AllergyWatch®

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

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Dose Adjustments for Local Reactions: How Common and Why?

FOR patients undergoing allergen immunotherapy, local reactions at the injection site are a common occurrence. Dose adjustments have been suggested as a means of reducing the subsequent risk of local and systemic reactions--even though research suggests that local reactions do not predict future systemic reactions. American allergists were asked whether and why they made dose adjustments in response to local reactions.

An electronic survey was sent to 2,797 practicing allergists who were members of the American College of Allergy, Asthma and Immunology. The allergists were asked what approaches they used to prevent and minimize local reactions, including dose adjustments. Allergists who made dose adjustments were asked about their rationale for this practice.

The response rate was 27%. Nearly 95% of the responding allergists had completed an allergy/immunology fellowship. When asked about strategies to prevent and minimize local reactions, 79% reported making dose adjustments based on local reactions to previous injections. Seventy percent of allergists gave antihistamine pretreatment.

Overall, 92% of allergists reported using dose adjustments for local reactions to allergen immunotherapy. When making dose adjustments, the allergists followed protocols based on criteria for repeating and decreasing the immunotherapy dose, depending on the size of the local reaction. The most common rationale, cited by 89% of allergists, was that the discomfort associated with local reactions led to patient noncompliance. Local reactions were thought to predict additional local reactions by 46% of allergists and future systemic reactions by 29%.

In allergen immunotherapy, most allergists will make dose adjustments for local reactions at the injection site. The main reasons for this practice are to avoid discomfort that may reduce patient noncompliance and to reduce the risk of future local reactions. Most ➤➤

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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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allergists do not believe that local reactions increase the risk of future systemic reactions.

COMMENT: *Studies such as this do not provide a scientific explanation for clinical decision making, but do provide the practicing community with information potentially helpful to make us more consistent. Large local reactions are not predictive of systemic reactions, but we continue to make a variety of dosing changes based upon this occurrence. Adherence is a valid justification for making a dosage change, but all other apprehensions are not valid concerns in my opinion.*
D. K. L.
Coop CA, Tankersley MS: Dose adjustment practices among allergists for local reactions to immunotherapy.
Ann Allergy Asthma Immunol. 2007;99:77-81. ♦♦

Skin Test or Blood Test?

IN evaluation of suspected allergy, serum specific IgE antibody measurement provides useful information on the magnitude of sensitization and the likelihood of true allergic reactions. Previous studies have suggested discrepancies between the various laboratory techniques used to measure specific IgE levels. This study compared the results of three common systems for specific IgE measurement.

The three systems were ImmunoCAP, Immulite, and Turbo radioallergosorbent test (RAST). The study included 60 clinical samples taken for measurement of peanut-specific IgE and 20 for measurement of soy-specific IgE; all tests were performed at Clinical Laboratory Improvement Act-certified reference laboratories. The analysis also included mouse-human IgE chimeric antibodies specific for the major birch pollen allergen Bet v 1 and for the house dust mite allergen Der p 2.

On qualitative evaluation using the accepted cutoff level of 0.35 kU_A/L, 10 of 60 peanut samples was classified as negative by ImmunoCAP, 10 by Immulite, and 9 by Turbo RAST. For soy samples, all three tests classified 3 samples as negative. The Turbo RAST system yielded the most variable results. However, on quantitative evaluation of the clinical samples, there was significant variation between the three systems: the Immulite test tended to overestimate specific IgE levels and the Turbo RAST to underestimate them, compared with ImmunoCAP. The mouse-human chimeric antibody measurements showed a similar pattern.

The results confirm significant discrepancies between different systems for measurement of specific IgE antibody levels. Laboratories should make clear which system they are using, and users should understand the differences between systems. The fact that two of the systems studied present their results in units of kU_A/L does not mean that their results are interchangeable.

COMMENT: *We all recognize the important role of in vitro IgE assessment in the practice of allergy. These data highlight the notion that there is no perfect system currently available. There appears to be poor agreement among the three studied systems. Allergy specialists as well as primary care physicians need to be aware of the system that they utilize and, more importantly, the clinical consequences of a false-positive or false-negative test.*
A. M.
Wood RA, Segall N, Ahlstedt S, Williams PB: Accuracy of IgE antibody laboratory results.
Ann Allergy Asthma Immunol. 2007;99:34-41. ♦♦

Polish Birch Pollen Invades Denmark!

BIRCH is a major cause of pollen allergy in central and northern Europe. Forecasts of pollen levels play an important role in planning for treatment needs. Under certain weather conditions, birch pollen can be transported over long distances in the atmosphere. This phenomenon was evaluated as a cause of "pre-seasonal" outbreaks of birch pollen allergy in Denmark.

In the spring of 2006, pollen level measurements and botanic observations were carried out in Copenhagen and in an agricultural region of Poland. In addition, the investigators analyzed Danish pollen records for several previous years to assess possible episodes of long-range transport, using maps of potential birch pollen sources in Poland and Germany.

During the period studied, bi-hourly birch pollen levels of greater than 500 grains/m^3 were measured in Copenhagen nearly 2 weeks before birch trees in the region began to flower. Detailed weather and trajectory analysis suggested that Poland was the source of this early birch pollen; atmospheric transport took about one day. The historical data showed that Copenhagen had episodes of high pre-seasonal pollen counts every year from 2000 to 2006. In each year, trajectory analysis implicated Poland or Germany as the source of the pollen.

At least in Denmark, long-range atmospheric transport appears to contribute to significant pre-seasonal concentrations of birch pollen. This source of pollen may have a full allergic impact, as hay fever patients are unlikely to have adequate protective medications during this time. The mechanism of long-range transport should be incorporated into the models used in making pollen forecasts.

