AllergyWatch®

A Synopsis of Allergy and Asthma Literature, Resulting from an Unbiased, Comprehensive Review of Nineteen Major Medical Journals.

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Grass Pollen SLIT: Five-Year Outcome Study

LONG-term follow-up studies are needed to document lasting changes in immune function responsible for the clinical effectiveness of specific immunotherapy. Previous reports have shown the efficacy of sublingual immunotherapy (SLIT) using a standardized grass pollen extract. This study presents the long-term outcomes of grass pollen SLIT, including 2 years' follow-up after the end of treatment.

The 5-year randomized, double-blind trial included 634 patients with grass pollen-induced allergic rhinoconjunctivitis, with or without asthma. They were assigned to 3 years of SQ-standardized grass allergy SLIT using the Grazax immunotherapy tablet (*Phleum pratense* 75,000 SQ-T/2,800 BAU) or placebo. The final analysis included 238 study completers with 2 years of follow-up after treatment. Clinical, safety, and immunologic outcomes were analyzed.

In all five seasons, the mean rhinoconjunctivitis daily symptom score was reduced by 25% to 36% in patients receiving grass pollen SLIT, compared to placebo. There was also a 20% to 45% reduction in rhinoconjunctivitis daily medication score and a 27% to 41% reduction in the weighted rhinoconjunctivitis combined score. Patients receiving active SLIT also had fewer days with severe symptoms during times of peak grass pollen exposure: relative difference 49% to 63%.

Immunologic studies showed lasting reductions in allergen-specific antibody responses, including specific IgG_4 levels, specific IgE-blocking factor, and facilitated antigen presentation. There were no episodes of anaphylaxis or other safety issues related to study treatments.

This clinical trial with long-term follow-up supports the efficacy of grass pollen SLIT for patients with moderate to severe allergic rhinoconjunctivitis. Clinically relevant improvements in symptoms, medication use, and symptom-free days are accompanied by sustained immunologic changes. Grass pollen SLIT is an ➤➤

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The American College of Allergy, Asthma & Immunology expresses its appreciation to MERCK for its grant in support of the publication of *AllergyWatch*®.

The following journals have been selected as the primary focus of review in the preparation of materials within "AllergyWatch®".

- Annals of Allergy, Asthma and Immunology
- Journal of Allergy and Clinical Immunology
- American Journal of Respiratory and Critical Care Medicine
- Chest
- Clinical Experimental Allergy
- Allergy
- International Archives of Allergy and Immunology
- Annals of Internal Medicine
- Pediatrics
- Journal of Pediatrics
- Thorax
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- European Respiratory Journal
- Pediatric Allergy and Immunology

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"important treatment option" for rhinoconjunctivitis that is not controlled by symptomatic medications.

COMMENT: *Using a study design that had previously shown a sustained clinical benefit as well as persistent immunologic changes after subcutaneous immunotherapy, these authors report similar results for patients with grass allergic rhinitis receiving SLIT. The clinical efficacy of the SLIT treatment was impressive, with an average 33% improvement in symptom and medication scores over the course of the study. Interestingly, immunologic changes--including specific IgE blocking factor, specific IgG4, and facilitated allergen inhibition--also had a statistically significant sustained improvement compared to placebo, although there was some decline in the actual numbers. It is reassuring to see that SLIT is also a potentially long-term, disease-modifying therapy.*
S.M.F.

Durham SR, Emminger W, Kapp A, et al: SQ-standardized sublingual grass immunotherapy: Confirmation of disease modification 2 years after 3 years of treatment in a randomized trial.
J Allergy Clin Immunol. 2012;129:717-725. ♦♦

FOCUS ON EIB

In this issue, we look at a number of recent reports on exercise-induced bronchonconstriction in athletes (and others).

Elite Swimmers Show Airway Changes

UP to three-fourths of elite-level swimmers have airway hyperresponsiveness, often without asthma symptoms. It remains unclear whether these changes are chronic, and how they affect airway structure and function. Airway inflammation and remodeling were assessed in a sample of competitive swimmers.

Twenty-three elite Canadian swimmers underwent exhaled nitric oxide measurement, methacholine challenge testing, eucapnic voluntary hyperpnea challenge testing, allergy skin prick testing, and bronchoscopy. Tests were performed off-season, when the athletes were not in training. The findings were compared with 10 age-matched patients with mild asthma and 10 nonallergic controls.

The elite swimmers had elevated airway mucosa eosinophil counts and mast cell counts, compared to controls. Swimmers also had increased goblet cell hyperplasia and increased mucin expression, compared to both controls and asthma patients. Submucosal type I and III collagen expression and tenascin deposition were also higher in swimmers than nonallergic controls.

However, exhaled nitric oxide and airway responsiveness to methacholine or eucpanic voluntary hyperpnea challenge were unrelated to these airway inflammatory and remodeling changes. Of the 23 swimmers, 18 had atopy.

This study demonstrates significant airway inflammatory and remodeling changes in elite-level swimmers, apparently related to exposure to chlorinated swimming pools. The changes are similar to those of patients with mild asthma, but with higher mucin expression and independent of airway hyperresponsiveness. Pending further studies of the long-term physiologic and clinical effects, the results highlight the need for special attention to respiratory health in competitive swimmers.

COMMENT: *In this carefully designed study, the authors report that elite-competitive swimmers who train at indoor chlorinated pools have increased airway inflammation and airway remodeling, compared to normal controls and even patients with asthma. Surprisingly, this airway* ➤➤

inflammation does not result in airway hyperresponsiveness or increased exhaled NO. The authors suggest that swimmers may need to take preventive measures to avert these airway effects resulting from exposure to chlorinated pools.
S.M.F.
Bougault V, Loubaki L, Joubert P, et al: Airway remodeling and inflammation in competitive swimmers training in indoor chlorinated swimming pools.
J Allergy Clin Immunol. 2012;129:351-358. ♦♦

Should We Screen for EIB in Athletes?

ATHLETES have an increased rate of exercise-induced bronchoconstriction (EIB), compared to the general population. The authors previously reported high rates of undiagnosed EIB in collegiate athletes, based on eucapnic voluntary hyperventilation (EVH) testing. They performed a further study to evaluate the use of EVH to screen for EIB among athletes in specific sports.

The study included 144 athletes in six sports--men's and women's soccer, lacrosse, and ice hockey--at one Division I collegiate athletic program. Baseline assessment included questions about asthma symptoms during exercise. Each athlete underwent exhaled nitric oxide measurement, followed immediately by EVH testing. Those with a 10% or greater decline in FEV_1 on EVH were classified as having EIB.

