AllergyWatch®

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

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Many Allergens Show Good Stability in Combination

COMBINATIONS of allergen extracts have been suggested for use in immunotherapy vaccines. However, mixing extracts creates the potential for interactions that could change their allergenic properties; there are limited data on allergen compatibility. This study assessed the stability of standardized pollen, dust mite, and cat extracts after mixing with fungal and cockroach extracts.

The investigators prepared mixtures of grass, short ragweed, dust mite, and cat allergens with fungal and cockroach extracts at differing glycerin concentrations. The final concentrations of the mixtures were comparable to those recommended for maintenance immunotherapy. After 1 year of storage at 2° to 8° C, the mixtures were tested to assess the structural integrity and potency of the standardized extracts.

Mixing with fungal or cockroach extracts interfered with the stability of meadow fescue grass allergens. However, dust mite extracts from various commercial sources remained stable in the presence of fungal or cockroach extracts. For fescue and dust mite, allergen recovery depended on the specific mold extract with which they were combined. Mixing with cockroach allergen reduced the potency of dust mite allergen, but cat and short ragweed allergen activity were fairly well retained. For all combinations, higher glycerin concentrations were associated with higher allergen recovery.

The results suggest that many allergen extract combinations considered unstable in current immunotherapy practice parameters actually show significant biochemical compatibility. The findings have implications for the use of combined allergen extracts in clinical practice. The authors call for systematic approaches to improving the compatibility of extracts used in allergen immunotherapy.

COMMENT: *We have clearly entered the era of increasing need for standardization of allergen immunotherapy. This type of data is desperately* ➤➤

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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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needed so that preparation of allergen solutions is not based on anecdotal observations. The observation that grass and dust mite allergen are compatible is reassuring indeed!
A. M.
Grier TJ, LeFevre DM, Duncan EA, Esch RE: Stability of standardized grass, dust mite, cat, and short ragweed allergens after mixing with mold or cockroach extracts.
Ann Allergy Asthma Immunol. 2007;99:151-160. ♦♦

Exhaled NO--Not What It's Cracked Up to Be?

THERE is interest in using exhaled nitric oxide (eNO), a noninvasive measure of airway inflammation, to guide anti-inflammatory treatment for asthma. Two recent studies have found no reduction in the asthma exacerbation rate with eNO, although one reported a reduction in inhaled steroid dosage. The effects of using eNO to adjust corticosteroid dose were compared with traditional asthma management.

The single-blind trial included 118 adult primary care patients with asthma. In one group, corticosteroid therapy was based on eNO measurements. In the other group, the stepwise management guidelines of the British Thoracic Society were followed. Through 1-year follow-up, the two groups were compared for severe asthma exacerbations and other outcomes.

Mean exacerbation frequency was 0.33 per patient per year in the eNO group versus 0.42 in the comparison group. The -21% difference between groups was not significant. Inhaled corticosteroid consumption was 11% higher with eNO-guided therapy. However, the final daily dose was significantly lower with eNO: 557 versus 895 µg.

Using eNO to guide asthma management does not significantly reduce the risk of asthma exacerbations during follow-up. There is also no reduction in cumulative corticosteroid use. The trial, the largest yet performed, does show that eNO-guided management is feasible in primary care.

COMMENT: *This is a negative study that does not support the study by Smith et al. in* The New England Journal of Medicine *(NEJM. 2005;352:2163-2173). It is slightly underpowered, but it does begin to put a chink in the armor regarding eNO as a preferred method to titrate steroid dose. Also see the accompanying editorial by Robin Taylor (Am J Respir Crit Care Med. 2007;176:221-223).*
B. E. C.
Shaw DE, Berry MA, Thomas M, et al: The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial.
Am J Respir Crit Care Med. 2007;176:231-237. ♦♦

Reduced IgG: What Does It Mean and What Do We Do?

LOW serum IgG is a common reason for referral to immunologists. The authors review the clinical evaluation and interpretation of reduced IgG levels.

Nephelometry allows rapid assessment of immunoglobulin levels, although reference values for IgG vary by age. In adolescent and adults, an IgG level of 300 to 600 mg/dL is classified as mildly to moderately reduced, 100 to 299 mg/dL as significantly reduced, and less than 100 mg/dL as profoundly reduced. A total immunoglobulin of greater than 600 mg/dL--IgG plus IgM plus IgA--with normal antibody responses likely rules out humoral immune deficiency.

In infants less than 2 years, low IgG levels may result from transient hypogammaglobulinemia of infancy. X-linked agammaglobulinemia is usually diagnosed in the first few years of life, prompted by family history or➤➤

recurrent sinopulmonary infections. These patients have profound hypogammaglobulinemia and very low circulating B cells. The hyper-IgM syndromes are associated with deficiencies of IgG and IgA. When serum IgG is more than 2 standard deviations below the mean, with deficiencies of IgA or IgM, common variable immunodeficiency may be present.

