What's in a Name???

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

**NEIGHBOR** - friend, near

**ALLIANCE** - affiliation, association, marriage, relationship

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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, would 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 basking 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

Disclosure of Financial Interests
Joseph Friedman, MD, Consultant: Acerta Pharmacy, Ovation, Transoral; Grant Research Support: Cephalon, Teva, Novartis, Boehringer-Ingelheim, Sepracor, Glaxo; Speakers’ Bureau: AstraZeneca, Teva, Novartis, Boehringer-Ingelheim, GlaxoAcadia, Sepracor, GlaxoSmithKline
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? Reworking 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.

Correspondence
e-mail: SMAMD@cox.net
In the 35 years since the publication of the last allergy update in this journal, 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.

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.

REFERENCES
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. 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. Rhode Island has an 11% prevalence rate of current asthma in children 0-17 years old—the 5th highest in the US.

Children from racial and ethnic minorities experience a disproportionate asthma burden. 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. Non-Hispanic black and Hispanic children, particularly those of Puerto Rican descent, experience higher prevalence rates and morbidity than white children.

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. 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. In children, BMI is often converted to percentiles by age and sex utilizing Centers for Disease Control and Prevention (CDC) 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%). Between 2001-2005, one in five children entering kindergarten in RI was obese. As with asthma, racial/ethnic disparities are present: non-Hispanic blacks and Hispanics, most notably Mexican-Americans, have higher prevalence rates than whites.

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. Overweight and obese children are at increased risk for detrimental short- and long-term outcomes, including early development of cardiovascular disease risk factors, early onset type 2 diabetes, psychosocial maladjustment and the persistence of obesity into adulthood. Additionally, research studies implicate obesity in the development and course of asthma.

**The Asthma-Obesity Relationship**

Schaub and von Mutius 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, cough/wheeze with exercise, missed school days, and emergency department visits. 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 found that obese patients required longer courses of supplemental oxygen, continuous albuterol and intravenous ste-

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**Figure 1.** Estimated number of children with self-reported 12 months (1980-1985) or current (2001-2005) asthma.

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

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*Data from the National Health Interview Survey, United States, 1980-2005 (35)

*Percentage of youth with sex- and age-specific BMI > 95th percentile.
Table 1. Body Mass Index categories for adults and children

<table>
<thead>
<tr>
<th>Category</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult (19 years &amp; older)</td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5 - 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>&gt; 25.0</td>
</tr>
<tr>
<td>Obese</td>
<td>&gt; 30.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (2 to 19 years)</td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>&lt; 5th percentile</td>
</tr>
<tr>
<td>Normal weight</td>
<td>5th - &lt; 85th percentile</td>
</tr>
<tr>
<td>Overweight</td>
<td>&gt; 85th percentile</td>
</tr>
<tr>
<td>Obese</td>
<td>&gt; 95th percentile</td>
</tr>
</tbody>
</table>

*Terminology for BMI categories follows recent expert guidelines [17]*

Table 2. Demographic and BMI information for children at camp

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>11.3</td>
<td>1.3</td>
<td>9</td>
<td>13.8</td>
</tr>
<tr>
<td>Household income</td>
<td>$20,631</td>
<td>$16,400</td>
<td>$4,099</td>
<td>$50,000</td>
</tr>
<tr>
<td>Body Mass Index (percentile)</td>
<td>78^1</td>
<td>23^1</td>
<td>15^1</td>
<td>99^1</td>
</tr>
<tr>
<td>Asthma Control Test score°</td>
<td>16.9</td>
<td>5.5</td>
<td>12</td>
<td>25</td>
</tr>
</tbody>
</table>

*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 Conanicus 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).
During the camp session children completed several questionnaires including the Fels Physical Activity Questionnaire, 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, which assesses children's asthma-related physical limitations and the Asthma Control Test (ACT), 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). 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 medications, 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.

**REFERENCES**

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-
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 Capitol Hill Health Center site thirty years ago, serving mainly inner-city and minority Rhode Islanders (of whom almost 2/3 are Spanish speaking).

Since asthmas 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, spacer, 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
Asthma affects 300 million people globally. 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” (EPR-3): 274.

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.

In fact, strong evidence links anti-inflammatory therapy with inhaled corticosteroids to a reduction in asthma mortality. 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 airflow obstruction that is reversible either spontaneously or as a result of treatment.”

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

The author has no financial interests to disclose.

CORRESPONDENCE

Stanley Hoyt Block, MD, FAAAAI
The Providence Community Health Centers Inc.
375 Allens Ave
Providence, RI 02905-5010
Phone: (401) 444 0400
e-mail: sblockmd@providencechc.org

Disclosure of Financial Interests

The author has no financial interests to disclose.
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;4 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 the 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 under-treated 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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Sidney S. Braman, MD, FCCP, is Director, Division of Pulmonary and Critical Care Medicine, Rhode Island Hospital, and Professor of Medicine, The Warren Alpert Medical School of Brown University.

Arul Vigg, MBBS, was a visiting student.