Just 4 athletes had a positive EVH screening result--a rate of 2.7%. Among 64 athletes who reported a history of asthma symptoms during exercise, the rate of positive screening results was 3%. Two out of the four athletes with EIB reported no history of asthma symptoms. Mean exhaled nitric oxide was 13.25 ppb in the athletes with EIB, compared to 24.5 ppb in those with negative screening results.

The results show a "surprisingly low" rate of EIB in a sample of collegiate athletes undergoing screening with EVH. Neither athlete-reported symptoms nor baseline exhaled nitric oxide level is useful in predicting the presence of EIB. Because of the low prevalence of EIB in collegiate athletes, the use of EVH screening is not justified.

COMMENT: *Is screening for EIB in athletes meaningful? The authors conclude that screening is not recommended, as the prevalence low and there is no consensus on a gold standard for determination of EIB. The presence or absence of self-reported symptoms and exhaled NO were not predictive of EIB. Only 2 out of 64 (3%) symptomatic athletes were positive by EVH, the standard for elite athletes. Of the 4 out of 144 (2.7%) athletes screened who were positive for EVH, 2 were asymptomatic. The take-home message is that screening for EIB in athletes is "not ready for prime time," as history is unreliable and there is no consensus on a gold standard in a condition that has low prevalence.*
C.C.R.
Parsons HP, Cosmar D, Phillips G, et al: Screening for exercise-induced bronchoconstriction in college athletes.
J Asthma 2012;49:153-157. ♦♦

Is EIB a Problem for Asthma Patients?

THE use of the term "exercise-induced bronchoconstriction" recognizes the fact that not all people with EIB have asthma. The author reviewed the literature on the prevalence of EIB and its impact on quality of life.

Exercise-induced bronchoconstriction is present in most patients with asthma and is an indicator of poor disease control. One study reported a 19% prevalence of EIB in "causal exercisers" without asthma--similar to the rates reported in elite athletes. A wide range of factors may affect EIB prevalence, including family history, atopy, and respiratory infections, among others. Reported prevalences of EIB among elite athletes vary considerably, depending on type of sport, maximum exercise level, and environmental factors including chlorine in swimmers and emissions from ice resurfacing machines in ice arena athletes.

Studies of the burden of EIB have appeared only within the last decade. In children and adolescents EIB has been linked to reduced scores on standard quality of life assessments. A recent survey of parents of asthmatic children identified cough, wheezing, and shortness of breath as the most common exercise-related symptoms. About 22% of children and 32% of adolescents had limitations in desired activities because of EIB symptoms. Misdiagnosis or lack of recognition of EIB is another potential burden, particularly in elite athletes.

Evidence suggests a significant prevalence and burden of EIB, including adults as well as children and causal exercisers as well as elite athletes. Allergist/immunologists play an important role in recognizing EIB and providing appropriate management to improve quality of life, including the ability to perform athletic and other activities.

COMMENT: *Since EIB is common in patients with asthma--especially elite athletes--the need for control is of utmost importance. Part of the dilemma for athletes is lack of recognition due to excellent physical conditioning, which often necessitates objective testing for proper diagnosis. This article reminds us that patients of any age may experience negative impacts on quality of life if EIB is not controlled.*
V.H.-T.
Kahn DA: Exercise-induced bronchoconstriction: burden and prevalence.
Allergy Asthma Proc. 2012;33:1-6. ♦♦

Asthma Is Overdiagnosed in Elite Athletes

MANY studies have reported on the high rate of exercise-induced bronchoconstriction (EIB) among elite athletes. This diagnosis is typically made on the basis of patient-reported symptoms, which may be of limited value in highly trained athletes. This study evaluated the accuracy of physician diagnoses of EIB in English professional soccer players.

The study was performed after a change in ➤➤

World Anti-Doping Agency regulations requiring pulmonary function testing to confirm the need for inhaled β_2-agonists among athletes. Tests were carried out in 65 elite male soccer players with physician-diagnosed asthma and/or EIB. Testing included bronchial provocation with dry air in 42 athletes, mannitol challenge in 18, and bronchodilator testing in 5 athletes who had abnormal results on resting spirometry.

Of the 65 players, 57 were using asthma medications regularly; the same number reported respiratory symptoms during exercise. The results of bronchodilator or bronchial provocation testing were positive in just 51% of tested athletes. The findings of pulmonary function tests were not predicted by either symptoms or inhaled corticosteroid use. Of the 8 players who did not report exercise-related respiratory symptoms, 3 had positive results on bronchial provocation testing.

In this sample of elite soccer players with physician-diagnosed asthma, about half had no evidence of reversible airway obstruction or airway hyperresponsiveness to indirect stimuli. Neither symptoms nor medication use are useful in predicting the test results. The findings highlight the need for objective pulmonary function testing to confirm the symptom-based diagnosis of asthma and/or EIB in athletes.

COMMENT: *Although an increased prevalence of EIB among elite athletes is generally well-accepted, reliance on symptoms alone to diagnose EIB is problematic. In this study, the majority of subjects underwent eucapnic voluntary hyperpnea testing, which is widely accepted as the most sensitive way to identify subjects with EIB. Remarkably, only about half of the athletes regularly receiving treatment were confirmed to have EIB. The results underscore the importance of using objective testing to confirm this diagnosis.*
S.A.T.

Ansley L, Kippelen P, Dickinson J, Hull JHK: Misdiagnosis of exercise-induced bronchoconstriction. **Allergy**. 2012;67:390-395. ♦♦

Asthma 'Remissions' Are Common--But Most Patients Have Active Disease

THE course of asthma is highly variable, including any combination of remissions and relapses, and thus the prognosis is difficult to predict. Previous follow-up studies of asthma have had important limitations in terms of population size and how long and how often patients were followed up. A population-based, 15-year follow-up study of asthma disease activity is presented.

Using Ontario health data, the researchers identified 613,394 patients with asthma in 1993 and followed them up to 2009. The proportion of patients with active asthma, defined as any physician claim for asthma, was assessed. Factors associated with active asthma were analyzed as well.

Of all patients with asthma in the baseline year, 82.3% had active asthma during follow-up, with a median of 4 asthma-related claims per person. Of 421,164 patients with complete follow-up data, 74.6% had at least a 2-year gap between claims. Longer gaps were more likely for females, middle-aged patients, and patients without chronic obstructive pulmonary disease. Factors associated with increased asthma activity included a higher number of previous asthma claims; older and younger age, particularly 65 years or older; and presence of chronic obstructive pulmonary disease.

Long-term follow-up of asthma patients in Ontario shows that most patients have active asthma, although with periods of "remission" when they did not require asthma care. These gaps are often prolonged, lasting 2 years or longer. The researchers write, "These findings…support the hypothesis that once a person has asthma, he or she will continue to have it for life."