Deficiencies of IgG subclasses, especially IgG1 and IgG2, may be difficult to interpret--without clear defects of antibody function, they are unlikely to be clinically significant. There are many secondary causes of hypogammaglobulinemia--including medications, malnutrition, and other injuries and diseases--which should be considered before a primary immunodeficiency is diagnosed.

Decisions about immunoglobulin replacement therapy depend on many factors, including history of infections and other diseases. Treatment is generally recommended for patients with profoundly or significantly reduced IgG. Patients are monitored every 4 to 6 months to ensure adequate trough levels. For patients with mild to moderate IgG reductions and normal antibody responses, specialist monitoring without IgG replacement is appropriate.

COMMENT: *This three page article is loaded with information useful in the clinic. Using the sum of IgG, IgA and IgM was a point I have not used previously. This is a great article to quote in consultations. Who better to quote than Drs. Agarwal and Cunningham-Rundles?*
D. K. L.
Agarwal S, Cunningham-Rundles C: Assessment and clinical interpretation of reduced IgG values.
Ann Allergy Asthma Immunol. 2007;99:281-283. ♦♦

Can Montelukast Reduce 'Back-to-School' Asthma?

EACH September when children go back to school, "epidemics" of childhood asthma exacerbations occur. This randomized trial evaluated the effects of add-on therapy with montelukast on asthma symptoms and unscheduled physician visits.

One hundred ninety-four children and adolescents with asthma received 6 weeks of montelukast or placebo, in addition to usual treatment, beginning on September 1. Asthma symptoms were worse on 3.9% of days with montelukast versus 8.3% with placebo. Numbers of unscheduled physician visits for asthma were 4 versus 18, respectively. Reductions in days with worse asthma were greater in boys aged 2 to 5 years (0.4% with montelukast versus 8.8% with placebo) and in girls aged 10 to 14 (4.6% versus 17.0%, respectively).

Adding montelukast to usual treatment may reduce the impact of "back-to-school" asthma. It is unclear why the effects differ by age and sex.

COMMENT: *In Canada, approximately one-fourth of childhood asthma exacerbations requiring hospitalization occur in September, coincident with resuming school. The addition of montelukast in this study did significantly reduce overall symptomatic days compared to placebo. However, my assessment of the data yields an overall improvement of 1.8 days per treated patient (compared to placebo) during 45 days of therapy. Whether this finding justifies the duration of therapy is unclear. More convincing was the reduction of physician visits (and oral corticosteroid use): 4 in montelukast group (of 98) versus 18 in placebo group (of 96). There were no reports of hospitalization in either study group. Interestingly, improvements with montelukast versus placebo were age- and gender-skewed, with the best results seen in younger boys and adolescent girls.*
K. R. M.
Johnston NW, Mandhane PJ, Dai J, et al: Attenuation of the September epidemic of asthma exacerbations in children: a randomized, controlled trial of montelukast added to usual therapy.
Pediatrics. 2007;120:e702-e712. ♦♦

Add-on Montelukast Reduces Late Asthmatic Response

UP to half of patients with asthma have a late asthmatic response to bronchial allergen challenge. Treatment with the leukotriene receptor antagonist montelukast reduces both the early- and late-phase reactions to allergen. This randomized study evaluated the effects of a single dose of montelukast, in addition to short-acting β-agonist, on the late-phase airway response to inhaled allergen.

Thirty-five young adult patients with mild asthma and sensitization to house dust mite underwent bronchial allergen challenge on two occasions. A single dose of salbutamol was given after the early allergic response. In double-blind crossover fashion, patients then received montelukast 10 mg or placebo.

Baseline exhaled nitric oxide levels were lowest for subjects with no early allergic response, higher for those with an early response, and highest for those with a dual response. The difference was significant for patients with no early response versus those with a dual response. In 12 subjects with a dual response, area under the FEV_1 time-response curve from 3 to 8 hours after allergen challenge compared to baseline was -0.77 with montelukast versus -2.47 with placebo.

For patients with mild asthma, a single dose of montelukast given immediately after the early response to inhaled allergen significantly reduces the late allergic response. Clinical trials of "on-demand" treatment with montelukast are warranted.

COMMENT: *This study supports the effectiveness of montelukast in blocking the late-phase reaction. Further evidence indicates that Singulair has important, if not potent, anti-inflammatory activity.*
B. E. C.
Rosewich M, Rose MA, Eickmeier O, et al: Montelukast as add-on therapy to β-agonists and late airway response.
Eur Respir J. 2007;30:56-61. ♦♦

Montelukast vs Placebo vs Salmeterol for Prevention of EIB

BETA-2 Agonist is the standard for prevention of exercise-induced bronchoconstriction (EIB). Montelukast has also shown to protect against EIB. This randomized trial assessed the onset and duration of montelukast's protective effect against EIB, including comparison with salmeterol.

