (41.4)	325 (38.9)
	Non-poverty	1351 (58.6)	510 (61.1)
Total discharges**		2633 (100.0)	980 (100.0)

*Discharges with a principal diagnosis of respiratory illness only.
**Items may not add to totals due to missing data.

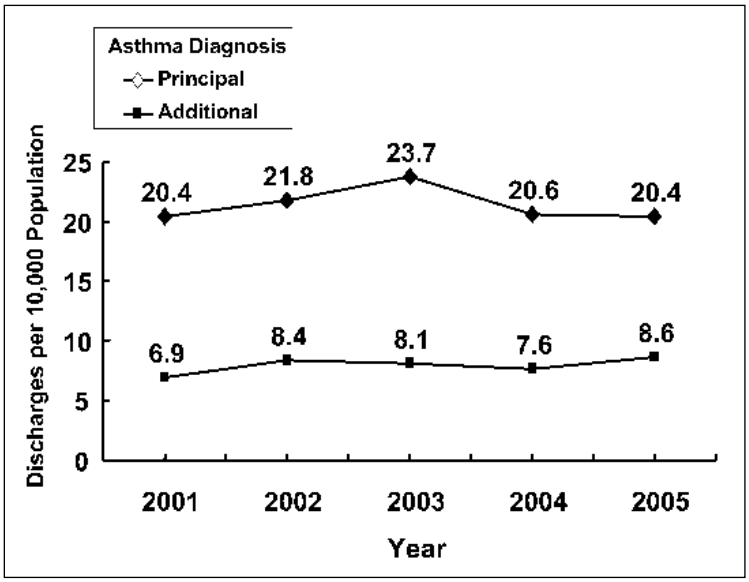

Figure 1. Hospital inpatient discharges with a diagnosis of asthma per 10,000 population, by position of asthma diagnosis and year of discharge, ages 0 – 17, Rhode Island, 2001 –2005.

Table 2.
Mean total charges and mean length of stay for hospital inpatient discharges with a diagnosis of asthma, by position of asthma diagnosis and poverty / non-poverty census tract of patient residence, ages 0 – 17, Rhode Island, 2001 –2005.

Position of Asthma Diagnosis / Measure	All census tracts	Poverty census tracts	Non-poverty census tracts
Principal			
Mean total charges	$19,427	$25,065	$14,579
Mean length of stay	6.0 days	7.4 days	4.9 days
Additional*			
Mean total charges	$23,045	$23,713	$22,369
Mean length of stay	7.4 days	7.8 days	7.3 days

*Discharges with a principal diagnosis of respiratory illness only.

Results

Over the period 2001-2005, there were 2,633 pediatric discharges with a principal diagnosis of asthma, and 980 discharges with a principal diagnosis of respiratory illness and an additional diagnosis of asthma. (Table 1) Children in both groups were more likely to be younger than age five, boys, non-Hispanic white, and live in non-poverty census tracts. Children hospitalized for a respiratory illness with asthma as an additional diagnosis were also significantly more likely to be younger than age five than children with a principal diagnosis of asthma. For both groups, slight majorities were enrolled in publicly-funded insurance. Nearly all had coverage to pay for their care.

Between 2001 and 2003, the rate of discharges per 10,000 children where asthma was the principal diagnosis increased by 16%, then declined in 2004 and 2005, returning to the same level as in 2001. (Figure 1) The rate for discharges where respiratory illnesses were the principal diagnosis and asthma an additional diagnosis increased by 25% between 2001 and 2005.

The average total charge for a pediatric asthma hospitalization with a principal diagnosis of asthma during 2001-2005 was $19,427, with a mean length of stay of 6.0 days. (Table 2) For hospitalizations with a principal diagnosis of respiratory illness and an additional diagnosis of asthma, average charges ($23,045) and length of stay (7.4 days) were both significantly higher than the average charges and length of stay when asthma was the principal diagnosis. Average charges and length of stay for a hospitalization with a principal diagnosis of asthma were significantly higher for children living in poverty neighborhoods ($25,065 and 7.4 days, respectively), than for children in non-poor communities ($14,579 and 4.9 days, respectively).