COMMENT: *"When will I 'outgrow' my asthma?" How often do we hear that question? These Canadian researchers used data over a 15-year period from the Ontario public health insurance program to analyze asthma activity, based on CPT coding. Three-fourths of patients had a gap of at least 2 years in their asthma activity, suggesting that the natural course of asthma is to wax and wane--but that it doesn't really resolve. Patients may continue to have exacerbations of asthma even years after what appears to be a long remission.*
S.M.F.

Gershon A, Guan J, Victor C, et al: The course of asthma activity: a population study.
J Allergy Clin Immunol 2012;129:679-686. ♦♦

IgG4: The Good, the Bad, and the Ugly

FIRST recognized as extrapancreatic manifestations of autoimmune pancreatitis, IgG4-related disease is a fibroinflammatory condition characterized by tumefactive lesions; an IgG4-rich lymphoplasmacytic infiltrate; storiform fibrosis; and less consistently, elevated serum IgG4 levels. It has been described in nearly every organ system, with very similar histopathologic findings across sites. The authors review the characteristics of IgG4-related disease along with possible mechanisms and treatment implications.

A structurally and functionally unique antibody, IgG4 has a characteristic half-antibody exchange reaction, sometimes called fragment antigen-binding (Fab)-arm exchange. Although traditionally viewed as an anti-inflammatory antibody, IgG4 can play an inflammatory role under certain immune-mediated conditions. Biopsy and histologic analysis showing the typical morphologic features are the key to diagnosis of IgG4-related disease, but immunohistochemical confirmation with IgG4 immunostaining is necessary as well. Several immune-mediated mechanisms likely contribute to the fibroinflammatory disease process; possible initiating mechanisms include genetic factors, bacterial infection and molecular mimicry, and autoimmunity.

Although there have been few epidemiologic studies, most patients with IgG4-related disease are men over 50. The presentation is generally subacute, or the con-➤➤

dition is found incidentially. Allergic features such as atopy, asthma, and eczema are present in some patients. Major tissue damage and organ failure can occur, generally through a subacute process. Most but not all patients have elevated serum IgG4, with widely varying levels. Although there have been few randomized trials, aggressive treatment is essential for IgG4 disease involving vital organs. Treatment with glucocorticoids is generally effective, but may be followed by disease flares. Azathioprine, mycophenolate mofetil and methotrexate have been used as glucocorticoid-sparing or remission-maintenance drugs. B-cell depletion with rituximab can be effective in recurrent or refractory cases.

Recognized only recently, IgG4-related disease unifies a large number of diagnoses previously regarded as single-organ disease. Further study is needed to clarify the molecular basis, pathophysiology, and management of this condition.

COMMENT: *Allergists are familiar with the concept that selective induction of IgG4 responses in the setting of a Th2 cell-dominant immune reaction is a good thing. What is probably surprising is that this immunoglobulin, traditionally viewed as anti-inflammatory, also plays a not-so-good-role in immune-mediated, fibroinflammatory conditions called IgG4-related disease. Interestingly--in addition to tumefactive lesions and dense IgG4-positive plasma cell infiltrates--patients may have allergic features such as atopy, eczema, asthma, peripheral blood eosinophilia and chronic sinusitis.*
C.D.

Stone JH, Zen Y, Deshpande V: IgG4-related disease.
N Engl J Med. 2012;366:539-551. ♦♦

Diversity Is Good-- Particularly in Gut Bacteria

THE association between gut microbiota and the incidence of allergic disease in children continues to be debated. It is unclear whether total diversity of the gut microbiota or the presence of particular bacterial species is the more important factor. This issue was addressed using powerful new noncultivation-based microbiologic techniques enabling analysis of the total microbiome, down to genus level, in a large number of subjects.

The investigators used barcoded 16S rRNA 454-pyrosequencing to analyze stool samples from 20 infants with IgE-associated eczema and the same number of infants with no evidence of allergic disease through the first 2 years of life. Samples were obtained at 1 week, 1 month, and 1 year of age. Total diversity of the gut microbiota and the dominant bacteria present, and their association with atopic eczema, were analyzed.

In the 1-month samples, infants with atopic eczema had lower total diversity of the gut microbiota, as well as lower diversity of the phylum Bacteroidetes and the genus Proteobacteria. Eczema was also associated with lower diversity of the phylum Proteobacteria in 12-month samples. The gut microbiota was less uniform at 1 month than at 12 months, and varied significantly between individuals. After the microbiota had stabilized at 12 months, Proteobacteria and the gram-negative organisms belonging to this phylum made up a larger part of the gut microbiota among infants free of allergic disease.

Infants with low microbial diversity in 1-month stool samples may be at higher risk of atopic eczema. The results support the importance of the bacterial phyla Baceteroidetes and Proteobacteria, as reported in previous studies. The significance of other bacteria previously linked to allergic disease, including bifidobacteria and clostridia, was not confirmed.

COMMENT: *There is ongoing controversy as to whether microbial diversity or prevalence of specific taxa is a greater contributor to the development of atopy. The researchers use a novel noncultivation-based microbiologic method to add support to the emerging hypothesis that the diversity of the infant gut microbiome plays a significant role in the development of IgE-mediated eczema. While infants with lesser diversity have a greater chance of developing eczema, specific bacterial phyla and genera (Bacteroidetes and Proteobacteria) appear to influence the impact of diversity to a greater extent. The analytical challenges of clinical microbiome studies are discussed in the informative editorial by Harris and Wagner* (**J Allergy Clin Immunol**. 2012;129:441-442).
C.D.

Abrahamsson TR, Jakobsson HE, Andersson AF, et al: Low diversity of the gut microbiota in infants with atopic eczema.
J Allergy Clin Immunol. 2012;129:434-440. ♦♦

Could Mannitol Be Used for ICS Titration in Persistent Asthma?

UNDER current asthma guidelines, the dose of inhaled corticosteroid (ICS) is adjusted according to the patient's symptoms, lung function, and use of reliever medications. However, this does not account for the effects of persistent airway inflammation and associated airway hyperresponsiveness (AHR), which lead to airway remodeling even in asymptomatic asthma. This study evaluated the use of AHR to mannitol challenge for ICS dose adjustment in patients with persistent asthma.

The randomized trial included 164 primary care patients with persistent asthma. After an initial ICS step-down period, patients were assigned to titration using an AHR strategy or a reference strategy. In the AHR strategy, ICS (ciclesonide) dose was titrated against the provocative dose of mannitol causing a 10% drop in FEV_1 (PD_{10}). In the reference group, titration was based on symptoms, reliever medication use, and lung function.