COMMENT: *Seasonal birch pollen hay fever symptoms preceding birch tree pollination? This appears to have occurred in Copenhagen in 2006. This fascinating study utilized meteorologic and botanic analyses to implicate birch pollen trees in Poland as the cause of "pre-seasonal" symptoms in Copenhagen. This illustrates the remarkable efficiency of pollen grain dissemination by wind. Forget about advising that patient to cut down the birch tree in the backyard.*
S. A. T.

Skjøth CA, Sommer J, Stach A, et al: The long-range transport of birch (Betula) *pollen from Poland and Germany causes significant pre-season concentrations in Denmark.*
Clin Exp Allergy. 2007; 37:1204-1212. ♦♦

Cord Blood Adiponectin Predicts Wheezing Risk

IN utero exposures may influence the risk of respiratory infections and wheezing in young children. Adipokines such as adiponectin and leptin, secreted by adipose tissues, play a role in regulating various inflammatory processes. They are found at high levels in cord blood from term infants. Cord blood adipokine levels were evaluated as predictors of early childhood wheezing.

The study used prospective birth cohort data on 740 German mothers and newborns. Adiponectin and leptin levels were measured in cord blood samples. Associations between cord blood adipokine levels and physician-reported asthma or obstructive bronchitis during the first 2 years of life were analyzed.

By age 2 years, 19.6% of the children were reported as having asthma or obstructive bronchitis. There was a strong interaction between cord blood adiponectin level and maternal history of atopic disease in terms of the risk of these wheezing disorders. Among children whose mothers had a history of atopy, the odds ratio for pediatrician-reported asthma or obstructive bronchitis was 2.12 for those in the top quintile of cord blood adiponectin level, compared to those in the middle quartile. In contrast, for children in the lowest quartile, the odds ratio was 0.14. These associations were independent of other risk factors for early childhood wheezing; no associations were noted for cord blood leptin levels.

For infants of atopic mothers, high levels of adiponectin in cord blood are associated with an increased risk of wheezing disorders by age 2. Wheezing risk appears reduced for infants with low cord blood adiponectin levels. Additional studies are needed to explore associations of cord blood adiponectin with inflammatory cytokine levels and respiratory infection risk.

COMMENT: *Among offspring of atopic mothers, a higher cord blood adiponectin level correlated with wheezing in the first 2 years of life. Although adiponectin is produced by adipose tissue, this effect appears to have nothing to do with the correlation between obesity and asthma, because the effect was independent of both leptin levels and maternal body mass index. However, it is possible that adiponectin may have a role as a biomarker.*
S. A. T.

Rothenbacher D, Weyermann M, Fantuzzi G, Brenner H: Adipokines in cord blood and risk of wheezing disorders within the first two years of life.
Clin Exp Allergy. 2007;37:1143-1149. ♦♦

What's New in Peanut Allergy?

IN adults, peanut allergy is most often associated with IgE recognition of the allergens Ara h1 and Ara h2. Recent studies suggest that Ara h6 may also play an important role. In peanut-allergic children, sensitization may be more dynamic than in adults. This study assessed IgE reactivity to major peanut allergens in peanut-allergic children, including possible changes over time.

The study included 20 children and adolescents with peanut allergy, confirmed by double-blind placebo-➤➤

controlled food challenge. Each patient underwent immunoblot measurement of IgE reactivity to purified Ara h1, Ara h2, Ara h3, and Ara h6 on two occasions: once just before peanut challenge and again 20 months later. Skin prick testing was performed at the same times.

On initial assessment, all of the children showed IgE recognition of Ara h2, while 16 of 20 also recognized Ara h6. Recognition of Ara h1 and Ara h3 was seen in 10 patients each. Median peanut-specific IgE level was 28.2 kU/L. Patterns of major peanut allergen recognition remained similar at 20 months' follow-up, as did the peanut-specific IgE level: median 23.0 kU/L.

Most patients were skin-prick positive for Ara h2 and Ara h6, with Ara h6 producing the largest wheals. About half of patients had positive skin reactions to Ara h1 and Ara h3. Neither the IgE recognition nor skin-prick results were correlated with the severity of peanut allergy.

Among peanut-allergic children, Ara h2 and Ara h6 are the major peanut allergens most frequently recognized by IgE. This pattern is similar to that in adults. Recognition of peanut allergens remains stable over nearly 2 years' follow-up, even after food challenge. Following an initial early increase, the specific IgE levels and recognition of major peanut allergens may be highly stable over time.

COMMENT: *The more we learn about peanut allergy the more complex it becomes. This study highlights the importance of allergy to Ara h6 in children. However, it appears that we are still far away from the day when we can perform a profile of peanut tests to accurately predict the prognosis of this disease.*
S. A. T.
Flinterman AE, van Hoffen E, den Hartog Jager CF, et al: Children with peanut allergy recognize predominantly Ara h2 and Ara h6, which remains stable over time.
Clin Exp Allergy 2007 37:1221. ♦♦

ACCURATE food labeling is essential for the safety of patients living with peanut allergy. Under the Food Allergen Labeling and Consumer Protection Act, the presence of peanut and other commonly allergenic foods must be declared on food labels. Manufacturers may also include advisory statements that products are manufactured in the same facility or on equipment also used for peanut-containing products. This study assessed patient attitudes toward such advisory labels and the presence of peanut allergen in labeled foods.

Surveys were administered to attendees of Food Allergy & Anaphylaxis Network conferences in 2003 and 2006. Surveys were completed by 625 and 645 attendees, respectively; most were parents of food-allergic children. Respondents were presented with various advisory labels and asked how likely they would be to purchase products with those labels. In addition, 200 packaged foods with allergy advisory labels or with peanut listed as a minor ingredient were tested for the presence of peanut.

The percentage of respondents who said they would "never" purchase a product with an advisory label decreased from 85% in 2003 to 75% in 2004. Responses varied according to the language used--consumers were more likely to heed a label that mentioned manufacturing or processing than one that mentioned product packaging.