The three-way crossover trial included 47 adult patients with EIB, defined as a 20% to 40% reduction in FEV_1 (Δ FEV_1) after exercise. In separate sessions, patients received oral montelukast 10 mg, inhaled salmeterol 50 µg, and placebo in random order. Each treatment was followed by exercise challenges at 2, 8.5, and 24 hours. The main outcome of interest was maximum Δ FEV_1 2 hours after treatment.

Least squares mean for maximum Δ FEV_1 magnitude at 2 hours were 13.2% with montelukast versus 21.8% with placebo. Montelukast was also associated with a smaller Δ FEV_1 magnitude at 8.5 hours, 11.7% versus 16.8%; and 24 hours, 10.0% versus 14.0%. Other outcome measures, including recovery time and need for rescue β-agonists, also favored montelukast. Salmeterol was about as effective as montelukast at 2.5 and 8 hours, but less effective at 24 hours.

A single dose of montelukast before exercise is effective in preventing EIB. The protective effect begins within 2 hours and lasts through at least 24 hours. The protective effect of montelukast is similar to but longer-lasting than that of salmeterol.

COMMENT: *Montelukast has previously been shown to protect against EIB with just a single dose taken 2 hours before exercise. This study shows that montelukast also protects against EIB up to 24 hours after a single dose. Using salmeterol as a positive control comparator strengthens the study, and it is of interest that the magnitude of protection with montelukast was similar to that afforded by salmeterol. It would be of interest to study refractory EIB patients to see if the combination of an inhaled β-agonist plus a leukotriene antagonist is superior to either agent alone.*
S. A. T.
Philip G, Pearlman DS, Villarán C, et al: Single-dose montelukast or salmeterol as protection against exercise-induced bronchoconstriction.
Chest. 2007;132:875-883. ♦♦

Montelukast Doesn't Help in Atopic Eczema

MONTELUKAST has proven effective in the treatment of asthma and seasonal allergic rhinitis. Preliminary results suggest that it may also be helpful in atopic eczema, which involves inflammatory cells and mediators similar to those involved in asthma. Montelukast was evaluated for efficacy in atopic eczema.

The randomized controlled trial included 66 adult patients with moderately severe atopic eczema, defined as a six-area, six-sign atopic dermatitis (SASSAD) score of 12 to 50. After 2 weeks of single-blind treatment with placebo, patients received 8 weeks of double-blind treatment with montelukast 10 mg/d or placebo. A seven-point scale was used to assess treatment response. Assessment also included monitoring of SASSAD scores, along with other outcomes.

Fifty-four patients completed the study; baseline disease severity was similar between groups. All outcomes were comparable with montelukast compared to placebo--improvement in mean SASSAD score was 1.41 versus 1.76, respectively. Most adverse effects were mild, although there was one episode of septicemia in the montelukast group.

Montelukast does not appear effective in the treatment of atopic eczema. The results argue against the theory that cysteinyl leukotrienes play an important role in the pathogenesis of this disease.

COMMENT: *Since montelukast has been successful in treating asthma, allergic rhinitis, and chronic urticaria, why not use it for eczema? This carefully controlled trial addressed that question, and the results suggest that in fact montelukast is not an effective treatment for atopic dermatitis.*
S. A. T.
Friedmann PS, Palmer R, Tan E, et al: A double-blind, placebo-controlled trial of montelukast in adult atopic eczema.
Clin Exp Allergy. 2007;37:1536-1540. ♦♦

What's the Risk of Asthma after Atopic Eczema?

THE "atopic march" refers to the common pattern in which young children with atopic eczema (AE) progress to asthma by school age. Reported rates of asthma developing among young children with AE have varied widely. A systematic review and meta-analysis was performed to clarify the relationship between early childhood AE and later asthma risk.

A review of the literature identified 13 prospective cohort studies of childhood asthma risk among children with AE developing in the first 4 years of life. In four birth cohort studies including 3,103 children, the pooled odds ratio for asthma among children with AE was 2.14, compared to children without eczema. In nine eczema cohort studies, asthma prevalence at age 6 was 35.8% in inpatients and 29.5% in a combined group of inpatients and outpatients.

Atopic eczema in early childhood is associated with an increased risk of asthma at school age. Nevertheless, only about one-third of young children with AE will go on to develop asthma--a lower risk than previously thought. More research is needed to clarify the complex relationship between AE and asthma.