At 12 months' follow-up in 119 study completers, the number of mild exacerbations was 27% lower in patients assigned to the AHR strategy--a nonsignificant difference. Severe exacerbations were almost identical between groups. The mannitol PD_{10} was significantly higher in the AHR group, with a 1.52 doubling dose difference. The AHR strategy was also associated with a higher final mean daily ciclesonide dose: 514 versus ➤➤

208 µg, with no significant suppression of overnight urinary cortisol/creatinine. Patients in the AHR group--but not the reference group--had significant improvements in the methacholine PD_{20}, salivary eosinophilic cationic protein, and exhaled nitric oxide, as well as symptoms and reliever medication use.

An AHR strategy based on mannitol challenge can be used for ICS dose adjustment in primary care patients with persistent asthma. The AHR strategy leads to a higher ICS dose, with mixed effects on exacerbation rate but no evidence of adrenal suppression. The findings warrant larger studies of mannitol for ICS titration in patients with more severe asthma.

COMMENT: *Thirteen years ago, Sont and colleagues demonstrated that asthma control was better using methacholine to monitor airway hyperreactivity. This study confirms the concept but with a different measure of airway reactivity. As in the Sont study, control was associated with higher doses of ICS. Remodeling actually was less in the Sont study, but bronchial biopsies were not performed in the new study. Guidelines do not use measures of airway reactivity in assessing either impairment or risk. Doing so would be costlier but may lead to better outcomes. Long-term use of higher ICS doses might be associated with increased frequency of steroid side effects in susceptible individuals.*
S.F.W.

Lipworth BJ, Short PM, Williamson PA, et al: A randomized primary care trial of steroid titration against mannitol in persistent asthma: STAMINA trial.
Chest. 2012;141:607-615. ♦♦

Many Obese Patients Misdiagnosed with Asthma

THE reported association between asthma and obesity is a factor in the rising prevalence of physician-diagnosed asthma. Since both of these conditions cause breathlessness, there may be a risk of asthma misdiagnosis among patients with obesity. This possibility was evaluated in a group of obese patients with physician-diagnosed asthma, including the association between body mass index (BMI), health-related quality of life (HRQoL), and traditional measures of asthma severity.

The researchers evaluated 91 participants from a trial of weight loss for obese patients with asthma. The patients had a mean BMI of 38, FEV_1% of 85.8%, FEV_1/FVC of 70.0%, and exhaled nitric oxide of 25.1 ppb. The patients were taking a mean chlorofluorocarbon-beclomethasone equivalent dose of 1,273.5 µg/d.

On methacholine challenge testing, 36.3% of patients showed no evidence of bronchial hyperresponsiveness, indicating possible misdiagnosis of asthma. Body mass index was significantly related to respiratory-specific HRQoL and to both the physical and mental health components of generic HRQoL. In contrast, obesity-specific HRQoL was unrelated to measures of airway inflammation or bronchial reactivity. Quality of life scores were similar for patients with and without bronchial hyperreactivity.

A substantial proportion of obese patients with physician-diagnosed asthma show no evidence of bronchial hyperresponsiveness. The negative association between BMI and HRQoL in this group of patients may contribute to the potential for asthma misdiagnosis. The authors discuss the complexities of identifying respiratory disease in obese patients, along with the study's implications for diagnosis and management of this group of patients.

COMMENT: *These findings should raise alarms in the evaluation and management of obese patients with "diagnosed" asthma. Fully one-third of such patients who were being treated with high-dose inhaled steroids did not show evidence of airway hyperreactivity. Shortness of breath and impairment do not diagnose asthma, and normal lung function while taking asthma medications may not reflect control if that patient doesn't have asthma!*
S.F.W.

Scott S, Currie J, Albert P, et al: Risk of misdiagnosis, health-related quality of life, and BMI in patients who are overweight with doctor-diagnosed asthma.
Chest. 2012;141:616-624. ♦♦

Do We Need a Math-Free Approach to Immunotherapy Preparation?

UPDATED practice parameters have led to changes in recommendations for immunotherapy dosing with specific allergens. There has been no convenient approach to incorporating dose changes or targets for use in maintenance vial formulations for individual patients. This paper compares immunotherapy dose recommendations for recent practice parameter updates, and presents convenient tables translating dose targets for use in preparing maintenance vials.

The author tabulated and compared dose recommendations from 2003, 2007, and 2011 immunotherapy practice parameters. He then created conversion tables, based on mathematical relationships between extract concentrate strengths and maintenance immunotherapy dose targets and accounting for stock mixes, glycerin levels, and allergen compatibilities.

Based on the successive practice parameters, there were significant changes to immunotherapy dose ranges, including adjustment of upper limits for short ragweed, of lower limits for pasture grasses, and of both upper and lower limits for cat, dust mite, and Bermuda grass. There were also changes in dose ranges for nonstandardized products. The article includes conversion tables giving the concentrate volumes or percentages needed to provide minimum, midrange, and maximum doses of various extracts at 0.5 mL injection volumes.

The author presents dosing guides for maintenance immunotherapy, based on the most recent practice parameters. Used with information on cross-reactivity, compatibility, and glycerin tolerance, the tables provide a convenient approach to preparing immunotherapy vials at various dose levels. This method will help in optimal maintenance immunotherapy mixtures for patients with a wide range of allergen sensitivities and specificities. ➤➤

COMMENT: *The author provides convenient dosing guidelines for ascertaining numbers and strengths of extracts that can be combined into treatment vials for maintenance immunotherapy in patients with a wide array of different sensitivities. Based on the 2003, 2007, and 2011 practice parameters, the guidelines provide a mathematics-free formula for preparing standardized extracts for any patient. This is an invaluable template for convenient preparation of allergen extracts, based on current recommendations.*
C.C.R.
Grier TJ: How's my dosing? A one-step, math-free guide for comparing your clinic's maintenance immunotherapy doses to current practice parameter recommendations.
Ann Allergy Asthma Immunol. 2012;108:201-205. ♦♦

Poor Follow-up after ED Visits for Asthma in Children on Medicaid

LOW use of controller medications contributes to the high rate of acute care visits for asthma. Current recommendations for emergency department (ED) management of asthma exacerbations include the initiation or continuation of inhaled corticosteroids (ICS) on ED discharge. Medicaid data were analyzed to determine rates of ICS initiation and outpatient follow-up among children and adolescents with ED visits for asthma.

A review of South Carolina Medicaid data from 2007 to 2009 identified 3,435 patients, aged 2 to 18 years, with an ED visit for asthma. The study excluded patients who had been hospitalized for asthma or had a claim for ICS within the previous 2 months. The outcomes of interest were an ICS prescription filled and attendance at a follow-up appointment (with a primary diagnosis of asthma) within 2 months after the ED visit.