Disclosure of Financial Interests
Sidney S. Braman, MD, FCCP. Consultant: Nycomed, GlaxoSmithKline. Grant Research Support: GlaxoSmithKline, Boehringer Ingelheim. Speaker’s Bureau: GlaxoSmithKline, Pfizer, Boehringer Ingelheim.

Arul Vigg, MBBS, has no financial interests to disclose.

CORRESPONDENCE
Sidney S. Braman, MD, FCCP
Rhode Island Hospital
593 Eddy Street APC 7
Providence, Rhode Island 02903
Phone: (401) 444-8410
e-mail: sidney_braman@brown.edu
New XYZAL® Oral Solution—
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XYZAL is indicated for the relief of symptoms associated with allergic rhinitis (seasonal and perennial), and the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 years of age and older.

The use of XYZAL is contraindicated in: patients with a known hypersensitivity to levocetirizine or any of the ingredients of XYZAL, or to cetirizine (observed reactions range from urticaria to anaphylaxis); and pediatric patients aged 6 to 11 years with impaired renal function.

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 (CNS) depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

In clinical trials 4 to 6 weeks in duration, the most common adverse reactions in ≥2% of pediatric patients (6-12 years of age) taking XYZAL 5 mg included pyrexia (4% vs 2% placebo), cough (3% vs <1% placebo), somnolence (3% vs <1% placebo), and epistaxis (2% vs <1% placebo).

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Please see adjacent brief summary of Prescribing Information.

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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.

Dosage and Administration: Xyzal is available as 5.0 mg (1 tablet) or 10 mg (2 tablets) oral solution once daily in the evening. Some patients may be adequately controlled by 5.0 mg (1 tablet) or 10 mg (2 tablets) oral solution once daily in the evening.

Children 6 to 11 Years of Age: The recommended dose of Xyzal is 5.0 mg (1 tablet) or 10 mg (2 tablets) oral solution once daily in the evening. The 5.0 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.

Adjustment for Renal and Hepatic Impairment: In patients ≥12 years of age with mild to moderate renal impairment (CrCl = 50–80 mL/min) or mild to moderate hepatic impairment (total bilirubin ≤1.5 × upper limit of normal), Xyzal can be used without dosage adjustment in patients with mild to moderate renal or hepatic 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.
- Patients with active or acute stage renal disease (CrCl < 10 mL/min) and patients undergoing hemodialysis should not receive Xyzal.
- Patients 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, drowsiness, and sedation has been reported in some patients under therapy with Xyzal. Patients should be advised to avoid engaging in hazardous activities requiring mental alertness, e.g., driving or operating machinery, while taking Xyzal.

NURSING MOTHERS: It is not known if cetirizine is excreted in human milk. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the benefit to the woman justifies the potential risk to the fetus.

Potential for Drug–Drug Interactions: Levocetirizine, a CYP3A4 inhibitor, and cimetidine, a CYP2C19 inhibitor, are both found to increase the plasma AUC of cetirizine. As such, concomitant use of these combinations with cetirizine may increase the plasma AUC of cetirizine.

USING 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, this drug should be used during pregnancy only if the benefit to the woman justifies the potential risk to the fetus.

NURSING MOTHERS: It is not known if cetirizine is excreted in human milk. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the benefit to the woman justifies the potential risk to the fetus.

Potential for Drug–Drug Interactions: Levocetirizine, a CYP3A4 inhibitor, and cimetidine, a CYP2C19 inhibitor, are both found to increase the plasma AUC of cetirizine. As such, concomitant use of these combinations with cetirizine may increase the plasma AUC of cetirizine.

Usual dose: 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 children ≥6 years of age is 5.0 mg once daily (see Clinical Studies in Full Prescribing Information).

The recommended dose of Xyzal in patients ≥6 years of age for the treatment of the symptoms of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria is based on the systemic exposure of Xyzal in adults and pediatric patients and on the safety profile of Xyzal in both adults 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 pediatric patients 12 years of age and older by the pharmaco-kinetic comparison in adults and children.

Cross-study comparisons indicate that administration of a 5 mg dose of Xyzal to 6- to 12-year-old pediatric patients with seasonal allergic rhinitis resulted in a 2-fold increase in serum 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).

Safety: Xyzal is generally well tolerated in children. The most common adverse reactions were headache and somnolence. In clinical trials, the most common adverse reactions in ≥2% of patients were headache, generalized edema, dry mouth, and pharyngitis.

Antihypertensive agents, diuretics, and calcium channel blockers may have additive effects with Xyzal (see Drug Interactions). Xyzal should be used with caution in patients with hypertension and in those with a history of cardiovascular disease.

Xyzal should be used with caution in patients with a history of cardiovascular disease. Xyzal should be used with caution in patients with a history of cardiovascular disease. Xyzal should be used with caution in patients with a history of cardiovascular disease.

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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, although this is not universally accepted. The Babylonian Talmud, c. second century BC to third century AD, refers to a fatal wasp sting.

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." 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. 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. 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. Relatively mild systemic reactions that are limited to the dermis with hives, flushing and angioedema don’t strictly meet the criteria for anaphylaxis; 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. 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, 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. In adults, the dosage is 0.3 to 0.5 mg; in children the dosage is 0.01 mg/kg up to 0.3 mg. It may be necessary to repeat the dose for persistent or recurrent symptoms. There is no con-
traindication to the use of epinephrine in a life-threatening situation, such as anaphylaxis. 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. 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.