Of the 200 products tested, 20 contained detectable peanut allergen. Of these, 13 products contained clinically significant peanut levels: more than 1 mg of peanut or 0.25 mg of peanut protein.

The parents of children with food allergies appear less likely to heed allergy advisory labels than they were only a few years ago. Peanut allergen is detected in up to 10% of products with such labels, indicating a significant risk to peanut-allergic patients who eat these products. The labeling language influences consumer behavior, but does not predict the presence of peanut or peanut allergen.

COMMENT: *In the United States, manufacturers are legally required to declare on their label the presence of certain commonly allergenic foods, including peanut. However, there is concern over hidden, unlabeled allergenic contents as a result of shared manufacturing equipment. Many food companies are voluntarily making advisory statements (like "manufactured on shared equipment") about this risk on their labels. This may seem like an advance, but in reality such statements are becoming so common as to be ignored. What is the risk, then, of hidden peanut in a food labeled with an advisory statement? Read this. (Answer: 10% for peanut.)*
R. J. M.
Hefle SL, Furlong TJ, Niemann L, et al: Consumer attitudes and risks associated with packaged foods having advisory labeling regarding the presence of peanuts.
J Allergy Clin Immunol. 2007;120:171-176. ♦♦

Nonsurgical Approach to Adenoid Enlargement

ADENOIDAL hypertrophy (AH) is common in children, and may cause symptoms including nasal obstruction and obstructive sleep apnea syndrome. Adenoidectomy is the standard treatment for severe AH. This randomized trial evaluated mometasone furoate aqueous nasal spray as an alternative to surgery for children with severe AH.

The study included 60 children referred for evaluation of AH. All had chronic nasal obstruction with the adenoid pads obstructing at least 75% of the nasopharynx on nasal endoscopy. In the first stage of the study, one group of patients received 40 days of treatment with mometasone furoate, 50 µg per nostril per day, while the other group received placebo. After 40 days, mometasone-treated children who showed clinical improvement received either topical intranasal steroids (on alternate days for the first 2 weeks per month) or continued mometasone (daily for the first 2 weeks per month). ➤➤

Final outcomes were evaluated after 3 months.

All but 3 children completed the study protocol. Initial treatment with mometasone furoate led to symptom improvement and decreased adenoid size in 21 children, a rate of 77.7%. Placebo-treated children showed no improvement. Children assigned to continued mometasone treatment had greater reductions in adenoid size than those switched to intranasal steroids. Symptoms remained similar between groups. Mometasaone was well tolerated.

For children with severe AH, mometasone fuorate nasal spray can reduce adenoid size and symptom severity. For children who have AH without tonsillar hypertrophy, a trial of intranasal mometasone should be considered before adenoidectomy.

COMMENT: *For years, we have had evidence that topical nasal corticosteroids may reduce adenoid size. This randomized, placebo-controlled study, done by a pediatric otolaryngology department in Italy, adds support to this idea. As a result, our ENT colleagues may have fewer adenoidectomies to perform. One critique of this study is the lack of crossover design--ie, children in the placebo group were scheduled for adenoidectomy, rather than treated with the nasal corticosteroid before surgical intervention.*
K. R. M.

Berlucchi M, Salsi D, Valetti L, et al: The role of mometasone furoate aqueous nasal spray in the treatment of adenoidal hypertrophy in the pediatric age group: preliminary results of a prospective, randomizedstudy.
Pediatrics. 2007;119:e1392-e1397
(doi:10.1542/peds.2006-1769). ♦♦

Maternal Asthma and Smoking Increase Bronchiolitis Risk

ABOUT half of infants hospitalized for bronchiolitis are healthy term infants with no apparent risk factors. No large, population-based studies have evaluated the interactive effects of factors like maternal smoking and maternal asthma among infants without confounding conditions such as heart or lung disease. Tennessee Medicaid data were used to evaluate maternal asthma and smoking during pregnancy as risk factors for bronchiolitis in otherwise healthy term infants.

The retrospective analysis included 101,245 non-low-birth weight infants enrolled in Tennessee's state-based Medicaid managed care program between 1995 and 2003. About half of all infants born in Tennessee during that time were Medicaid patients; the analysis included only infants of black or white race. Data on health care visits and hospitalizations were used to analyze the occurrence and severity of bronchiolitis during the first year of life. Maternal asthma and maternal smoking during pregnancy were evaluated as predictors of bronchiolitis.

Twenty percent of the infants had a clinic or emergency department (ED) visit or hospitalization for bronchiolitis. Risk was highest for infants whose mothers had asthma and smoked during pregnancy, adjusted hazard ratio (HR) 1.47. For the two variables individually, HRs were 1.39 for maternal asthma and 1.14 for maternal smoking. Risk of ED visits for bronchiolitis was increased for infants whose mothers had asthma, with or without smoking. The risk of being hospitalized with bronchiolitis for 3 days or longer was highest with maternal asthma, HR 1.52; followed by both risk factors, HR 1.38; and maternal smoking only, HR 1.19.

For healthy term infants, maternal asthma and maternal smoking during pregnancy are both independent risk factors for bronchiolitis. For infants with both risk factors, risk is about 50% higher than when neither factor is present. The findings suggest that genetic or host factors influence the infant's response to common respiratory viruses, thus affecting the risk of viral lower respiratory infections.

COMMENT: *In full-term infants, the risk of bronchiolitis increases with maternal asthma and maternal cigarette smoking during pregnancy. Maternal asthma, in particular, increases the odds of prolonged hospitalization for bronchiolitis. This large study assessed over 100,000 healthy, term infants; in this population, more than two thousand infants were admitted with bronchiolitis. Certainly, a number of these infants are likely to have a future asthma diagnosis. Future respiratory syncytial virus preventive strategies should focus on these additional high-risk populations.*
K. R. M.