Fifty-seven percent of the patients with ED visits for asthma were male. Age was 2 to 6 years in 43% of patients, 7 to 12 years in 33%, and 13 years or older in 24%. In this Medicaid population, 76% of patients were of minority race/ethnicity and 69% lived in an urban area.

Within 2 months after their ED visit, just 18% of patients had filled an ICS prescription and 12% had a follow-up outpatient visit. Both outcomes were more likely for the 10% of patients with severe asthma: odds ratio 2.9 for ICS prescription and 2.0 for follow-up appointments. Follow-up was less likely for younger children and adolescents: odds ratio 0.71 for 2- to 6-year-olds and 0.62 for those aged 13 years or older.

For pediatric Medicaid recipients with ED visits for asthma, rates of ICS prescription and outpatient follow-up visits are low. The authors believe that ED clinicians should "consider being more aggressive" in prescribing ICS for children with asthma. Important topics for further study include the costs and side effects of ED prescription of ICS and barriers to appropriate follow-up care.

COMMENT: *The most recent Global Initiative for Asthma guidelines recommend that ICS be started on discharge from the ED for patients with an exacerbation-related visit. But is it really feasible for the ED to start these patients on ICS? And will patients be compliant with the prescriptions? Even assuring proper follow-up is daunting--that only one-eighth of patients pursued such follow-up in this study underscores the problem. A vicious circle continues, until a better approach can be applied.*
K.R.M.
Andrews AL, Teufel RJ II, Basco WT Jr: Low rates of controller medication initiation and outpatient follow-up after emergency department visits for asthma.
J Pediatr 2012;160:325-330. ♦♦

Assessment of a QI Program for Asthma Care in Urban Children

PREVIOUS studies have reported promising results of community-based environmental interventions for children with asthma. These programs--incorporating comprehensive home visits by trained community health workers with environmental remediation and office-based nurse management--have been reported to lead to improved asthma outcomes. A Community Asthma Initiative (CAI) was evaluated as an approach to quality improvement (QI) in urban neighborhoods disproportionately affected by childhood asthma.

The CAI program targeted urban, low-income children with asthma, identified through logs of ED visits or hospitalizations. The program offered enhanced care, including home visits by community health workers and nurse case managers. Outcomes for QI evaluation included ED visits and hospitalizations for asthma, physical activity limitations, and missed school/work days. Hospital costs in neighborhoods served by the CAI were compared with those of a neighboring community with similar demographic characteristics.

The evaluation included 283 children receiving services from the CAI program. Fifty-five percent of the children were male; most were Latino or African-American and were covered by Medicaid. At 12 months' follow-up, the program was associated with a 68.0% reduction in ED visits (from 68.5% to 21.0%) and an 84.8% reduction in hospitalizations, from 51.1% to 7.7%. Days with physical activity limitations, missed school days by the child, and missed school days by the parent all showed decreases between 40% and 50%.

The number of home visits was higher, and home visits by nurses were more likely, for children with greater functional impairment, activity limitations, and missed school days. The CAI program cost about $2,500 per child but produced savings of about $3,800 per child over 2 years of follow-up, for a return on investment of 1.46--ie, $1.46 saved on ED visits and hospitalizations for every $1 spent.

This community-based QI program led to reduced ED and hospital visits and improvements in other outcomes for urban children highly affected by asthma. The combination of case management and home visits can lead to better asthma control in patients targeted as needing a higher level of care. The investigators conclude, "These remarkable results provide a model of effective care for high-risk asthma patients with substantial cost savings." ➤➤

COMMENT: *Underserved children with asthma have a particularly difficult time receiving preventive care and follow-up, and with access to (and compliance with) maintenance therapy. While initially costly, a comprehensive program like the one described here could ultimately lead to great savings in terms of ED utilization and hospitalization, in the end paying for itself.*
K.R.M.
Woods ER, Bhaumik U, Sommer SJ, et al: Community Asthma Initiative: Evaluation of a quality improvement program for comprehensive asthma care.
Pediatrics. 2012;129:465-472. ♦♦

Asthma Medications during Pregnancy and Risk of Birth Defects

ASTHMA may affect 4% to 12% of pregnant women. However, few studies have looked at the possible association between maternal asthma medication use and the risk of birth defects in offspring. This issue was addressed using data from a population-based, case-control study of birth defects.

Using data from the National Birth Defects Prevention Study, the analysis included 2,853 infants with at least one of a list of selected birth defects--diaphragmatic hernia, esophageal atresia, small intestinal atresia, anorectal atresia, neural tube defects, omphalocele, or limb deficiencies--and 6,726 unaffected infants born from 1997 through 2005. Mothers provided information on medications used, along with other possible risk factors, in telephone interviews. Associations between periconceptional use (from 1 month before pregnancy through the third month of gestation) of asthma medications (bronchodilators or anti-inflammatory drugs) and the risk of individual birth defects were assessed.

Most birth defects were unrelated to periconceptional use of asthma medications. However, significant positive associations were noted for isolated esophageal atresia and bronchodilators, adjusted odds ratio (OR) 2.39; isolated anorectal atresia and anti-inflammatory drugs, OR 2.12; and omphalocele and either type of asthma medication, OR 4.13. The associations were significant only for mothers who took the implicated drugs during the periconceptional period--not for those exposed only after the third month of pregnancy.

Certain individual birth defects show a possible association with maternal use of asthma medications during the periconceptional period. Other birth defects, including neural tube defects, do not appear to be related to asthma drugs. Further studies are needed to clarify whether the associations are attributable to asthma medications or the severity of asthma itself.

COMMENT: *Analysis of the medications we use to treat pregnant women with asthma, in terms of both efficacy and risk of birth defects, is of paramount importance. Although asthma and concurrent medication use are common, potential associated birth defects are infrequent or rare. The research presented here raises additional questions on birth defects. Could the results from this case-control study be from chance alone? Or can the findings be explained by asthma severity in the critical periconceptional period? Hypoxia could explain defects related to fetal growth; future studies should include assessments of maternal asthma severity/control.*
K.R.M.
Lin S, Munsie JPW, Herdt-Losavio ML, et al: Maternal asthma medication use and the risk of selected birth defects.
Pediatrics. 2012;129:e317-e324. ♦♦

Oral Immunotherapy for Cow's Milk Allergy-- Not Ready For Clinical Practice

COW'S milk is one of the main causes of pediatric food allergy. Although most children 'outgrow' cow's milk allergy (CMA) by age 3 to 5, some have persistent symptoms. Recent observational studies have suggested that oral immunotherapy is a useful treatment for IgE-mediated CMA. The evidence of oral immunotherapy for CMA was evaluated in a systematic review and meta-analysis.