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 of the initial episode. 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. 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.

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.

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-
tured 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.6

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.3

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.

References


Alan Gaines, MD, FAAAAI, is Clinical Assistant Professor of Pediatrics, The Warren Alpert School of Medicine of Brown University.

Disclosure of Financial Interests

The author has no financial interests to disclose.

Correspondence

Alan Gaines, MD, FAAAAI
95 Pitman Street
Providence RI 02906
Phone: (401) 331-8426
e-mail:againes@cox.net
The Role of Pollens In Allergy

Henry B. Freye, MD, FAAAAI

One foundation of allergy practice is the physician’s knowledge of regional aeroallergens. 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.

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 Niño in 1997-1998.

HISTORICAL PERSPECTIVES

Over 130 years ago, Blackley 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. In 1981 Jack Farnham 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.

PHYSICAL ATTRIBUTES OF AEROALLERGENS

Airborne pollen allergens are primarily proteins associated with biogenic particles measuring 2 to 60 μm. 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 reaginic 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. 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.

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.

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 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.

Although oral hyposensitization to pollens has been attempted in this country, the consensus is that despite its effectiveness in certain individuals, treatment in general is less effective than parenteral therapy. 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 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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Henry B. Freye, MD, FAAAAI, is a locum tenens allergist.

Disclosure of Financial Interests

The author has no financial interests to disclose.

CORRESPONDENCE

Henry B. Freye, MD, FAAAAI
22 Elizabeth Court
Mystic, CT 06355
Phone: (860) 536-1570
e-mail: HBfrey@aol.com

Medical Office Building

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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.†

**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 Patient).

**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 23 of 4127 (0.5%) XOLAIR-treated patients compared with 5 of 2238 (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 assessed for the risk of exacerbating any other asthma medications unless otherwise instructed by their physician. The adverse reaction most commonly observed among patients treated with XOLAIR in clinical studies included injection site reaction (4.5%), viral infections (2.3%), acute respiratory tract infection (2.0%), arthralgias (1.6%), headache (1.5%), and pruritus (1.1%). 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; 2022.

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

**Xolair Omalizumab Anti-IgE therapy that helps protect**

8788108-C-XOL-100036
Severe injection-site reactions occurred more frequently in Xolair-treated patients compared with patients in the placebo group. The majority of injection-site reactions involved the injection site. Severe injection-site reactions occurred in 11 patients (12%) in the Xolair group and 6 patients (7%) in the placebo group. Local symptoms of injection-site reactions included redness, swelling, warmth, pain, tenderness, and bruising. Severe injection-site reactions were generally mild and transient, and generally decreased in frequency at subsequent dosing visits.

Conclusions
Low levels of antibodies to Xolair were detected in approximately 1/123 (0.8%) of patients. The frequency of antibodies to Xolair was estimated to be at least 0.2% of patients. Diagnostic criteria for antibodies to Xolair, skin or mucous tissue inwomen, and, in the absence of urticaria, cold-induced redness and flushing, were used in patients with negative history and negative laboratory findings. Although low-level Xolair antibodies have been identified in patients treated with Xolair, the incidence of antibodies to other products may be misleading.

Postmarketing Reports
Anaphylaxis. Based on spontaneous reports and an estimated exposure of about 9300 patients to Xolair during the first year of treatment, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2%. Diagnostic criteria for anaphylaxis included skin rash or urticaria, urticaria, angioedema of the throat or tongue, nausea, vomiting, hives, angioedema, and/or angioedema. Pulmonary involvement was reported in 5% of the cases. Hypersensitivity or anaphylaxis was reported in 1% of patients previously experienced anaphylaxis or urticaria only.

Skin rash, urticaria, angioedema, and/or angioedema have been reported in postmarketing use of Xolair.

Monitoring of appropriate dose of Xolair has not been determined. Single intramuscular doses of 400 mg or greater have been administered to patients without apparent adverse reactions. The cumulative dosage administration to patients was 44,000 mg over a 22 month period, which was not associated with toxicity.

Adverse Reactions
In clinical trials Xolair patients treated with Xolair experienced a higher incidence of injection-site reactions compared to patients treated with placebo. Injection-site reactions occurred in 11% of patients treated with Xolair and 0% of patients treated with placebo. Injection-site reactions were generally mild and transient.

Table 1: Adverse Events in Patients Receiving Xolair and Placebo

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<thead>
<tr>
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<th>Placebo (%)</th>
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<tr>
<td>Adverse event</td>
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</tr>
<tr>
<td>Body as a whole</td>
<td>75</td>
<td>17 (12)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>4</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>3</td>
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</tr>
<tr>
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<td>2</td>
<td>1 (2)</td>
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</tr>
<tr>
<td>Skin and appendages</td>
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</tr>
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</tr>
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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 (lopatadine hydrochloride) Nasal Spray

Initial U.S. Approval: 1996

INDICATIONS AND USAGE
Patanase Nasal Spray is an H1 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 μg of lopinavir 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 complex 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.
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
RI Responds
When you respond, RI Responds!