Carroll KN, Gebretsadick T, Griffin MR, et al: Maternal asthma and maternal smoking are associated with increased risk of bronchiolitis during infancy.
Pediatrics. 2007;119:1104-1112. ♦♦

Antibiotics in Infancy Increase Asthma Risk in Childhood

EPIDEMIOLOGIC data suggest that early exposure to antibiotics may be a risk factor for childhood asthma. This association was investigated using data from a population-based birth cohort study with long-term follow-up.

The analysis included 13,116 children born in Manitoba, Canada, during 1995. Prescription and health care records were used to assess antibiotic exposure during the first year of life and the presence of asthma at age 7.

With adjustment for known risk factors, antibiotic treatment during the first year of life was associated with an increased risk of asthma at age 7. For children receiving antibiotics for non-respiratory tract infections, the adjusted odds ratio (OR) for asthma was 1.86. The association was strongest among children receiving more than four courses of antibiotics: OR 1.46. The latter association was most pronounced for children living in rural areas, for those whose mothers did not have asthma, and for those without a dog at home during the first year of life. These subgroups had elevated rates of broad-spectrum cephalosporin use. ➤➤

These population-based data add to the evidence identifying early-life exposure to antibiotics as a risk factor for childhood asthma. Efforts to reduce the use of broad-spectrum cephalosporin antibiotics may help to lower asthma risk.

COMMENT: *Intestinal microflora suppression is an alternative explanation for increased asthma compared to the hygiene hypothesis. Antibiotics may alter the protective effect of gut flora of rural children but have little effect on the gut flora of urban children who are already predisposed to atopy. Broad-spectrum antibiotics, especially, administered during the first year of life have a higher association with asthma at 7 years of age. This is another reason for judicious and appropriate use of antibiotics in young children.*
S. F. W.
Kozyrskyj A, Ernst P, Becker A: Increased risk of childhood asthma from antibiotic use in early life.
Chest 2007;131:1753-1759. ♦♦

Methacholine Challenge Testing: The Basics

METHACHOLINE challenge testing (MCT) plays an important role in research and clinical management of pulmonary diseases. The authors outline the procedure, indications, testing protocols, and other key issues related to the use of MCT.

Also called "bronchoprovocation testing," MCT is done by having the patient inhale a prepared solution of the acetylcholine analog methacholine. The response is calculated by comparing the results of pulmonary function tests performed before and after administration. A 20% reduction in FEV_1 or a 35% to 45% reduction in specific airway conductance, compared with baseline, is defined as a positive response.

To avoid false negative results, the patient should discontinue inhaled corticosteroid therapy for several weeks before MCT. Several dosing protocols have been described; current American Thoracic Society guidelines endorse the 2-minute tidal breathing method and the 5-minute dosimeter method. These two protocols produce differing results, with the tidal breathing method offering higher sensitivity.

Methacholine challenge testing is done to rule out the diagnosis of airway hyperresponsiveness or hyperactivity. It is especially valuable in making the diagnosis of asthma, with its nonspecific clinical findings. The test should not be performed in patients with ventilatory impairment and poorly controlled hypertension, among other contraindications.

Testing should follow specific protocols, including recording of the number of breaths and breathing patterns. Blood pressure and pulse should be monitored; bronchospasm responds promptly to albuterol treatment. After a positive response to MCT, bronchodilators should be given to hasten recovery. The test should always be performed under direct physician supervision. Several factors influence test interpretation; in the case of asthma, the most important consideration is pretest probability.

The test is reimbursed by Medicare and most commercial insurance. Reimbursement for MCT varies considerably; Centers of Medicare and Medicaid Services (CMS) reimbursement is about $175. Most commercial insurers accept the CMS guidelines and coding methods, although some companies "bundle" the components into a single reimbursement. Other key issues related to proper coding are presented.

Methacholine challenge testing is a valuable but underused test for the diagnosis of asthma. Particularly when initial bronchodilator therapy does not relieve symptoms, MCT is indicated.

COMMENT: *This is an important summary of the diagnostic role, procedure of testing, coding and reimbursement of MCT. An example of proper coding for reimbursement is unusual for a peer reviewed journal but quite relevant for practitioners. Protocols for indications and methodology interpretations with appropriate references make this an important reference for those of us utilizing MCT.*
S. A. T.
Birnbaum S, Barreiro TJ: Methacholine challenge testing: identifying its diagnostic role, testing, coding, and reimbursement.
Chest. 2007;131:1932-1935. ♦♦

What Happens after Inhaled Steroid Withdrawal in Asthma?

QUESTIONS remain about neutrophil involvement in the process of asthma exacerbations. The effects of corticosteroid withdrawal on sputum markers of inflammation were investigated in patients with asthma.

The randomized trial included 24 patients with moderate stable asthma. After a 2-week run-in period, one group received 10 weeks of treatment with budesonide only while the other group received placebo. Exacerbation rate and sputum inflammatory markers were compared between groups.

During 10 weeks without steroids, 8 of 12 patients in the placebo group had loss of asthma control. In contrast, exacerbation occurred in just 1 of 10 budesonide-treated patients. Exacerbations were associated with significant increases in the sputum interleukin-8 (IL-8) level and sputum neutrophil count, with initial rises occurring 2 weeks before the exacerbation. The sputum neutrophil count was significantly and positively correlated with the change in sputum IL-8.

For patients with moderate asthma, abrupt discontinuation of inhaled corticosteroid leads to loss of disease control. Before exacerbations occur, there are significant increases in sputum neutrophil count and IL-8 level. The findings contrast with previous studies of gradual corticosteroid withdrawal, which reported increases in sputum eosinophils.

COMMENT: *The authors observed asthma exacerbations artificially induced by steroid withdrawal.* ➤➤

In contrast to previous studies, neutrophils and IL-8 predominated over eosinophils before and during the exacerbation. This finding may be related to abrupt withdrawal instead of tapering, asthmatic phenotypic differences, or underlying respiratory infection. Asthma exacerbations are not uniform in nature.
S. F. W.
Maneechotesuwan K, Essilfie-Quaye S, Kharitonov SA, et al: Loss of control of asthma following inhaled corticosteroid withdrawal is associated with increased sputum interleukin-8 and neutrophils.
Chest 2007;132:98-105.