A literature review identified five eligible randomized trials and five observational studies of oral immunotherapy for IgE-mediated CMA. The randomized trials, including a total of 218 patients, showed a much higher likelihood of achieving full tolerance with oral immunotherapy, compared to an elimination diet alone: relative risk 10.0.

Oral immunotherapy was also associated with high rates of local symptoms, 16% of doses; mild laryngospasm, RR 12.9; and mild asthma, rate ratio 3.8. There were also significant rates of more serious reactions requiring oral glucocorticoids, RR 11.3; and intramuscular epinephrine, rate ratio 5.8. Analysis of observational study data yielded similar conclusions.

The results show "important uncertainty" regarding the use of oral immunotherapy for CMA in children. Despite randomized trials, the overall quality of the evidence is low, with imprecise estimates of effects and a high likelihood of publication bias. Oral immunotherapy carries the potential for full tolerance, but a risk of frequent and potentially severe adverse effects. The authors call for larger randomized trials focusing on outcomes of importance to patients.

COMMENT: *This detailed Cochrane review with meta-analysis reminds us that, although oral desensitization has exciting potential for enabling milk-allergic patients to become completely tolerant, the available literature suggests that serious limitations remain. These include the occurrence of serious allergic reactions to treatment, variability in treatment effect, and likely publication bias. It appears that this procedure is not yet ready to integrate into clinical practice.*
S.A.T.
Brozek JL, Terraciano L, Hsu J, et al: Oral immunotherapy for IgE-mediated cow's milk allergy: a systematic review and meta-analysis.
Clin Exp Allergy. 2012;42:363-374. ♦♦

Low HDL Cholesterol Predicts Adolescent Asthma

EXPERIMENTAL studies have identified an anti-inflammatory effect of high-density lipoprotein (HDL) cholesterol, consistent with a possible protective effect against asthma. Human studies of this issue have yielded conflicting results. A large population-based study was used to assess the relationship between HDL cholesterol levels and the later development of asthma in children.

As part of a national health study, 3,982 children in Cyprus underwent measurement of serum lipid levels, body mass index, and maximal oxygen consumption at age 11 to 12 years. Follow-up data at age 15 to 17 years were used to examine associations between HDL cholesterol and the prevalence of asthma.

The HDL cholesterol level at age 11 to 12 was significantly lower for children who ever reported asthma in adolescence: 58.2 versus 60.0 mg/dL. A similar difference was noted for active asthma in adolescence: 57.5 versus 59.9 mg/dL. There was no such association for total cholesterol, low-density lipoprotein (LDL) cholesterol, or triglycerides.

Baseline HDL cholesterol levels of less than 40 mg/dL were associated with particularly high asthma rates, with estimated odds ratios of 1.89 for both ever asthma and active asthma in adolescence. These associations remained significant after adjustment for body mass index, maximal oxygen consumption, and other potential confounders.

Children with low HDL may be at increased risk of developing asthma by adolescence. This result is consistent with the experimental finding of anti-inflammatory effects of HDL cholesterol in a variety of tissues, including the lung. The implications for asthma pathogenesis and intervention require further study.

COMMENT: *Prior animal studies and cross-sectional human epidemiologic studies have suggested a relationship between lipoproteins and asthma that is independent of obesity and other potential confounders. In this large longitudinal study, low HDL cholesterol at age 12--but not elevated LDL or total cholesterol--correlated with asthma at ages 15 to 17. The accompanying editorial by Fessler (Clin Exp Allergy 2012;42:340-342) points out that, since HDL cholesterol is a complex with multiple components, future studies should include a better characterization of both lipoprotein profile and asthma phenotypes.*

S.A.T.

Yiallouros PK, Savva SC, Kolokotroni O, et al: Low serum high-density lipoprotein cholesterol in childhood is associated with adolescent asthma.
Clin Exp Allergy. 2012;42:423-432. ♦♦

ED Visits for Anaphylaxis in Children: Population-Based Series

FOODS are thought to be the main cause of anaphylaxis, especially in children. However, few population-based studies have focused on the overall rates and characteristics of anaphylaxis in children. The authors report on the incidence of anaphylaxis among Swedish children, including reactions to foods in relation to patient and clinical characteristics and management.

Medical records from three pediatric hospitals in Stockholm County were reviewed to identify children making ED visits for adverse reactions to foods or anaphylaxis. Of 382 patients identified, 371 had reactions to foods. Of these children, 128 met criteria for anaphylaxis; 70 did not meet anaphylaxis criteria, but had been treated with epinephrine; and 173 did not have anaphylaxis and did not receive epinephrine.

The overall incidence of anaphylaxis from all causes was 32 per 100,000 person-years. Ninety-two percent of cases were caused by foods. In children younger than 3 years, tree nuts (especially cashew) and peanut were the most common causes--reactions to these foods were as frequent as reactions to milk and egg. Children with pollen allergy had a higher rate of ED visits for food-related anaphylaxis during tree-pollen season, compared to other times of year. Lower-airway symptoms occurred in 49% of children without underlying asthma, compared to 72% of those with both anaphylaxis and asthma.

This large series of pediatric ED visits for anaphylaxis suggests that peanuts and tree nuts are an important cause of food reactions even in children under age 3. Seasonal exposure to pollen may increase the rate of anaphylactic reactions to foods. Wheezing is a frequent symptom in children with anaphylaxis, even in the absence of asthma.

COMMENT: This population-based Swedish study reports an impressive quantity of detail about nearly 400 ED visits for anaphylaxis in children. Perhaps the most provocative finding is that pollen-allergic patients were more likely to be treated in the ED for food anaphylaxis during the tree pollen season. The reason for this is unclear and requires further study.

S.A.T.

Vetander M, Helander D, Flodstrom C, et al: Anaphylaxis and reactions to food in children--a population-based case study of emergency department visits.
Clin Exp Allergy. 2012;42:568-577. ♦♦

Causal Link between Allergic Sensitization and Rhinovirus Wheezing

THE risk of asthma during early childhood is affected by both aeroallergen sensitization and virus-induced wheezing episodes. Information on which of these events occurs first is needed to clarify the causal mechanisms leading to the development of asthma. This issue was addressed in a birth cohort study with prospective follow-up.

The study included 289 children from the Childhood Origins of ASThma (COAST) study, all with a parental history of asthma and allergic sensitization. Annual follow-up data through age 6 were analyzed to determine the timing and causes of viral respiratory illnesses ➤➤

causing wheezing. Aeroallergen sensitization was assessed by allergen-specific IgE measurement.

The risk of developing viral wheezing was nearly twice as high in children with aeroallergen sensitization: hazard ratio (HR) 1.9, compared to nonsensitized children. This association was specific to wheezing illness caused by human rhinovirus (HRV)--sensitization did not increase the risk of wheezing caused by respiratory syncytial virus infection. The relative risk of viral wheezing in sensitized children increased with age, although the absolute risk was greatest at age 1. In contrast, episodes of viral wheezing were not followed by an increased risk of aeroallergen sensitization.