COMMENT: *Using 13 prospective cohort studies pooling data from 5,381 children, these Dutch researchers report a twofold increased risk of developing asthma in infants with AE, compared to those without AE. Interestingly, only one-third of younger* ➤➤

children with AE will actually develop asthma in later childhood. This can be very reassuring when counseling parents of infants with eczema. Most patients don't continue with the "allergic march."
S. M. F.
A van der Hulst A, Klip H, Brand PLB, et al: Risk of developing asthma in young children with atopic eczema: a systemic review.
J Allergy Clin Immunol. 2007;120:565-569. ♦♦

Early Eczema Predicts Later Atopy

ALLERGIC sensitization in early childhood increases the risk of later wheezing and airway hyperresponsiveness. However, little is known about early clinical predictors of sensitization developing later in childhood. This question was addressed using data from 18-month and 5-year evaluations in subjects from the Childhood Asthma Prevention Study.

Among children who were not sensitized at age 18 months, eczema was associated with an increased likelihood of sensitization at age 5: adjusted relative risk (RR) 1.67. Wheezing, asthma, or rhinitis at 18 months did not predict the onset of sensitization by age 5. For children who were symptom-free at 18 months, sensitization increased the risk of several allergic disease outcomes at age 5: wheezing, RR 2.41; asthma, RR 4.66; and rhinitis, RR 1.77. However, early sensitization did not predict later onset of eczema.

Eczema in young children is a risk factor for onset of sensitization later in childhood. Thus early treatment of eczema may reduce the risk of later sensitization.

COMMENT: *The "atopic march" is very familiar to those of us who care for small children, and it is well-known that atopic infants and toddlers who have eczema are at high risk of developing asthma. This study focused on a nonsensitized subset of 18-month-olds, and showed that eczema is a stronger risk factor than early wheezing for the subsequent development of atopy.*
S. A. T.
Almqvist C, Li Q, Britton WJ, et al: Early predictors for developing allergic disease and asthma: examining separate steps in the 'allergic march.'
Clin Exp Allergy. 2007;37:1296-1302. ♦♦

Asthma Increases Risk of Adverse Pregnancy Outcomes

MATERNAL asthma is present in up to 8% of pregnancies. There have been few studies on the risks of using inhaled medications for asthma during pregnancy--recommendations to continue taking asthma medications are based on reports of adverse outcomes in women with severe asthma or requiring hospital care. A Medicaid database was analyzed to assess the effects of maternal asthma and disease control on pregnancy outcomes.

The analysis included data on 140,299 singleton pregnancies in black or white women enrolled in the Tennessee Medicaid program between 1995 and 2003. About 40% of the women were black. Claims data were used assess the impact of maternal asthma and asthma exacerbations on the pregnancy and perinatal outcomes.

Overall, 6.5% of the pregnant women in the study had asthma: 7.8% of white women and 4.6% of black women. Twenty-three percent of women had "exacerbated" asthma, defined as emergency department or hospital care for asthma during pregnancy. Infants of asthmatic mothers had reduced birth weights, after controlling for race and other factors: an average of 38 g lower overall, and 56 g lower for infants of mothers with exacerbated asthma.

Asthmatic women had higher rates of hypertensive disorders of pregnancy, membrane-related disorders, preterm labor, antepartum hemorrhage, and cesarean delivery. All of these risks were further increased with exacerbated asthma. Risks of preterm birth and birth defects were not increased for asthmatic women.

Medicaid data suggest that pregnant women with asthma are at increased risk of preterm labor and other adverse pregnancy outcomes. Risks are further elevated for women with poorly controlled asthma. Efforts to improve asthma treatment during pregnancy might improve maternal-fetal outcomes, particularly for African-American women.

COMMENT: *The data from this large population of 9,154 pregnant women on Medicaid are revealing in that there was a very low rate of continued use of controller medication, with only a 6.5% refill rate. Not surprisingly there was a high incidence of asthma exacerbations--23% of patients. We need to improve our education of this population to reassure them that using controller medications during pregnancy will not harm the baby, and in fact, should improve overall outcomes.*
S. M. F.
Enriquez R, Griffin MR, Carroll KN, et al: Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes.
J Allergy Clin Immunol. 2007;120:625-630. ♦♦

Omalizumab Yields Responses in EGIDs

THE increasingly recognized eosinophil-associated gastrointestinal disorders (EGIDs) are associated with atopy in about three-fourths of patients. Many questions remain about the pathogenesis and treatment of these conditions. A clinical trial of anti-IgE therapy for EGIDs is reported.

The open-label study included 9 patients with EGID, based on the presence of typical gastrointestinal symptoms with 25 or more eosinophils per hpf in stomach or duodenal biopsy specimens and exclusion of other diagnoses. All patients received subcutaneous omalizumab every 2 weeks for a total of eight treatments. In addition to clinical outcomes, evidence for the role of IgE in the pathogenesis of EGID was evaluated. ➤➤

After 16 weeks of omalizumab treatment, absolute eosinophil count had decreased by 34%. Eosinophil counts in duodenum and gastric antrum biopsies non-significantly decreased, with no change in esophageal eosinophil count. Free IgE was significantly decreased, as were basophil and dendritic cell FcεRI expression. There was a 170-fold increase in allergen concentration needed to produce half-maximal basophil activation.