♦♦

Placebo Effect on Bronchial Hyperreactivity in Asthma

ANY benefits of placebos are thought to result from their effects on patient expectations. It has been suggested that while placebos can improve subjective measures such as pain, they are unlikely to influence objective physiologic outcomes. This study evaluated placebo effects on asthma.

The randomized, double-blind, crossover trial included 55 patients with mild intermittent or persistent asthma and stable airway hyperreactivity. In random order, patients received salmeterol or placebo before methacholine challenges. An additional set of tests was performed under two physician behavior conditions, which communicated positive or neutral expectations of the treatment effect. The presence and magnitude of the placebo effect on airway hyperreactivity were assessed, along with predictors of the placebo response.

Compared to baseline, placebo treatment was associated with a significant reduction in bronchial hyperreactivity. The calculated methacholine concentration needed to provoke a 20% decrease in FEV_1 nearly doubled under the placebo condition. Even by a conservative definition, 18% of patients were classified as placebo responders. While the differing physician behaviors affected patient perceptions of the physician, they did not influence the presence or magnitude of the placebo effect.

Placebo treatment can affect a key physiologic outcome measure in patients with asthma. The observed change in methacholine provocative dose is large enough to be clinically meaningful and is independent of manipulation of physician behavior. The findings have important implications for asthma research and clinical care.

COMMENT: *Examples of psychosomatic patient responses and the "mind-body" linkage are not uncommon in clinical practice. This study documents a clear placebo response to the use of inhalers in asthmatic patients with mild asthma. Interestingly, physician attitude and behavior did not influence the clinical outcome. More research about the placebo response will be helpful for clinicians and patients dealing with chronic illnesses.*
S. M. F.
Kemeny ME, Rosenwasser LJ, Panettieri RA, et al: Placebo response in asthma: a robust and objective phenomenon.
J Allergy Clin Immunol. 2007;119:1375-1381.

♦♦

Controlling Eosinophil Count Reduces COPD Exacerbations

THE inflammatory response associated with exacerbations of chronic obstructive pulmonary disease (COPD) is generally regarded as neutrophil dependent. However, eosinophilic airway inflammation may also contribute, particularly to severe exacerbations. This study evaluated the effects of treatment to lower sputum eosinophil counts on the rate and severity of COPD exacerbations.

The randomized trial included 82 patients with COPD. One group was treated according to current British Thoracic Society guidelines. In the intervention group, patients received additional treatments to minimize eosinophilic airway inflammation, based on sputum eosinophil counts. The two groups were matched for FEV_1, baseline eosinophil count, and hospitalization for COPD within the past year. The main outcome of interest was the frequency of mild, moderate, or severe COPD exacerbations.

The frequency of severe exacerbations was 0.5 per patient per year with conventional treatment, compared with 0.2 in the intervention group: a mean 62% reduction. Most of the reduction was achieved in patients with eosinophilic airway inflammation; there was no significant effect on mild or moderate exacerbations. Forty percent of patients in the intervention group needed oral corticosteroids to control the sputum eosinophil count.

For patients with COPD, adding treatment to minimize eosinophilic airway inflammation helps to reduce the risk of severe exacerbations. Further study is needed to simplify the treatment approach and to define the costs and benefits.

COMMENT: *This study reinforces that even in non-allergic obstructive lung disease, airway eosinophilia is an appropriate marker to use regarding the evaluation and treatment of exacerbations.*
B. E. C.
Siva R, Green RH, Brightling CE, et al: Eosinophilic airway inflammation and exacerbations of COPD: a randomised controlled trial.
Eur Respir J. 2007;29:906-913.

Cat Allergen Linked to Increased BHR in Asthma

THE contributions of allergen sensitization and exposure to the incidence and prevalence of asthma remain unclear. Data from the European Community Respiratory Health Survey (ECRHS) were used to ➤➤

assess the effects of allergen exposure and IgE sensitization on bronchial hyperresponsiveness (BHR) in asthma.

The analysis included 1,884 adult asthma patients enrolled in the ECRHS. As part of that study, levels of house dust mite and cat allergen were measured in mattress dust sample and patients underwent measurement of specific IgE to four common allergens. Bronchial challenge testing was done to assess BHR.

Higher exposure to cat allergen was associated with increased BHR. This trend was more pronounced among patients sensitized to any of the four allergens tested, compared to nonsensitized patients. There was no apparent interaction between cat sensitization and cat allergen exposure; mite exposure was unrelated to BHR. Among subjects at the highest versus lowest level of cat allergen exposure, the difference in methacholine PD_{20} was approximately two doubling doses. The difference in BHR was nearly as great for patients with moderate exposure to cat allergen.

Even moderate exposure to cat allergen is associated with increased BHR in asthmatic adults. The results suggest that all atopic patients might benefit from reduced cat exposure, even if they are not sensitized to cat allergen.

COMMENT: *It appears that there is a pervasive nonspecific effect for cat exposure in increasing bronchial hyperresponsiveness to a wide range of other stimuli.*
B. E. C.
Chinn S, Heinrich J, Antó JM, Janson C, et al: Bronchial responsiveness in atopic adults increases with exposure to cat allergen.
Am J Respir Crit Care Med. 2007;l76:20-26. ♦♦

Mattress Dust Exposure Affects Allergy Risk

THE so-called Hygiene Hypothesis suggests that early childhood exposure to microbial products reduces the risk of subsequent allergies. Most studies of this association have focused on endotoxin, but other components of house dust also have immune stimulatory properties. This study assessed the effects of other bacterial and mold components, in addition to endotoxin, on the risk of allergic sensitization in children.