Prospective follow-up of young children at high risk of asthma finds that allergic sensitization occurs before HRV-induced wheezing, not the other way around. This finding supports a causal role of allergic sensitization in the development pathway leading to childhood asthma. Treatments to prevent allergic sensitization may modify the risk of viral wheezing illness and thus the risk of asthma.

COMMENT: *Further data from the COAST study include the very important observation that allergic sensitization precedes viral wheeze. This again supports the notion, as documented in the MAS study from Germany, that early sensitization and exposure continues to be a major factor in the inception and persistence of wheezing. Reinforcement that HRV is a major precipitant for asthma is again shown in this study. The accompanying editorial by Alan Smyth (**Am J Respir Crit Care Med**. 2012;185:238-239) adds further insight.*
B.E.C.
Jackson DJ, Evans MD, Gangnon RE, et al: Evidence for a causal relationship between allergic sensitization and rhinovirus wheezing in early life.
Am J Respir Crit Care Med. 2012;185:281-285. ♦♦

CLINICAL TIDBITS

Differences in FP Bioavailability with Different VHC/Mask Devices

THERE are questions about the delivery of inhaled drugs to the lung in young children using valved holding chambers (VHCs). A population pharmacokinetic approach was used to compare lung bioavailability of fluticasone propionate (FP) using two VHCs with facemasks: AeroChamber Plus and Babyhaler.

The study included 17 children, aged 1 to less than 4 years, with stable asthma. In crossover fashion, the children received 88 µg of FP hydrofluroalkane twice daily for 8 days using the two VHC/mask devices. On pharmacokinetic analysis, population mean area under the FP plasma concentration-time curve was 97.45/pg/h/mL with AeroChamber Plus vs 51.55 pg/h/mL with Babyhaler. Thus the relative bioavailability with the Babyhaler was about half that with AeroChamber Plus.

This study shows a substantial difference in FP bioavailablity using two different VHC/mask devices in young children with asthma. As this and other studies show, "VHCs are not interchangeable"--the authors discuss the implications for inhaled corticosteroid dosing in young children.

COMMENT: *This is a follow-up study from the authors' previously published data. The results suggest that higher doses of systemically active corticosteroids such as FP and beclomethasone dipropionate may be enhanced, depending on the spacer type used. It is important that higher doses of inhaled corticosteroids be appropriately managed by choosing spacers that will not enhance lung deposition.*
B.E.C.
Blake K, Mehta R, Spencer R, et al: Bioavailability of inhaled fluticasone propionate chambers/masks in young children.
Eur Respir J. 2012;39:97-103. ♦♦

Are Inhaled Glucocorticoids Safe during Pregnancy?

MOST studies on the safety of inhaled corticosteroid therapy for asthma during pregnancy have focused on obstetric outcomes and congenital malformations (with no increases in risk). Data from a Danish national birth cohort study were used to assess the association between inhaled glucocorticoids during pregnancy and the risk of a wide range of diseases in children.

The analysis included 4,083 live singleton offspring born to women who had asthma during pregnancy. Associations between inhaled glucocorticoid therapy during pregnancy and offspring diseases during childhood were assessed. Of 1,231 mothers receiving inhaled glucocorticoids during pregnancy, 79.9% used budesonide. Offspring were followed up to a median age of 6.1 years.

Most categories of disease were not significantly increased in offspring whose mothers used inhaled glucocorticoids. The exception was an increased risk of endocrine, metabolic, and nutritional disorders: hazard ratio 1.84. The results were similar on analysis of mothers using budesonide.

Asthmatic women using inhaled corticosteroids during pregnancy may be reassured that these medications do not affect the risk of most types of disease in offspring. The possible association with endocrine, metabolic, and nutritional disorders warrants further study.

COMMENT: *Another large cohort study provides reassuring data that glucocorticoids during pregnancy are not related to adverse events in offspring. Currently only budesonide has a class B indication for pregnancy, and in fact approximately 80% of this study cohort was treated with budesonide. However, the safety may be a class effect and extrapolated to other corticosteroids. The accompanying editorial (**Am J Respir Crit Care Med**. 2012;185:476-478) is of interest.*
B.E.C.
Tegethoff M, Greene N, Olsen J, et al: Inhaled glucocorticoids during pregnancy and offspring pediatric diseases: a national cohort study.
Eur Respir J. 2012;185:557-563. ♦♦

No Surprise--Food Allergies Continue to Increase

STUDIES have reported rising rates of food allergies over the past decade. Trends in the prevalence and characteristics of pediatric food allergy at an urban tertiary care center were analyzed.

Using an electronic medical record system, the researchers searched for patients seen at Texas Children's Hospital for a diagnosis of food allergy in 2003 and 2008. As a percentage of all allergy and immunology patients, food allergy cases increased from 3% to 8%. The severity of initial reactions to foods increased, while the mean initial food-specific IgE level decreased: from 52 to 400 kU/L. Age at diagnosis decreased from 2.64 to 1.36 for cow's milk allergy and from 5.10 to 2.86 years for fish allergy. In 2008, peanuts and shellfish were more commonly associated with severe reactions, including anaphylaxis.

These data from a children's hospital suggest an increased prevalence and worsening severity of pediatric food allergies. Other trends include lower specific IgE level and younger age at presentation. The factors associated with changes in the presentation of food allergy require further study.

COMMENT: *The study describes increased numbers of patients with food allergy presenting to a tertiary center were described over a 5-year period. Despite increases in the severity of initial symptoms of food allergies, initial food specific IgE levels decreased--even for peanuts and shellfish. During this time, allergies to cow's milk and fish presented earlier in life. The authors suggest that clinical characteristics of food allergy may change over time; this warrants observation to determine whether genetic or environmental factors may play a role.*
V.H.-T.

Amin AJ, Davis CM: Changes in prevalence and characteristics of IgE-mediated food allergies in children referred to a tertiary care center in 2003 and 2008.
Allergy Asthma Proc. 2012;33:95-101. ♦♦

New Polymorphism Linked to Both Eczema and Asthma

ECZEMA has been linked to a region on chromosome 1q21, which includes the gene for filaggrin. However, *FLG* alone cannot fully account for this association. This study links variations in the gene encoding small proline rich protein 2B (SPRR2B), a skin and lung epithelial protein, with asthma and eczema.

Genotyping for both *FLG* and *SPRR2B* were performed in 2 independent cohorts of children. After adjustment, variations in *SPRR2B* were not associated with eczema in either cohort. However, the CC genotype of the *SPRR2B* single-nucleotide polymorphism (SNP) rs6693927 was associated with a fourfold increase in the risk of eczema plus asthma: adjusted odds ratio 4.1 in one cohort and 4.0 in the other. The associations were unrelated to the effects of variations in *FLG*.