Are you a licensed healthcare professional? Register to volunteer now!

Working together, we can ensure that Rhode Island is prepared to respond to an emergency.

When a public health emergency or other large-scale disaster occurs, many agencies will need volunteers who are licensed healthcare professionals. RI Responds is a statewide system for the registration and coordinated placement of healthcare professional volunteers.

By registering for RI Responds, you can:
- Choose one of the three volunteer opportunities that best matches your availability and skills.
- Submit individual contact information to a secure database. We want to know the best way to reach you if we need your help.
- Provide details about your individual skills and competencies. We want to put your skills to the best use possible during an emergency.
- Permit your license(s) to be verified before an emergency. We want to organize qualified volunteers quickly and effectively.

Register today at www.RIResponds.org

RI Responds is a partnership among the Rhode Island Department of Health, Rhode Island Disaster Medical Assistance Team and Rhode Island Medical Reserve Corps.
• Offering both 1.5T High Field & Higher Field OPEN MRI Systems

• Advanced CT with multi-slice technology, 3D reconstruction

• Digital Ultrasound with enhanced 3D/4D technology

• Digital Mammography with CAD (computer assisted diagnosis)

• Preauthorization Department for obtaining all insurance preauthorizations

• Fellowship, sub-specialty trained radiologists

• Friendly, efficient staff and convenient, beautiful office settings

• Transportation Service for patients
ketoconazole, a potent inhibitor of cytochrome P450 3A4, increased the exposure (AUC) of des-ciclesonide in adults or children treated with oral corticosteroids. Cross-species differences in oral corticosteroid dosages may cause a severe exacerbation of their symptoms.

Because children have a smaller body mass compared to adults, the plasma protein binding of des-ciclesonide was not affected by warfarin or salicylic acid, indicating no potential for protein binding-based drug interactions.

Drug Interactions

Based on in vitro studies in human liver microsomes, des-ciclesonide appears to have no inhibitory or inducive activity toward 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 administered ciclesonide and oral ethinyl estradiol, an inhibitor of cytochrome P450 3A4, resulted in an increase in the plasma concentration of ethinyl estradiol due to an increase in plasma exposure (AUC) of ethinyl estradiol, by approximately 3.6-fold at steady state, while levels of ciclesonide remained unchanged. Therefore, ketonazole should be administered with caution with intranasal ciclesonide.

Carcinogenesis

Ciclesonide demonstrated no carcinogenic potential in a study of oral dosages up to 900 mcg/kg (approximately 35 times the maximum human daily intranasal dose in adults based on mcg/m2). 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/m2) produced no teratogenicity or other fetal effects. However, intranasal administration of ciclesonide to rabbits at 50 mcg/m2/day for 2 months produced a decrease of less than the maximum human daily intranasal dose in adults based on mcg/m2) or greater produced fetal toxicity. This included fetal death, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at 1 mcg/m2 (less than the maximum human daily intranasal dose based on mcg/m2).

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. The long-term effects of exposure of oral corticosteroids to the fetus in utero has not been assessed. In rats, repeated intranasal administration of ciclesonide throughout pregnancy resulted in an increased incidence of fetal resorptions at an AUC approximately 10 times the maximum human daily intranasal dose based on mcg/m2). In rabbits, repeated intranasal administration of ciclesonide throughout pregnancy resulted in an increased incidence of fetal resorptions at an AUC approximately 5 times the maximum human daily intranasal dose based on mcg/m2). However, subcutaneous administration of ciclesonide to rabbits at 5 mcg/kg/day for 12 weeks produced no evidence of teratogenic effects from ciclesonide to the fetus. There was also no evidence of teratogenic effects from ciclesonide to the fetus in rats when treated intranasally throughout pregnancy. This is consistent with the absence of teratogenic effects observed in rabbit studies at an AUC approximately 5 times the maximum human daily intranasal dose based on mcg/m2).

In clinical trials, it was 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 children 6 to 11 years of age and for 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 safety and effectiveness 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 2 years of age have not been conducted. Studies in children under 2 years of age were waived because of local and systemic safety concerns. Controlled clinical studies have shown that intranasal ciclesonide 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 growth parameters. In healthy children, the long-term effects of this reduction in growth velocity associated with systemic 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 aged 65 or over to determine whether they respond differently from younger persons. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection in the elderly should be cautious, usually starting at the low end of the dosing range, and 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 clinical controlled studies conducted in the US and Canada, a total of 5245 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 due to adverse events; this rate was similar for patients treated with placebo. The common adverse event for patients treated with ciclesonide was rhinitis (13.9% vs 11.6%), runny nose without sneezing, nasal discharge, nasal congestion, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal application of corticosteroids. The dose follow-up is warranted in patients with a change in vision and with a history of glaucoma and/or cataracts.

Information for Patients

Patients who are using drugs that suppress the immune system are more susceptible to infections than nonimmunosuppressed patients. Therefore, patients who are on immunosuppressive doses of corticosteroids, should be warned to avoid exposure to live virus vaccines. 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 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 substitute for the written label, which is the final authority in terms of prescribing. Patients who are on immunosuppressive doses of corticosteroids should be warned to avoid exposure to live virus vaccines. Close follow-up is warranted in patients with a change in vision and with a history of glaucoma and/or cataracts.