Discussion

Ongoing surveillance of childhood asthma is necessary to understand changes and patterns in prevalence and to evaluate the impact of practice guidelines and interventions. One impediment to pediatric asthma surveillance is the lack of a "gold standard" definition for hospitalization for childhood asthma. In this analysis, the addition of pediatric hospital discharges with a principal diagnosis of respiratory disease and an additional diagnosis of asthma increased the number of discharges by 37% over the number of discharges with a principal diagnosis of asthma. Furthermore, the age distribution, mean total charges, and mean length of stay for the additional hospitalizations differed significantly from the corresponding measures for hospitalizations with a principal diagnosis of asthma. Most surveillance systems for pediatric asthma in the US capture only hospitalizations with a principal diagnosis of asthma. The findings from this report suggest that asthma surveillance systems designed to inform community- and clinical-based initiatives to decrease hospitalizations for childhood asthma should consider tracking discharges where respiratory illnesses are the principal diagnosis and asthma is the secondary or tertiary diagnosis.

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The authors have no financial interests to disclose.

Department of Health Promotes e-Licensing for Physicians, Spring 2008

Michael Simoli and Robert Crausman, MD

After a successful 95% adoption rate during the 2006 physician renewal cycle, the Rhode Island Department of Health is pleased to announce that the online renewal process will continue for physician licenses for the renewal period from May 1, 2008 through June 30, 2008. During the month of April 2008 physicians eligible for license renewal will have received a notification card in the mail with complete instructions about the renewal process. If you did not receive your renewal notification by May 1, 2008, please contact the Licensing Data Entry Unit at 401-222-1800 or by e-mail at elicense@health.ri.gov.

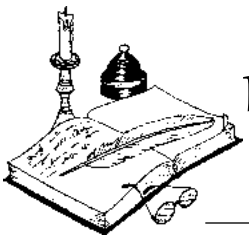
Online license renewal (e-Licensing) continues to be one of the most successful steps toward increasing the Department's efficiency and improving its customer service.

In addition to renewing your license and updating your address information, the Department will again include a workforce survey in the renewal process. This survey will allow the Department to collect summarized information about such topics as availability for emergency volunteering, specialty information, and physician employment in Rhode Island. Participating in this survey is entirely voluntary; responses to the survey will not in any way affect the renewal of your license.

Renewing online is fast, easy, and secure. You will be able to renew online any time during the renewal period, day or night, using your Visa or MasterCard credit or debit card. The Department also has personal computers available on-site for renewing your license during regular business hours. Staff will be available 8:30am through 3:30pm Monday through Friday to assist you with the online renewal process from May 1, 2008 through September 30, 2008.

Disclosure of Financial Interests

The authors have no financial interests to disclose.



Physician's Lexicon

A Planetary Vocabulary

Astrology, centuries ago, was a major component of medical education in Western Europe. Memorizing the constellations, their configurations and the celestial journeys of the planets was at least as important as learning human anatomy or the principles of purging. Fortunately, the alleged relationship of the stars to our individual destinies has now become little more than an eccentricity. Astronomy, or astrobiology, may yet return to the medical curriculum. But until that time, the names of the planets persist, in the vocabulary of contemporary medicine, largely as adjectives describing human mood or behavior, reminding us of our discarded past beliefs.

Mercury, the Roman messenger to the gods, defines the toxic metal formerly used in antiluetic therapy and in certain antiseptics. And a mercurial personality, we are told, is one who is capricious, fickle, flighty and sprightly but volatile. Hermes was the Greek equivalent of Mercury and his name has become legion in medical vocabulary. Along with his fellow Greek divine named Aphrodite, the Greek counterpart of the Roman Venus, we encounter the hermaphrodite, the biological state of creatures bearing both male and female sex organs. Hermetic, describing an airtight sealing, has a more circuitous derivation. When Greek culture overtook Egypt following the Alexandrian expansion, Hermes, now called Hermes Trismegistus [thrice great], was equated with the Egyptian god, Toth [who, it was claimed, had invented glass and the ability to seal glass containers by heat.] Thus, to seal any container was to make it hermetic. Finally, there is the word hermeneutics, the art of explaining things.

The name Venus forms the basis for a variety of nouns and adjectives, many pejorative: venereal disease, venery, venality, venom and even venerable.