On allergen skin-testing, the wheal response was decreased by 78% and erythema by 82%. Symptom scores were reduced by 63% at 8 weeks and 70% at 16 weeks.

Responses to anti-IgE therapy suggest that IgE-mediated processes contribute to eosinophilic inflammation in EGIDs. The responses to omalizumab in this small trial suggest that anti-IgE therapy might be beneficial in patients with EGIDs.

COMMENT: *Eosinophilic gastrointestinal disorders can be difficult to treat. Often, major dietary changes and corticosteroids are necessary to achieve clinical improvement. The extent to which IgE-mediated processes contribute to the disease is not known. This was an open-label uncontrolled study of anti-IgE therapy for 16 weeks. It showed promising effects on tissue eosinophilia in some, but not all, tissue locations and on symptoms.*
R. J. M.
Foroughi S, Foster B, Kim N, et al: Anti-IgE treatment of eosinophil-associated gastrointestinal disorders.
J Allergy Clin Immunol. 2007;120:594-601. ♦♦

Allergen Sensitization in the Absence of Disease

THE reasons for racial and other variations in allergic sensitization and respiratory allergies remain unclear. Information on allergic sensitization in differing socioeconomic and racial groups has implications for understanding the contribution of environmental allergens. Racial and socioeconomic factors associated with allergic sensitization were analyzed in children with no family history of atopy.

The study included 275 children and adolescents, mainly of low socioeconomic status, recruited from an urban children's hospital dental clinic. None had any personal or family history of allergic disease and symptoms. Each child underwent skin prick testing using 11 allergen panels. Race and other factors associated with sensitization were assessed, along with the impact of sensitization on quality of life.

The overall rate of allergic sensitization was 39%. Of sensitized children, 68% tested positive to more than one allergen and 41% to three or more allergens. On multivariate analysis, African-American race was significantly associated with any sensitization, odds ratio 2.17; and with sensitization to any outdoor allergen, odds ratio 2.96. Mean atopic index was 0.63 for Caucasian children versus 1.54 for African-American children. Quality-of-life impact was low, with no significant difference between sensitized versus nonsensitized children.

About 40% of children with no personal or family history of atopy show evidence of allergic sensitization on skin-prick testing. Sensitization is more common among African-American than Caucasian children, especially to outdoor allergens. The clinical significance of this sensitization, which appears to have little or no impact on quality of life, warrants further study.

COMMENT: *This study assesses prevalence of allergen sensitization, defined by positive skin prick test, in the absence of a history of illness or family history. Thirty-nine percent of the pediatric subjects showed at least one positive skin test. No prospective assessment of potential allergic disease was undertaken, which would have been beneficial. After all, no test has perfect positive predictive value.*
K. R. M.
Stevenson MD, Sellins S, Grube E, et al: Aeroallergen sensitization in healthy children: racial and socioeconomic correlates.
J Pediatr. 2007;151:187-191. ♦♦

A Lie Is Still a Lie, No Matter How It Is Told

MOST studies of compliance with asthma treatment rely on patient and parent self-reports, which have been shown to be highly inaccurate. Several factors may influence the accuracy of self-reporting--including the potential for embarrassment. Different reporting modes were compared for their effects on the accuracy of self-reported medication use by children with asthma.

The study included 104 children with asthma who were being treated with inhaled corticosteroid delivered via metered-dose inhaler. The children and their parents were randomly assigned to one of three self-report formats: computer-assisted self-interview, face-to-face interview with research staff, or paper-and-pencil questionnaire. At four monthly visits, parents and children were separately asked to provide information on medication adherence in the previous day and week. Responses were compared with data from an electronic monitoring device.

For all three modes, both parents and children greatly overreported medication use over the past day and the past month. About one-third of reports claimed full adherence, whereas the inhaler had not been used at all. Even under the most accurate condition--children interviewed in person about medication use in the past day--only about half of reports were accurate. Nearly half of the remaining subjects overstated adherence by more than 25%.

The researchers had hypothesized that computer reporting would improve accuracy by reducing embarrassment. In fact, the largest overreports of adherence were noted in the computer-assisted interviews.