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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)\textsuperscript{1-3}
  - Based on average of AM and PM reflective TNSS\textsuperscript{*}
  - 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\textsuperscript{2}

• Well-tolerated\textsuperscript{2,4}

• Low-volume, alcohol-free, and scent-free\textsuperscript{2,5}

• Novel hypotonic formulation delivers medication to the site\textsuperscript{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 \textit{Candida albicans} has rarely occurred with 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%).

\textsuperscript{*} 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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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. 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. 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 manufactured 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. These particles can sensitize nearby persons or evoke symptoms in previously sensitized people.

Respirable particles can also be shed from powder-free latex gloves. 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.

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. 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. Workers in latex doll manufacturing plants have higher prevalence of latex sensitization.

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 membranes 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; and 9.5% of 325 consecutive adult inpatients awaiting surgical or urological procedures had positive latex skin tests. 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). Of health care workers responding to a self-reported questionnaire, 53% described a reaction to rubber gloves.

**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.

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<tr>
<td>Banana</td>
</tr>
</tbody>
</table>

**SOURCES OF LATEX EXPOSURE**

**MEDICAL**

- Gloves
- Tourniquets
- Wound drains
- Injection ports
- Bulb syringes
- Stethoscope

**HOUSEHOLD**

- Balloons
- Rubber bands
- Shoe soles
- 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 latex proteins. Symptoms include erythema, blisters, papules, vesicles, pruritus, 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. 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. One in four atopic health care workers has a positive skin prick test to latex. Only 50% of these persons, however, are clinically symptomatic.

Latex and Food Allergy

Bananas, kiwi fruit, chestnuts, avocados, and tomato may cross-react with the latex protein and cause anaphylactic reactions in latex sensitive persons. Apples, figs, melons, celery, potatoes, papayas, cherries, and peaches have caused oral pruritus, which can progress to more serious symptoms. 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. 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. 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.

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. 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.
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.

REFERENCES


Acknowledgements

The author wishes to thank Patricia C. Ricci, MD, for her help in preparation of this manuscript.

Anthony R. Ricci, MD, is a Clinical Instructor in Medicine at the Warren Alpert Medical School of Brown University and in Private Practice in East Greenwich, RI.

Disclosure of Financial Interests

The author has no financial interests to disclose.

Correspondence

Anthony R. Ricci, MD
63 Cedar Avenue, Suite 7
East Greenwich, RI 02818
Phone: (401) 885-5757
e-mail: aricci3640@msn.com
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 parameters3,4 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.5

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 partake 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 19679,10 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 home’s offending allergen(s) is eliminated or reduced.22,23

**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.9 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-
Understanding 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 Asthma5 (EPR-3 Asthma Guidelines) and recent practice parameters on rhinitis4 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.

POLLEN AND MOLD SURVEY
PROVIDENCE, R.I.
1949–1956

FRANCIS H. CHAFE M.D.
GUY A. SETTIPANE M.D.
1 – 10 – 69

KEY
PEAK SEASON — DARK SHADE
AVERAGE SEASON — LIGHT SHADE
FRINGE AREA — STIPPLED

Figure 2. Aeroallergen Survey, Providence RI. Adapted from Chafee FH, Settipane GA. Atmospheric pollen and mold survey. J Allergy Clin Immunol 1964 May-June;35:193-200.36
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 rhinitis28 (including ocular symptoms29-31), allergic asthma27,32,34-38, and stinging insect hypersensitivity30,31 and the therapy is effective in both adults and children.42-47

Allergic rhinitis

The robust research has shown subcutaneous immunotherapy to be effective in a dose dependent manner, with optimal doses determined. (Table 1) The physician should be familiar with the key allergens 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.39 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.32,53

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.5 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
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.3

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 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)
Powerful relief
to help patients face their allergies

POTENT

- Potent inhibition of histamine-induced wheal and flare
  - The clinical relevance of histamine wheal skin testing is unknown

CONSISTENT EFFICACY

- Consistent efficacy across 8 placebo-controlled clinical trials
  - Six clinical trials in allergic rhinitis (seasonal and perennial)
    and 2 in chronic idiopathic urticaria

FAST AND LONG-LASTING EFFECT

- Onset of efficacy was seen at 60 minutes and efficacy was demonstrated at
  the end of the 24-hour dosing interval (Environmental Exposure Unit study)

CONVENIENT ONCE-DAILY PM DOSING

(XYZAL 5 mg
actual size)

IMPORTANT SAFETY INFORMATION

XYZAL is indicated for the relief of symptoms associated with allergic rhinitis (seasonal and perennial), and the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 5 years of age and older.

The use of XYZAL is contraindicated in: patients with a known hypersensitivity to levocetirizine or any of the ingredients of
XYZAL or to cetirizine (observed reactions range from urticaria to anaphylaxis); and pediatric patients aged 6 to 11 years
with impaired renal function.

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 (CNS) depressants should be avoided because additional reductions in
alertness and additional impairment of CNS performance may occur.