The planet Earth gives rise to the adjective, earthy; while the planet Mars is the basis for the adjective, martial. Jupiter, sometimes called Jove, provides us with the adjective jovial.

The planet Saturn, sixth from the sun, crops up in words such as saturnalia, a licentious festival; saturnine, one with a gloomy disposition; and saturnism, describing systemic lead poisoning.

Pluto, the ninth planet from the sun, although some now doubt that it is even a planet. Nonetheless we have the diagnosis of plutomania [the mistaken believe that one is rich] as well as the radioactive plutonium. And then, of course, there is Uranus.

– Stanley M. Aronson, MD

Rhode Island Department of Health
David Gifford, MD, MPH
Director of Health

Vital Statistics

Edited by Colleen Fontana, State Registrar

Rhode Island Monthly Vital Statistics Report Provisional Occurrence Data from the Division of Vital Records

Underlying Cause of Death	Reporting Period			
	June 2007	12 Months Ending with June 2007		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	218	2,745	256.6	3,676.5
Malignant Neoplasms	180	2,264	211.6	5,822.0
Cerebrovascular Diseases	32	397	37.1	599.5
Injuries (Accidents/Suicide/Homicde)	46	575	53.8	9,100.0
COPD	30	437	40.9	392.5

Vital Events	Reporting Period		
	December 2007	12 Months Ending with December 2007	
	Number	Number	Rates
Live Births	1,118	13,341	12.5*
Deaths	894	9,925	9.3*
Infant Deaths	(10)	(100)	7.5#
Neonatal Deaths	(8)	(79)	5.9#
Marriages	363	6,786	6.4*
Divorces	216	2,983	2.8*
Induced Terminations	545	4,973	372.8#
Spontaneous Fetal Deaths	58	920	69.0#
Under 20 weeks gestation	(49)	(840)	63.0#
20+ weeks gestation	(9)	(80)	6.0#

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,067,610

(c) Years of Potential Life Lost (YPLL)

Note: *Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.*

* Rates per 1,000 estimated population

\# Rates per 1,000 live births

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Ninety Years Ago, June 1918

George S. Matthews, MD, in "Some Cardio-Vascular Considerations in Connection with Advisory Board Draft Examinations," noted that examiners could often easily separate the fit from the unfit; but "not a few, however, tax the mental acumen of the examiner." Indeed, the examiner can "get stranded on the rocks of doubt" or "eddy in the currents of uncertainty." The Advisory Board of northern Rhode Island was housed in the Out Patient Department building of Rhode Island Hospital – fortunately, a quiet spot for hearing heart beats. One writer had noted that of 9000 cases, 29% were rejected on physical grounds, with 2.5% because of the heart, although the author suggested that soldiers with "irritable heart" could be retrained.

Carl D. Sawyer, MD, in "Epidemic Meningitis," recommended isolation of carriers, because no immunizations had succeeded.

Henry A. Jones, MD, in "Report of the First Case of Pellagra in 1918," cited the "old belief" linking the disease to a corn diet. The 52 year-old patient, a widow and mother of 3, had left mill work because of swollen feet, to work as a charwoman by the day. Her diet favored johnnycakes and cornmeal puddings. She drank only condensed milk, never fresh milk. Dr. Jones recommended, for treatment, "tonics, strych and arsenic, milk and vegetables."

An Editorial, "The Irregular Cults in the War," praised the Surgeon General for recognizing only MDs as medical officers, excluding "osteopaths, chiropractics, and Christian Scientists." "This is not a time for trying out new systems and treatment. It is a time to rely upon that standard of medicine which has proved the standard for countless ages…"

Fifty Years Ago, June 1958

Carl E. Badgley, MD, Professor of Surgery, University of Michigan and past president, American Academy of Orthopedic Surgeons, delivered the First Murray S. Danforth Oration: "Some Problems in the Treatment of Traumatic Distortion of the Hip."