None of the three reporting formats assessed yields accurate self-report data on medication use by children with asthma. Electronic monitoring or other objective methods are needed to assess patient adherence to prescribed medication. ➤➤

COMMENT: *The findings of this thorough study are disturbing to consider, as many clinical studies of asthma still rely on patient or parent self-report of compliance. According to this study, a self-report from even the previous day was only 50% reliable, with a face-to-face interview; the reliability of the report declined further with computer reporting. Overestimations of compliance accounted for all inaccuracies, with one-third blatantly professing 100% compliance with an inhaler never used! In addition to their use in studies, wouldn't it be helpful to have electronic monitoring devices on the inhalers of all patients with poorly-controlled asthma?*
K. R. M.
Bender BG, Bartlett SJ, Rand CS, et al: Impact of interview mode on accuracy of child and parent report of adherence with asthma-controller medication.
Pediatrics. 2007;120:e471-e477. ♦♦

Parents' Medication Beliefs Affect Adherence

PARENTS' beliefs about their child's asthma and its treatment may affect medication adherence. One small study of urban children with asthma suggested that strong parental concerns about medications were associated with poor medication adherence. This study assessed parental beliefs regarding children's asthma medications and the impact of those beliefs on adherence.

A sample of parents of asthmatic children in southeast Michigan were surveyed using the Beliefs About Medications Questionnaire. This previously validated instrument addressed two subscales addressing positive and negative beliefs regarding the necessity for and concern about the children's medications. A "necessity-concern differential score" was calculated to reflect the parents' weighting of these beliefs. Adherence to daily preventive asthma medications was assessed using the Medication Adherence Scale.

The study included responses from parents of 622 children, representing a response rate of 72%. Eighty-four percent of the respondents were nonminority. Seventy-two percent of parents believed their child's medications were necessary, while 30% expressed strong concerns about the medications. Necessity scores outweighed concern scores for 77% of parents, while concerns exceeded necessity for 17%. Necessity was more likely to outweigh concern for nonminority parents: 79%, compared to 68% for minority parents.

Medication adherence increased along with the necessity-concern differential. Both nonminority status and higher necessity-concern differential were independent predictors of improved adherence.

Parents' beliefs regarding their child's asthma medications have a significant impact on medication adherence. A better understanding of the balance between positive and negative parental beliefs might lend useful insights for counseling to improve adherence.

COMMENTS: *This is the first study to assess the potential influence of both positive and negative medication beliefs on reported adherence, within the same study. The results may not be surprising: that positive beliefs correlate with possible increased adherence, and vice versa. I say "possible," in reference to the preceding study indicating that self-reported medication adherence is quite unreliable.*
K. R. M.
Conn KM, Halterman JS, Lynch K, Cabana MD: The impact of parents' medication beliefs on asthma management.
Pediatrics. 2007;120:e521-e526. ♦♦

Hygiene Hypothesis May Apply to Juvenile IBD Too

THE rising rate of Crohn's disease (CD) in industrialized countries suggests an environmental contribution to this and other inflammatory bowel diseases (IBDs). The "Hygiene Hypothesis" could play a role--studies of respiratory allergies report reduced disease rates among people exposed to farm animals at an early age. The multicenter study assessed the relationship between contact with farm animals and risk of juvenile IBD.

The case-control study included 748 children, aged 6 to 18 years, receiving treatment for IBD at German centers: 444 with CD and 304 with ulcerative colitis. Controls were 1,481 children undergoing strabismus surgery at the same hospitals. Cases with IBD were more likely to live in urban areas. Children with CD were more likely to be diagnosed with rhinitis--odds ratio (OR) 1.6.

Having regular contact with farm animals during the first year of life was associated with a lower likelihood of both forms of IBD: OR 0.5 for CD and 0.4 for ulcerative colitis. Neither diagnosis was related to pet exposure.

Early-life exposure to farm animals is linked to a lower risk of juvenile IBD. Although confirmatory studies are needed, the results suggest pathophysiologic similarities between atopic diseases and IBD.

COMMENT: *This German study is the first to assess the impact of early farm exposure on juvenile IBD, which has shown an increasing incidence in industrialized nations. Does this sound familiar? Just as in Th2-mediated illness, Th1-mediated diseases such as IBD might be promoted by lack of early immune stimulation. Interestingly, a study subset (those with Crohn's disease) also showed an increase in allergic rhinitis.*
K. R. M.
Radon K, Windstetter D, Poluda AL, et al: Contact with farm animals in early life and juvenile inflammatory bowel disease: a case-control study.
Pediatrics. 2007;120:354-361. ♦♦

Airway Function in Infancy Predicts Lung Function at Age 22

PULMONARY function in young adulthood is a major predictor of the later risk of chronic obstructive pulmonary disease (COPD). It is unclear ➤➤

whether airway function in newborns predicts lung function at maturity. This issue was addressed using long-term follow-up data from a birth cohort study.