In clinical trials, the most common adverse reactions in ≥2% of adult and adolescent patients (12 years of age and
older) taking XYZAL 25 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. In clinical trials,
the most common adverse reactions in ≥2% of pediatric patients (6-12 years of age) taking
XYZAL 5 mg included pyrexia (4% vs 2% placebo), cough (3% vs <1% placebo), somnolence (3% vs <1% placebo),
and epistaxis (2% vs <1% placebo).

For more information, visit www.XYZAL.com
Please see adjacent brief summary of Prescribing Information.

XYZAL is a registered trademark of the UCB Group of companies.
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INDICATIONS AND USAGE: Allergic Rhinitis: XYLAM® 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: XYLAM® 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: XYLAM® is available as 5 mg (1 tablet) or 2 tablets (1 tablet plus 1 tablet; 5 mL oral solution) once daily in the morning. Some patients may be adequately controlled by 2.5 mg (1 tablet) or 1 tablet (5 mL oral solution) once daily in the evening. Children 6 to 11 years of age: The recommended dose of XYLAM® is 2.5 mg (1 tablet) or 1 tablet (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).

XYLAM® 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 (CrCl 50-80 mL/min) 2.5 mg once daily is recommended; moderate renal impairment (CrCl 30-50 mL/min) 2.5 mg once daily or every other day (3 days on and 4 days off) is recommended. Patients with end stage renal disease (CrCl < 10 mL/min) and patients undergoing hemodialysis should not receive XYLAM®.

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

CONTRAINDICATIONS: The use of XYLAM® is contraindicated in:

- Patients with known hypersensitivity to lorazepam or any of the ingredients of XYLAM® or to xylazine.
- Obese patients with a body mass index (BMI) >35.

WARNINGS AND PRECAUTIONS: Activities/Requirements Mental Alertness: In clinical trials the occurrence of somnolence, fatigue, and asthenia has been reported in patients under therapy with XYLAM®. Patients should be advised to avoid hazardous activities or engaging in hazardous oculars such as operating machinery or driving a motor vehicle after ingestion of XYLAM®. Patients who are affected may not be capable of adequately performing the motor coordination such as operating machinery or driving a motor vehicle after ingestion of XYLAM®. Concomitant use of XYLAM® with other centrally nervous system depressants should be avoided because additional symptoms of sedation and impaired mental function may occur.

ADVERSE REACTIONS: Use of XYLAM® has been associated with somnolence, fatigue, and asthenia (see WARNINGS AND PRECAUTIONS, Activities/Requirements Mental Alertness). Clinical Trials Experience: the safety data described below reflect exposure to XYLAM® in 2743 patients with seasonal or perennial allergic rhinitis and chronic idiopathic urticaria (n=12) controlled clinical trials if 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: XYLAM® is usually administered once daily. The adult and adolescent patients were 32 years, 44% of the patients were men and 56% were women, and the large group from 17 to 12 years of age was Caucasian. In these trials 43% and 42% of the subjects in the XYLAM® 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, fatigue, asthenia, headache, nausea, vomiting, diarrhea, nasopharyngitis (6%, 4%, 3%), and other reactions are listed in the following table:

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Placebo (%)</th>
<th>XYLAM® 2.5 mg</th>
<th>XYLAM® 5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Headache, pressure</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Headache, tension</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nausea, vomiting,</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nausea, vomiting,</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Of the adverse reactions observed at a higher incidence than placebo in adults and adolescents aged 12 years and older exposed to XYLAM® in 2.5 mg or placebo, were the following:

- Somnolence (8%, 5%), fatigue (5%, 3%), headache (3%, 2%), dizziness (2%, 1%), nasopharyngitis (2%, 1%), and other reactions are listed in the following table:

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Placebo (%)</th>
<th>XYLAM® 2.5 mg</th>
<th>XYLAM® 5 mg</th>
</tr>
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<tbody>
<tr>
<td>Abdominal pain</td>
<td>1</td>
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<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>2</td>
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</tr>
<tr>
<td>Headache, pressure</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Headache, tension</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Nausea, vomiting,</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nausea, vomiting,</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Pregnancy: XYLAM® is not recommended for use during pregnancy.

Nursing Mothers: No nursing mothers animal studies have been conducted with XYLAM®.

Reproductive Use: the safety and effectiveness of XYLAM® in male patients under 6 years of age have not been established.

The recommended dose of XYLAM® is 2.5 mg once daily for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in children 12 to 17 years of age (based on extrapolation of efficacy from adults 18 years of age and older (see CLINICAL STUDIES in Full prescribing information)

The recommended dose of XYLAM® is 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 extrapolation of demonstrated efficacy of XYLAM® 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 XYLAM® to 6-12 year-old pediatric seasonal allergic rhinitis patients resulted in a 1:1 ratio of the systemic exposure (AUC) observed when 2.5 mg of XYLAM® 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 TRIALS IN Full Prescribing Information and CLINICAL PHARMACOLOGY/Pharmacokinetics in Full Prescribing Information.

Geriatric Use: Clinical studies of XYLAM® for each approved indication did not include sufficient numbers of patients 65 years and older to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be based on the following principles: in elderly patients the lower the risk of decreased hepatic, renal, or cardiac function and of concomitant disease or other drugs therapy.