George W. Waterman, MD, in "Problems of Medical Care 1957-58" [the Presidential Address, Rhode Island Medical Society], deplored the waning of the fee-for-service system: "The issue of the fee-for-service without intervention of the third party with its fixed-fee standard, is that where the fee-for-service is in force, and where there is free choice of physician or surgeon, better patient care will result. For when the bond between patient and doctor is close, and if there exists good understanding, as is the normal case, better feelings regarding financial arrangements is bound to exist, the patient being allowed to realize his obligations on his own responsibility and the doctor not being irked by having to accept a fee forced upon him…by a third party."

Saverio Caputi, JR, MD, in "Treatment of Lead Poisoning with Calcium Disodium Versenate: A Case Report," described a two year old girl, who emerged cured with the treatment, after 18 days in the hospital.

Twenty-Five Years Ago, June 1983

C.P. Pagonis, MD, T.A. Leclerq, MD, and S.R. Allegra, MD, in "Hypopituitarism with Normal Skull Film and Pituitary Tumor," discussed a 38 year-old man: "Microsurgery by the transsphenoidal approach was successful."

The Clinico-pathological Conference Case Record (Rhode Island Hospital) featured a 71 year-old retired truck driver with chronic lymphocytic leukemia and chronic obstructive pulmonary disease, who had smoked 2 packs a day for 50 years, and drunk 3-4 beers a night. He was hospitalized for "profound weakness, dyspnea and fever of four days durations." The findings were: disseminated aspergillosis with valvulitis and congestive heart failure."

Elihu S. Wing, Jr, MD, described the "First American Description of Calcific Aortic Stenosis." General William Whipple (1730-85), a signer of the Declaration of Independence, had ordered an autopsy on his own remains, providing "for this medical milestone."

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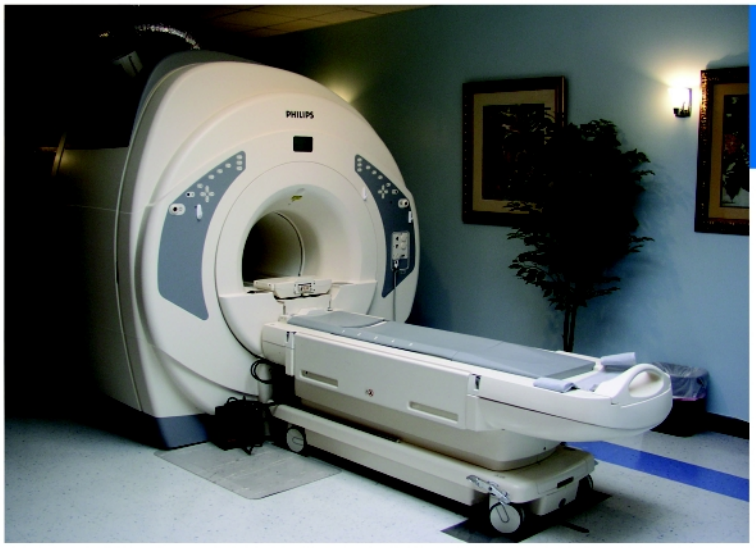

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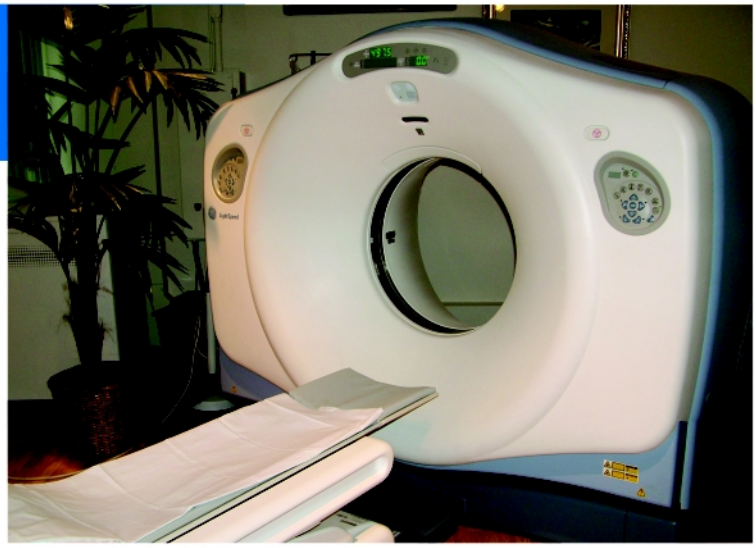