Using data from four birth cohort studies, the investigators identified approximately 180 sensitized and 180 nonsensitized children from each of three countries: Germany, The Netherlands, and Sweden. Levels of endotoxin, β(1,3) glucans, and fungal extracellular polysaccharides (EPS) were measured in mattress and living room dust samples from the homes of cases and controls.

Sensitization risk was significantly reduced for children exposed to higher levels of mattress dust and to higher concentrations of endotoxin, β(1,3) glucans, and fungal EPS. In adjusted analyses, mattress dust continued to have a significant protective effect: odds ratio 0.57. The effects of the individual components were no longer significant.

High exposure to mattress dust is linked to a decreased risk of allergic sensitization in children. The specific dust components responsible for this protective effect remain unclear.

COMMENT: *This study supports the hypothesis that early exposure to endotoxin as reflected by high levels of house dust sensitization may decrease the risk of inhalant allergen sensitivity.*
B. E. C.
Gehring U, Heinrich J, Hoek G, et al: Bacteria and mould components in house dust and children's allergic sensitisation.
Eur Respir J. 2007;29:1144-1153. ♦♦

Immunoproteomics Identifies New Aspergillus Allergens

ALLERGY to the mold *Aspergillus fumigatus* is common in asthma patients worldwide. Identification of specific IgE-inducing allergens is key to diagnosis and treatment of allergic aspergillosis. An immunoproteomics approach was used to identify potential *A. fumigatus* allergens.

The investigators used immunoproteomics with mass spectrometry to identify proteins potentially associated with *A. fumigatus*-specific immunoreactivity from a third-week culture filtrate. Two-dimensional gel electrophoresis using sera from patients with allergic bronchopulmonary aspergillosis (ABPA) was performed to test the allergenic potential of the identified proteins. This approach identified a total of 16 *A. fumigatus* allergens, 11 of which were previously unreported. Studies using individual patient sera showed evidence of sensitization, although patterns of sensitization varied. Three proteins showed specific IgE immunoreactivity in 6 of 8 sera tested.

This immunoproteomics approach identifies several possible allergenic proteins of *A. fumigatus*, which could be of value in the serologic diagnosis of allergic aspergillosis. The immunoreactivity observed in these experiments might also lead to new personalized immunotherapeutic approaches to APBA.

COMMENT: *These authors used an immunoproteomic approach to identify novel immunogenic aspergillus proteins. This is a major step forward toward improving the utility of aspergillus in vitro testing and opens the door for customized immunotherapeutic approaches to treating ABPA.*
S. A. T.
Gautam P, Sundaram CS, Madan T: Identification of novel allergens of Aspergillus fumigatus *using immunoproteomics approach.*
Clin Exp Allergy. 2007;37:1239-1249. ♦♦

CLINICAL TIDBITS

SLIT Shows Efficacy in Atopic Dermatitis

THIS randomized trial evaluated the clinical benefits of sublingual immunotherapy (SLIT) for children with atopic dermatitis. The study included 56 children and adolescent patients with a Scoring Atopic Dermatitis (SCORAD) of greater than 7. All patients were monosensitized to dust mite, with no food allergy or chronic asthma. The children received 18 months of active or placebo SLIT, in addition to standard therapy.

Among 48 study completers, active SLIT was associated with significant improvement in SCORAD beginning at 9 months. Patients in the SLIT group also had a reduced medication use, along with a trend toward improvement in visual analog scale score. The benefits of SLIT were apparent mainly in patients with mild to moderate atopic dermatitis, as opposed to severe disease. In 2 cases, SLIT was associated with worsening dermatitis.

The results suggest a clinical benefit of SLIT in dust mite-allergic children with mild to moderate atopic dermatitis. In properly selected cases, SLIT may offer a new treatment approach to extrinsic atopic dermatitis.

COMMENTS: *This study may raise more questions than answers about SLIT, particularly concerning its effectiveness and possible use in nonrespiratory disease states. If this study can be confirmed with a larger sample, SLIT could be an attractive option for our patients with chronic atopic dermatitis.*
S. M. F.

Pajno GB, Caminiti L, Barberio G, et al: Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: A randomized, double-blind, placebo-controlled study.
J Allergy Clin Immunol. 2007;120:164-170. ♦♦

ICS Improve Exercise Blood Gases in Asthma Patients

IN patients with asthma, airway inflammation might cause changes in pulmonary gas exchange and arterial blood gas levels during exercise. The effects of anti-inflammatory therapy on arterial blood gas status during exercise were examined in 19 active subjects with asthma.

The volunteers performed treadmill exercise to exhaustion before and after 6 weeks of treatment with inhaled corticosteroids (ICS) or placebo. In addition to improving pulmonary function at rest, ICS treatment was associated with reduced exercise-induced bronchospasm and postexercise sputum histamine. Asthma patients taking ICS showed improvements in exercise PaO_2: 37% of this improvement was related to increased alveolar ventilation and 63% to improved gas exchange efficiency. Time to exhaustion increased from 10 minutes before ICS treatment to 15 minutes afterward.

For patients with asthma, anti-inflammatory treatment with ICS improves arterial blood oxygenation during exercise. This is in addition to favorable effects on exercise-induced bronchoconstriction and endurance.

COMMENT: *This well-designed study shows ICS not only improve lung function in asthmatic patients, but also help exercise efficiency by improving alveolar ventilation. Interestingly, the degree of improvement correlated with the severity of asthma; those patients with the lower lung functions responded best to the ICS treatment. The results could be used to encourage sports-oriented asthmatic patients to be compliant with their ICS therapy.*
S. M. F.

Haverkamp HC, Dempsey JA, Pegelow DF, et al: Treatment of airway inflammation improves exercise pulmonary gas exchange and performance in asthmatic subjects.
J Allergy Clin Immunol. 2007;120:39-47. ♦♦

New Treatment for HAE Attacks?