Renal impairment: XYLAM® 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).

Medication: as lorazepam is mainly excreted unchanged by the kidneys, it is unlikely that the clearance of lorazepam is significantly decreased in patients with severe hepatic impairment (see CLINICAL PHARMACOLOGY/Pharmacokinetics in Full Prescribing Information).

OVERDOSAGE: Overdose has been reported with XYLAM®.

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 XYLAM®. Should overdose occur supportive or supportive treatment is recommended. XYLAM® is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent(s) is continuously circulated.

The acute maximal non-lethal oral dose of lorazepam was 240 mg/kg in mice (approximately 200 times the 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 maximum non-lethal oral dose was 240 mg/kg (approximately 100 times the maximum recommended daily oral dose in adults and approximately 240 times the maximum recommended daily oral dose in children on a mg/m² basis).

Manufactured for: UCB, Inc. • Syrmna, GA 30080 Co-marketed by safinoti-US LLC Bridgeville, NJ 80087

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MONOCLONAL ANTI-IGE

Description
Anti-IgE therapy targets an early point in the allergic inflammatory cascade. 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, is the sole FDA-approved anti-IgE available in the US. Omalizumab’s FDA approved indication is 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. 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. 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.)

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. 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. 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.

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. (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%. 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.

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

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-
erations and subsequent use of systemic ster-
roid 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 per-
sistent asthma incompletely controlled with
inhaled corticosteroids. 81 In many patients,
but not all, adding omalizumab to inhaled
corticosteroids therapy produced a signifi-
cant reduction in asthma exacerba-
tions, 68,69 and reduced asthma exacerbations and emergency
department visits. 82,83 Omalizumab appears to have a modest steroid-sparing effect, al-
lowing a median reduction of 25% over that of placebo in trials. 68,69 Omalizumab is the
only adjunctive therapy to demonstrate added efficacy to high-dose ICS plus LABA in patients who have severe persistent aller-
gic asthma. 83 In studies of patients with se-
vere persistent asthma, omalizumab resulted in clinically relevant improvements in qual-
ity-of-life scores in more patients than did placebo. 70,85,87

Safety
The XOLAIR prescribing information in-
cludes 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 treat-
ment of anaphylaxis, to observe pa-
tients following each injection (the opti-
mal length is not established and is left to
the clinician’s judgement), and to edu-
cate patients about anaphylaxis. In regard
to malignancy, a team of oncologists con-
cluded 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 pe-
rennial allergic rhinitis, 91-94 peanut sensi-
tivity, 93,94 sensitivity toward latex products, 95 chronic urticaria 96,97 and as an adjunct to
subcutaneous immunotherapy. 98,99

Use of anti-IgE as an adjunct to al-
lergy immunotherapy deserves attention. Among the potential shortcomings of con-
ventional subcutaneous immuno-
therapy are the inconvenience of re-
peated injections, and the risk of anaphyl-
cytic reactions. Thus, a potential use of
anti-IgE is the application to prime aller-
gic patients for more vigorous and safe
subcutaneous immunotherapy. Studies
have demonstrated that the combination of
omalizumab and subcutaneous immu-
notherapy confer added efficacy to either
treatment alone, and confer added safety
to rush immunotherapy. 100-103

SUMMARY
IgE is responsible for activation of al-
lergic 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, aller-
gic conjunctivitis, allergic asthma and sting-
ing insect hypersensitivity. Practice param-
eters help to guide the use of immuno-
therapy in conjunction with other phar-
macologic and nonpharmacologic ap-
proaches. Allergy immunotherapy should be considered in patients with poor symp-
tom control or adverse effects resulting from
medications. In the US, subcutane-
ounous immunotherapy remains the preferred
form of immunotherapy. Its major advan-
tages over sublingual immunotherapy ap-
ppear 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,
a FDA-approved formulation will expand
treatment choices; but for now, SLIT
should be considered investigational.

Whereas immunotherapy was first intro-
duced over one century ago, the monoclonal anti-IgE antibody,
omalizumab was introduced in 2004. Omalizumab works by nonspecifically inhibiting the IgE-mediated inflamma-
tory cascade before it starts. FDA ap-
proval is currently limited to adults and
adolescents (aged ≥ 12 years) with mod-
erate-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 commu-
nity programs, the health care commu-
nity, and policy makers produced The
With support by the State and other
agencies, together with the implementa-
tion 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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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 periappendical 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, 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. MRI has been reported to have a sensitivity of 100% and specificity of 93.6% for diagnosing appendicitis in the pregnant patient. 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. 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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Jill A. Steinkeler, MD, is a 2nd year Radiology Resident, Rhode Island Hospital.

Courtney A. Woodfield, MD, is Assistant Professor of Diagnostic Imaging, The Warren Alpert Medical School of Brown University.

Disclosure of Financial Interests

The authors have no financial interests to disclose.