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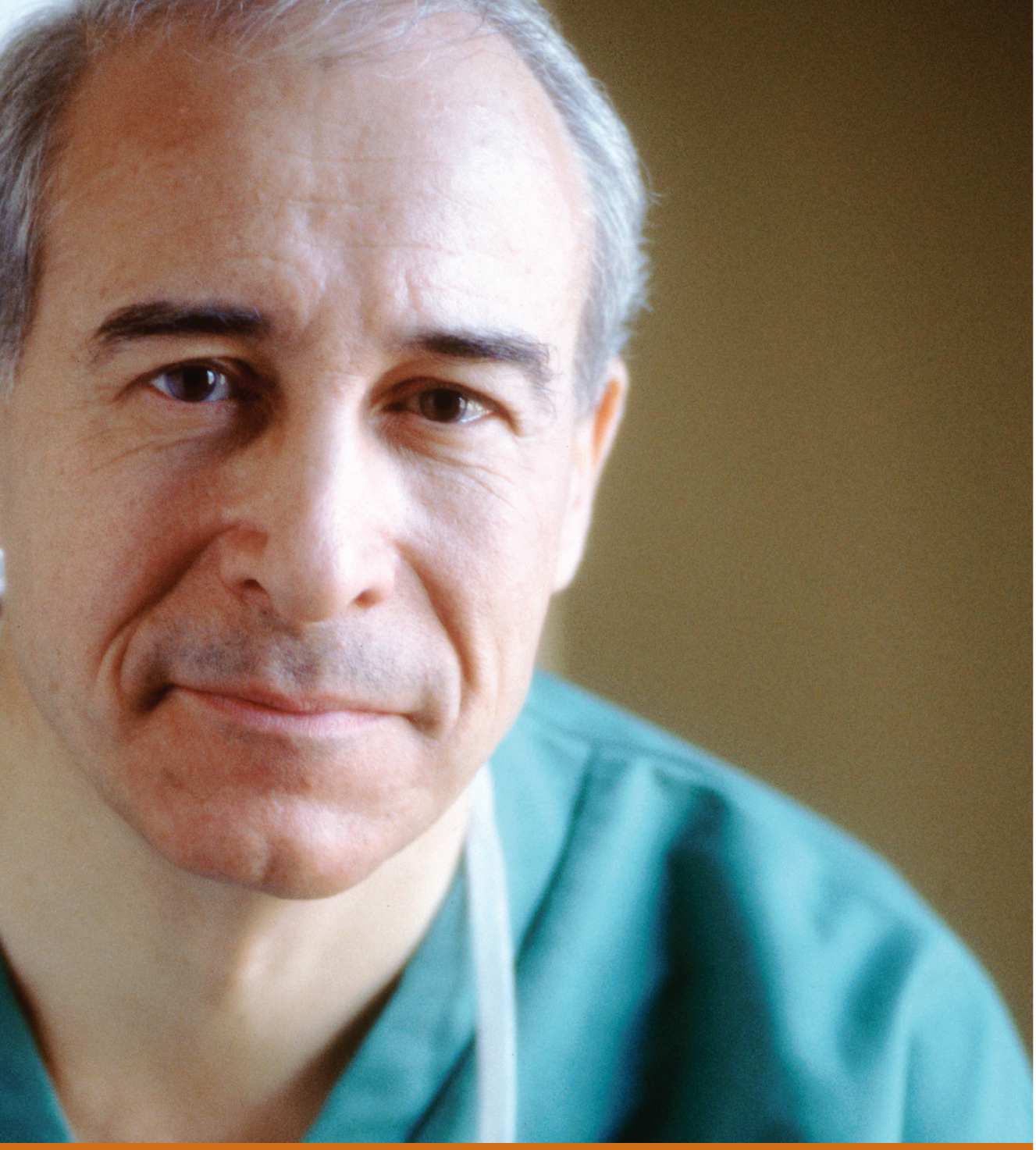

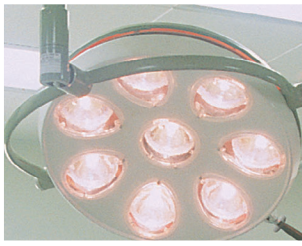

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