The analysis included 164 non-selected infants enrolled in the Tucson Children's Respiratory Study at birth, between 1980 and 1984. Airway function was measured shortly after birth using maximal expiratory flow at $Vmax_{FRC}$ and by chest compression at a mean age of 2.3 months. In addition, 123 children underwent lung function measurement at ages 11, 16 and 22 years, including FEV_1, FVC, and FEF_{25-75}.

Infants with low $Vmax_{FRC}$ in infancy had lower lung function at age 22. With adjustment for age, sex, height, and weight, being in the lowest quartile for $Vmax_{FRC}$ in infancy was associated with a 5.2% reduction in FEV_1/FVC ratio in young adulthood, compared to the three upper quartiles combined. There was also a 663 mL/s reduction in FEF_{25-75} and a 233 mL reduction in FEV_1. The associations were little affected by further adjustment for wheezing, smoking, atopy, or family history of asthma.

Newborns with poor airway function may be at risk of airway obstruction in young adulthood. Efforts to prevent COPD may need to begin even before birth.

COMMENT: *Prior studies have suggested that deficits in lung function during the third decade of life especially in individuals with a diagnosis of asthma--persist into late adulthood and predispose to COPD, along with smoking. Factors that affect pulmonary in utero development are not well understood. Lung morphogenesis is affected by both genetic and environmental factors. The new findings show that infants who have Vmax in the lowest quartile have lower values for FEV_1/FVC ratio, FEF_{25-75} and FEV_1 up to age 22 years. Poor airway function shortly after birth should be recognized as a risk factor for airway obstruction in young adults.*

M. F.

Stern DA, Morgan WJ, Wright AL, et al: Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study.
Lancet. 2007;370:758-764. ♦♦

Study Compares Subgroups of Chronic Urticaria

PATIENTS with chronic urticaria may fall into differing etiologic subgroups: physical urticaria (PU), autoimmune urticaria (AIU), and chronic idiopathic urticaria (CIU). The clinical and laboratory findings of these three subgroups were compared.

One hundred nine patients with chronic urticaria were evaluated, including a questionnaire, urticaria score, autologous serum skin test (ASST), basophil CD63 surface expression assay, and levels of thyroid autoantibodies. Clinical and laboratory parameters were compared for patients in the three diagnostic subgroups, along with the effectiveness of different treatments. The diagnosis of AIU was based on a positive basopil CD63 assay.

Patients with AIU had significantly higher total urticaria scores. Patients with AIU were also more likely to have a personal history of autoimmune diseases and a family history of other types of urticaria, and a higher rate of detectable antithyroid antibodies. Antihistamine therapy was effective in only 12.8% of AIU patients, compared with about 70% of the PU and CIU groups.

Of the three subgroups of chronic urticaria, AIU appears to be the most severe. Patients in the autoimmune subgroup are also less likely to respond to antihistamine therapy than those with PU and CIU, who are similar in most characteristics.

COMMENT: *Chronic urticaria presents a challenge to the allergist-immunologist. It is a heterogeneous disorder with estimates of 35% for both PU and CIU and 25% for AIU. Several investigators have evaluated AIU patients, who have serum antibodies to the α chain of the high affinity IgE receptor (FcεRIα), IgE alone using the ASST, or basophil histamine release test. These authors discuss references showing that there is no evidence that anti-thyroid antibodies have a pathogenic role in the development of chronic urticaria, and that the ASST cannot be used alone either to predict the severity of disease or define it as autoimmune. They also state that the CD63 assay, which is less expensive and less time consuming, seems to be a convenient reliable functional assay for AIU.*

M. F.

Irinyi B, Szeles G, Gyimesi E et al: Clinical and laboratory examinations in the subgroups of chronic urticaria.
Int Arch Allergy Immunol. 2007;144:217-225. ♦♦

Airway Remodeling Linked to Epithelial Cell Proliferation

PATIENTS with severe asthma are at risk of airway structural changes, or remodeling, including subepithelial fibrosis, smooth muscle hypertrophy, and blood vessel hyperplasia. This study evaluated airway epithelial structure and function in patients with severe asthma.

The investigators evaluated bronchial biopsy specimens from 31 patients with severe asthma, as well as from 11 patients with chronic bronchitis, 9 patients with mild asthma, and 21 normal controls. The study included evaluations of epithelial cell morphology, measures of cellular proliferation and death, and apoptotic activity.

Samples from patients with severe asthma showed increased airway epithelial and lamina reticularis thickness, while epithelial desquamation was similar across groups. Severe asthma was associated with decreased active, phosphorylated Rb expression and increased Ki67, consistent with increased cellular proliferation; and decreased Bcl-2 expression, reflecting reduced suppression of cell death. Airway cell apoptosis was also increased in severe asthma.

Airway specimens from patients with severe asthma show increased cellular proliferation, with thickening of the epithelium and lamina reticularis. These abnormalities may play a role in decreased pulmonary func-➤➤

tion and ongoing airway remodeling. Cellular proliferation may be a useful target for treatments to prevent airway remodeling in severe asthma.