BRADYKININ is thought to play a role in acute edema attacks in patients with hereditary angioedema (HAE). A pilot study of the bradykinin BR-2 receptor antagonist Icatibant was carried out in 15 patients with HAE. A total of 20 acute HAE attacks were treated, with either intravenous or subcutaneous administration of Icatibant.

Symptoms began to decrease within 4 hours after Icatibant administration; subcutaneous treatment yielded a somewhat faster response. There was a median 4 cm reduction on the 0 to 10 cm visual analog scale. Median bradykinin level decreased from 48.5 pmol/L before the attacks--seven times higher than normal--to 18.0 pmol/L after treatment. Icatibant is a promising treatment for acute attacks of HAE.

COMMENT: *This small proof-of-concept study showed that Icatibant, a bradykinin B2 receptor antagonist, appears to be beneficial in patients with acute attacks of HAE when administered either intravenously or subcutaneously. A small number of patients did have recurrence of their edema. If subcutaneous administration is proven helpful in larger studies, it may lead to a self-administered therapy for patients with this difficult-to-manage disease.*
S. M. F.

Bork K, Frank J, Grundt B, et al: Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant).
J Allergy Clin Immunol. 2007;119:1497-503. ♦♦

Maybe Not So Transient ....

IN infants with transient tachypnea of the newborn (TTN), tachypnea occurs soon after birth, resolving within a few days. There are generally thought to be no respiratory or other long-term sequelae. Using data from a Canadian birth cohort, the investigators identified 308 cases of TTN in a population of 12,763 term infants--a rate of 2.4%. On regression analysis, risk factors for TTN were maternal asthma, birth weight greater than 4,500 g, male sex, and urban location.

At follow-up to 7 years of age, children with a history of TTN were at increased risk of bronchiolitis, bronchitis, or asthma diagnosis or medication: adjusted hazard ratio 1.17. Thus TTN may lead to an increased risk of childhood wheezing syndromes, and may be an early manifestation of asthma.

COMMENT: *Once thought to be an entirely self-limiting condition, having TTN predisposes to wheezing in childhood. A maternal history of asthma also increases the risk of TTN, as would be anticipated. Manifestations of asthma may appear much earlier than previously suspected.*
K. R. M.
Liem JJ, Huq SI, Ekuma O, et al: Transient tachypnea of the newborn may be an early clinical manifestation of wheezing symptoms.
J Pediat. 2007;151:29-33. ♦♦

Occupational Exposures Increase Adult Asthma Risk

THERE are few population-based data the relationship between occupational exposures on new-onset asthma. This issue was addressed using prospective data on 6,837 subjects from the European Community Respiratory Health Survey. For subjects with exposures known to be related to occupational asthma, the relative risk (RR) of asthma was 1.6. When the definition of asthma included bronchial hyperreactivity in addition to symptoms, the risk was even higher: RR 2.4. The results suggest that many new cases of adult asthma are related to occupational exposures. Close follow-up is needed after accidental inhalations in the workplace.

COMMENT: *Occupational asthma has numerous triggers and approximately 15% of adult-onset asthmatics have reported occupational exposures. In this international health survey study from 1990-95 including over 6000 participants from 13 countries, asthma was assessed by methacholine challenge and asthma symptom questionnaires. Exposure assessment included asthma-specific job exposures, along with expert judgment and self-reported acute inhalation exposures. Risk ranged from 10% to 25%--equivalent to an incidence of new-onset occupational asthma of 250 to 300 cases per million individuals per year. A significant excess risk of asthma was seen for nursing and in subjects who reported an acute symptomatic inhalation with fire, mixing cleaning products, or chemical spills.*
M. F.
Kogevinas M, Zock, JP, Jarvis D, et al: Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II).
Lancet. 2007;28:370:336-341. ♦♦

Do hs-CRP Assays Detect Inflammation in Asthma?

NEW highly sensitive C-reactive protein (hs-CRP) assays can detect small changes in levels of this inflammatory marker, within the normal range. Associations between hs-CRP and bronchial asthma were evaluated using blood samples from 109 asthma patients--some with and some without attacks. Other assessments included pulmonary function testing.

In 70 controls, the mean hs-CRP level was 0.262 mg/L. This was significantly lower than hs-CRP values in asthma patients: mean 0.473 and 0.908 mg/L level in patients with and without attacks, respectively. Among the asthma patients, there was an inverse correlation between serum hs-CRP and the FEV_1/FVC ratio. Highly sensitive CRP assays may provide useful information on inflammation and exacerbation status in patients with asthma. Further study is needed to clarify the role of hs-CRP assays in clinical management.

COMMENT: *One challenge of caring for asthma is the lack of an objective, practical measure of airway inflammation. I think hs-CRP assays are too susceptible to influence from other diseases or conditions, and CRP is not linked to the type of inflammation that characterizes most asthma. However, these results are encouraging that someday we might have an objective, reasonably simple test or tests that reflect airway inflammation.*
D. K. L.
Fujita M, Ueki S, Ito W, et al: C-reactive protein levels in the serum of asthmatic patients.
Ann Allergy Asthma Immunol. 2007;99:78-53. ♦♦

Low Cross-Reactivity Between Meropenem and Penicillin

USE of meropenem is often avoided in patients with penicillin allergy, despite a lack of data on cross-reactivity. This prospective study evaluated the tolerability of meropenem in 104 patients with known penicillin allergy. All had a history of immediate hypersensitivity reactions to penicillins, along with positive skin test reactions to one or more penicillin reagents. One patient had a positive response to intradermal skin testing with meropenem, for a rate of 0.9%. The remaining 103 patients showed no reactions to escalating ➤➤

doses of meropenem. Thus cross-reactivity between meropenem and penicillins appears low. For penicillin-allergic patients who require meropenem treatment, negative results on meropenem skin testing are strongly associated with tolerability.