Correspondence

Jill A. Steinkeler, MD
Email: jsteinkeler@lifespan.org
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 intravesical 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 metastatic disease. Other medical history included chronic renal failure, with a baseline creatinine of approximately 2.5 mg/dl, hypertension; diet-controlled diabetes mellitus 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, mirtazapine 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 (SNFs) 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 hydronephrosis. 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.
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 return to normal after a few months. Both atorvastatin, and mirtazapine were stopped. The patient’s liver studies began to return to normal after a few months.

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Disclosure of Financial Interests

The authors have no financial interests to disclose.

The analyses upon which this publication is based were performed under Contract Number 500-02-R102, funded by the Centers for Medicare & Medicaid Services, an agency of the U.S. Department of Health and Human Services. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. The author assumes full responsibility for the accuracy and completeness of the ideas presented.
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). 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. In 2004, pediatric asthma hospitalizations in the US were responsible for $330 million in incurred charges.

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. Of the remaining asthma discharges, most were assigned a principal diagnosis of respiratory illness and an additional diagnosis of asthma. 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. 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.

Rates per 10,000 children aged 0 to 17 years were calculated using Rhode Island population for the years 2001-2005 from the US Censuses Bureau. 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.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Position of Asthma Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Principal (N, %)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>0 to 4 years</td>
<td>1645 (62.5)</td>
</tr>
<tr>
<td>5 to 11 years</td>
<td>688 (25.4)</td>
</tr>
<tr>
<td>12 to 17 years</td>
<td>320 (12.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1616 (61.4)</td>
</tr>
<tr>
<td>Female</td>
<td>1017 (38.6)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>315 (13.1)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>554 (22.3)</td>
</tr>
<tr>
<td>White</td>
<td>1551 (64.6)</td>
</tr>
<tr>
<td>Payor type</td>
<td></td>
</tr>
<tr>
<td>Medicaid/RIte Care</td>
<td>1363 (51.9)</td>
</tr>
<tr>
<td>Commercial/Other</td>
<td>1211 (46.1)</td>
</tr>
<tr>
<td>Self-pay</td>
<td>51 (2.0)</td>
</tr>
<tr>
<td>Census tract of residence</td>
<td></td>
</tr>
<tr>
<td>Poverty</td>
<td>954 (41.4)</td>
</tr>
<tr>
<td>Non-poverty</td>
<td>1361 (58.6)</td>
</tr>
<tr>
<td>Total discharges**</td>
<td>2833 (100.0)</td>
</tr>
</tbody>
</table>

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

ACKNOWLEDGEMENTS

We wish to thank Jeanne E. Moorman, MS, Centers for Disease Control and Prevention, National Center for Environmental Health, Division of Environmental Hazards and Health Effects and Annie Gjlesvik, PhD, Rhode Island Department of Health, Diabetes Prevention and Control Program for their insightful comments on statistical issues. This work was funded in part by the Agency for Healthcare Research and Quality (AHRQ) 2006-2007 Learning Partnership to Decrease Disparities in Pediatric Asthma and by the Centers for Disease Control and Prevention (CDC) Grant Cooperative Agreement Number IU59EH000199-01. The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of AHRQ or CDC.

<table>
<thead>
<tr>
<th>Position of Asthma Diagnosis / Measure</th>
<th>All census tracts</th>
<th>Poverty census tracts</th>
<th>Non-poverty census tracts</th>
</tr>
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<tbody>
<tr>
<td>Principal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean total charges</td>
<td>$19,427</td>
<td>$25,065</td>
<td>$14,579</td>
</tr>
<tr>
<td>Mean length of stay</td>
<td>6.0 days</td>
<td>7.4 days</td>
<td>4.9 days</td>
</tr>
<tr>
<td>Additional*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean total charges</td>
<td>$23,045</td>
<td>$22,368</td>
<td></td>
</tr>
<tr>
<td>Mean length of stay</td>
<td>7.4 days</td>
<td>7.8 days</td>
<td>7.3 days</td>
</tr>
</tbody>
</table>

*Discharges with a principal diagnosis of respiratory illness only.
REFERENCES

Deborah N. Pearlman, PhD, is Research Faculty in the Program in Public Health, Warren Alpert Medical School of Brown University, and Senior Epidemiologist, Rhode Island Department of Health.

Nancy Sutton, RD, MS, is Program Manager in the Asthma Prevention Program, Rhode Island Department of Health.

Sze Liu, MPH, is a PhD candidate in the Program in Public Health, Center for Population Health and Clinical Epidemiology, Warren Alpert Medical School of Brown University.

Janice Fontes, MS, is Data Manager in the Center for Health Data and Analysis, Rhode Island Department of Health.

Jay S. Buechner, PhD, is Chief, Center for Health Data and Analysis, and Clinical Assistant Professor of Community Health, Warren Alpert Medical School of Brown University.

Disclosure of Financial Interests
The authors have no financial interests to disclose.
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.
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 belief that one is rich] as well as the radioactive plutonium. And then, of course, there is Uranus.

– STANLEY M. ARONSON, MD
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. Leclercq, MD, and S.R. Allegra, MD, in “Hypopituitarism with Normal Skull Film and Pituitary Tumor,” discussed a 38 year-old man: “Microsurgery by the transphenoidal 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 Indepen- dence, had ordered an autopsy on his own remains, providing “for this medical milestone.”
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