A *SPRR2B* SNP is linked to the phenotype of eczema plus asthma in two independent cohorts. Further studies are needed to explore the mechanisms underlying this association.

COMMENT: *While filaggrin is important, this study looked at small proline rich proteins (SPRR), and found a markedly increased risk of eczema and asthma with a SNP in* SPRR2B. *This is another study that illustrates the importance of genetic predisposition in some patients. For allergists and immunologists, identifying the risk factors that could predict the presence of atopic disease in our patients is clearly the way of the future.*
V.H.-T.

Epstein TG, LeMasters GK, Bernstein DI, et al:
Ann Allergy Asthma Immunol. 2012;108:145-150. ♦♦

H_1/H_3 Agonist Combination Relieves Allergic Rhinitis Symptoms

NASAL H_3 receptors may be involved in histamine-induced symptoms of allergic rhinitis. A new oral H_3 receptor antagonist (PF-03654746) was evaluated as a treatment for allergic rhinitis, in combination with the oral H_1 receptor antagonist fexofenadine.

Nasal allergen challenge was performed in 20 patients with out-of-season allergic rhinitis. Single-dose treatment with the combination of PF-03654746 led to significant reductions in congestion, itching, rhinorrhea, and sneezing, compared to placebo. However, acoustic rhinometry showed no significant effect on minimum nasal cross-sectional area or nasal volume.

The combination of fexofenadine and PF-03654746 leads to significant reductions in allergen-induced nasal symptoms. More study is needed to examine the utility of H_3 receptor antagonists in the treatment of allergic rhinitis.

COMMENT: *Nasal congestion, the most common complaint of patients with allergic rhinitis, is also one of the most difficult symptoms to treat effectively. This proof-of-concept study used both symptomatic and objective measures to evaluate the efficacy of a new oral H_3 antagonist combined with fexofenadine in patients with allergic rhinitis after allergen challenge. Although the symptomatic improvement for congestion was impressive, there was no statistically significant difference between the H_1/H_3 combination versus for nasal volume measured by acoustic rhinometry. The bottom line is that H_3 antagonists, which have been shown to inhibit vasoactive mediators, may be useful for treating nasal congestion when combined with H_1 antagonists.*
S.M.F.

Stokes JR, Romero FA Jr, Allan RJ, et al: The effects of an H_3 receptor antagonist (PF-03654746) with fexofenadine on reducing allergic rhinitis symptoms.
J Allergy Clin Immunol. 2012;129:409-412. ♦♦

HRV as Asthma Trigger--And Possible Mediator

HUMAN rhinovirus (HRV) is suspected to be an important trigger for asthma exacerbations, but the causal nature of the association is unclear. This prospective study examined possible viral and immune mediators in 409 asthmatic children with upper respiratory infection, with or without wheezing.

The results showed a specific association between HRV infection and asthma exacerbation: odds ratio 1.90, after adjustment for prespecified demographic and clinical factors. Among HRV-infected children with and without wheezing, there were no differences in viral titers, HRV species, and inflammatory or allergic molecules.

However, HRV-infected children with wheezing had higher levels of type III interferon (IFN)-λ_1, which were further increased with worsening symptoms. After adjustment for IFN-λ_1, the association between HRV infection and wheezing was no longer significant.

The results support a specific association between HRV infection and acute asthma in children. Type III IFN-λ_1 responses appear to mediate these HRV-triggered asthma exacerbations, suggesting a possible new therapeutic target.

COMMENTS: *This provocative study gives us a greater insight into the role of HRV infection and asthma. It also provides a potential therapeutic target. A previous study using interferon-α as a therapeutic agent did not show significant effect. See the accompanying editorial by Jim Gern (Am J Respir Crit Care Med. 2012;185:468-470).*
B.E.C.
Miller EK, Hernandez JZ, Wimmenauer V, et al: A mechanistic role for type III IFN-λ_1 in asthma exacerbations mediated by human rhinoviruses.
Am J Respir Crit Care Med. 2012;185:508-516. ♦♦

REVIEWS OF NOTE

COMMENT: *This is an excellent general review of data from the National Heart, Lung, and Blood Institute's Severe Asthma Research Program (SARP) to date.*
B.E.C.
Jarjour NN, Erzurum SC, Becker ER, et al: Severe asthma: lessons learned from the National Heart, Lung, and Blood Institute Severe Asthma Research Program.
Am J Respire Crib Care Med. 2012;185:356-362. ♦♦

COMMENT: *In this "out-of-the-box" manuscript, the authors describe fictitious patients with asthma seen by a physician in 1828, 1928, and the present. Intriguing photographs and tidbits give us a peek into historical therapeutic strategies for asthma. The authors present the sobering perspective that, while asthma as a disease has remained stable over two centuries, we neither have a cure nor can we prevent its development. Immensely noticeable (and frustrating) by its absence is the lack of mention of immunotherapy as a therapeutic strategy in this patient with allergen triggered asthma, or use of non-invasive measures of monitoring airway inflammation.*
C.D.
von Mutius E, Drzaen JM: A patient with asthma seeks medical advice in 1828, 1928, and 2012.
N Engl J Med. 2012;366:827-834. ♦♦

COMMENT: *This concise review of hereditary angioedema is well-written and timely. The presentation, clinical course, and treatment of acute episodes as well as prophylaxis are outlined.*
S.F.W.
Longhurst H, Cicardi M: Hereditary angio-edema.
Lancet. 2012;379:474-481. ♦♦

COMMENT: *This is an elegant review of cilia structure, function, and myriad disorders which occur from their motor or sensory disruption. The known candidate genetic loci for these disorders are reviewed, indicating considerable heterogeneity.*
K.R.M.
Ferkol TW, Leigh MW: Ciliopathies: the central role of cilia in a spectrum of pediatric disorders.
J Pediatr. 2012;160:366-371. ♦♦

COMMENT: *This is an excellent review of the lipocalins, a family of mammalian protein respiratory allergens.*
S.A.T.
Virtanen T, Kinnunen T, Rytkönen-Nissinen M: Mammalian lipocalin allergens--insights into their enigmatic allergenicity.
Clin Exp Allergy. 2012;42:494-504. ♦♦

COMMENT: *This is an excellent review article on the approach to pulmonary nodules, which are becoming a greater clinical concern with the significantly enhanced resolution of currently available CT scans.*
B.E.C.
Ost DE, Gould MK: Decision making in patients with pulmonary nodules
Am J Respir Crit Care Med. 2012;185:363-372. ♦♦