COMMENT: *This paper confirms smaller reports of the successful use of meropenem in subjects with a history of penicillin allergy and negative meropenem skin tests. In the confusing, current era--resulting from the lack of major determinant--citation of studies such as this will help justify optimal care for patients with therapeutic needs, while helping to minimize loss of sleep for consulting allergists/immunologists.*
D. K. L.
Romano A, Viola M, Guéant-Rodriguez R-M, et al: Brief communication: tolerability of meropenem in patients with IgE-mediated hypersensitivity to penicillin.
Ann Intern Med. 2007;146:266-269. ♦♦

Exhaled NO Can Be Measured at Different Levels

EXHALED nitric oxide (NO) measurement provides a noninvasive measure of airway inflammation, but sampling is limited to the proximal airways. A technique of measuring NO at multiple exhalation flows was evaluated in 56 patients with asthma of varying severity. Mean bronchial NO was higher for patients with mild asthma, compared to patients with moderate stable asthma, severe asthma treated with inhaled corticosteroids, or healthy controls. In contrast, bronchial NO was no different for patients with mild asthma vs those with severe asthma receiving inhaled and oral corticosteroids. Patients with asthma exacerbations had the highest bronchial NO values.

Patients with severe asthma receiving oral corticosteroids had the highest alveolar NO, although no higher than in patients with asthma exacerbations. Values for NO diffusion were similar across groups. The measurements showed good reproducibility and low variability. Such differential flow NO measurement may aid in assessing the site of airway inflammation in asthma.

COMMENT: *Measurement of nitric oxide has been proposed as a surrogate to monitor airway inflammation. The authors used exhaled NO measurements obtained at varying flow rates to assess inflammation in large as well as small airways. Assessment of small airway lung function and inflammation is difficult or invasive. Alveolar NO may be a simple and noninvasive means to assess these airways.*
S. F. W.
Brindicci C, Ito K, Barnes PJ, Kharitonov SA: Differential flow analysis of exhaled nitric oxide in patients with asthma of differing severity.
Chest. 2007;131:1353-1362. ♦♦

Guidelines for Antiviral Treatment and Prevention in Children

IMMUNIZATION is the most important technique for prevention of influenza in children, but use of antiviral drugs is appropriate in some situations. The preferred agents are the neuraminidase inhibitors, oseltamivir and zanamivir--this is because of resistance problems associated with the adamantanes, amantadine and rimantadine. Antiviral therapy is recommended for children with risk factors for severe influenza infection. It may also help to reduce the duration of symptoms in children with moderate to severe influenza infection.

High-risk children should receive antiviral prophylaxis before and during the first 2 weeks after immunization. Immunized family members and health care professionals who have been in close contact with high-risk nonimmunized children or infants less than 6 months old should also be treated. Antiviral drugs may also be used to manage influenza outbreaks in nonimmunized children and staff in institutions.

Oseltamivir and zanamivir show evidence of effectiveness against H5N1 avian influenza virus strains. However, little is known about the efficacy, dosage, or duration of therapy in epidemic H5N1 influenza in either adults or children.

COMMENT: *Antiviral treatment of endemic influenza in at-risk pediatric patients is discussed in this clinical report from the American Academy of Pediatrics Committee on Infectious Disease. There is also a sobering discussion of pandemic influenza.*
K. R. M.
Committee on Infectious Diseases: Antiviral therapy and prophylaxis for influenza in children.
Pediatrics. 2007;119:852-860. ♦♦

REVIEWS OF NOTE

COMMENT: *This is an up-to-the-minute review of the role of airway smooth muscle in bronchial hyperresponsiveness in the phenotypic expression of asthma.*
B. E. C.
An SS, Bai TR, Bates JHT, et al: Airway smooth muscle dynamics: a common pathway of airway obstruction in asthma.
Eur Respir J. 2007;29:834-860. ♦♦

COMMENT: *These are excellent guidelines for the assessment and treatment of cough, similar to American Thoracic Society and British Thoracic Society guidelines.*
B. E. C.
Morice AH, Fontana GA, Belvisi GA, et al: ERS guidelines on the assessment of cough.
Eur Respir J. 2007;1256-1276. ♦♦

COMMENT: *If you didn't read a single allergy journal in all of 2006, you should read this short digest of that year's advances in the understanding and treatment of food allergies, anaphylaxis, drug allergy, urticaria, and atopic dermatitis.*
R. J. M.
Sicherer SH, Leung DYM: Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects.
J Allergy Clin Immunol. 2007;119:1462-1469. ♦♦

COMMENT: *Asthma is a heterogeneous disorder, and so is exercise-induced dyspnea. There are quite a few things in the differential diagnosis. This AAAAI work group report is a concise treatise on the subject. It is interesting that exercise-induced asthma is said to be more prevalent in elite athletes than in the general population.*
R. J. M.
Weiler JM, Bonini S, Coifman R, et al: American Academy of Allergy, Asthma & Immunology work group report: exercise-induced asthma.
J Allergy Clin Immunol. 2007;119:1349-1358. ♦♦

COMMENT: *This paper provides the conclusions of a select panel of experts who reviewed the treatment of anaphylaxis in the emergency department. Suggestions are offered for improving care, diagnosing anaphylaxis in the emergency department, and coordinating care between the allergist/immunologist and emergency department physician. An up-to-date reference list is provided.*
D. K. L.
Lieberman P, Decker W, Camargo CA, et al: SAFE: a multidisciplinary approach to anaphylaxis education in the emergency department.
Ann Allergy Asthma Immunol. 200798:519-523. ♦♦

COMMENT: *A succinct review of aspirin intolerance is provided. The primary focus is on respiratory reactions; the role of aspirin aggravating chronic urticaria is not discussed in much detail.*
D. K. L.
Jenneck C, Juergens W, Buecheler M, Novak N: Pathogenesis, diagnosis, and treatment of aspirin intolerance.
Ann Allergy Asthma Immunol. 2007;99:13-21. ♦♦

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