COMMENT: *This study of severe asthmatics from the Severe Asthma Research Program group allows better understanding of the mechanisms of structural changes in the airway.*
B. E. C.
Cohen L, E X, Tarsi J, et al: Epithelial cell proliferation contributes to airway remodeling in severe asthma.
Am J Respir Crit Care Med. 2007;176:138-145. ♦♦

Allergic Rhinitis Linked to Poor Performance on Summer Exams

SEASONAL allergic rhinitis (SAR) is a common childhood problem, with a peak age of onset during the teen years. Previous studies performed under laboratory conditions have suggested that SAR adversely affects learning ability. Important school exams are often given in the late spring/early summer, when grass pollen counts are highest. This study evaluated the effects of SAR on British adolescents' performance on national exams.

The case-control study included 1,834 students, aged 15 to 17 years, taking U.K. national exams, the results of which have important implications for the students' future education and career. The case group consisted of students who dropped one or more grade in any of three core subjects between the practice exams, given in winter; and the final exams, given in summer--36% of all students. The remaining students, whose grades remained the same or improved, served as controls. The day before the exam, students completed questionnaires assessing allergic rhinitis symptoms, clinician diagnosis of SAR, and medication use, along with potential confounders. Associations between SAR and exam performance were assessed using multilevel regression models

Symptoms of SAR were reported on exam days by 38% to 43% of students; medication use was reported by 19% to 23% of students. On adjusted analysis, case students were significantly more likely to experience allergic rhinitis symptoms during the exam period: odds ratio (OR) 1.4. Students with decreased performance were also more likely to have taken any SAR medications, OR 1.4; and to have taken sedating antihistamines, OR 1.7.

The results suggest that symptoms of SAR, along with the use of medications for allergic rhinitis, are associated with drops in performance on U.K. national exams by adolescent students. Further study would be needed to assess ways of addressing the bias against students with SAR--for example, through intensive case management or by changing the time of year in which exams are given.

COMMENT: *Using case-control methodology, these researchers found that British students with symptomatic SAR had poorer performance on standardized exams given in May and June than their non-afflicted counterparts. Fewer than half of the students took antihistamines, and only 28% of these used potentially sedating chlorpheniramine. The data suggest that student test performance can be detrimentally affected by allergen exposure during pollen season. Should we advise our patients not to schedule SATs during spring pollen season?*
S. M. F.
Walker S, Khan-Wasti L, Fletcher M, et al: Seasonal allergic rhinitis (SAR) is associated with a detrimental effect on examination performance in United Kingdom teenagers: case-control study.
J Allergy Clin Immunol. 2007;120:381-387. ♦♦

Kallikrein Inhibitor Is Effective for Acute HAE Attacks

HEREDITARY angioedema (HAE) is a rare genetic disorder caused by an autosomal dominant mutation of the C1 inhibitor gene. Recent studies have shown that HAE attacks result from overactivation of the kallikrein-kinin (contact) cascade, resulting in generation of bradykinin. Ecallantide is a new recombinant protein that acts as a potent kallikrein inhibitor. A placebo-controlled trial was performed to evaluate the effects of ecallantide on symptoms of recurrent HAE attacks.

The multicenter trials included 49 patients experiencing acute attacks of HAE. Patients were randomly assigned to receive one of four doses of ecallantide--5, 10, 20, or 40 mg/m^2 IV--or placebo. The main efficacy outcome was the percentage of patients reporting significant improvement at the primary attack site (abdominal, laryngeal, or peripheral)--within 4 hours after treatment.

Significant symptom improvement occurred within 4 hours in 72.5% of patients receiving ecallantide, compared with 25.0% of the placebo group. The response rate was highest, 90%, at the 40 mg/m^2 dose of ecallantide; the difference between ecallantide and placebo was significant for peripheral attacks. All four doses were well tolerated.

The kallikrein inhibitor ecallantide is a safe and effective treatment for acute HAE attacks. Ecallantide offers a new therapeutic approach to a condition with limited treatment options. The results also add to the evidence for involvement of the kallikrein-kinin cascade and bradykinin in the pathophysiology of HAE.

COMMENT: *Hereditary angioedema due to a deficiency of C1 esterase inhibitor is a life-threatening condition that has few treatment options, and they are cumbersome. Epinephrine has little or no acute effect. Lately it has been shown that bradykinin, produced by the action of kallikrein, is the mediator most responsible for the clinical condition. This is the first placebo-controlled study of a new kallikrein inhibitor, ecallantide, in humans. It works pretty well to attenuate acute attacks. Until we can get C1 inhibitor concentrate in this country, this may be our best option.*
R. J. M.
Schneider L, Lumry W, Vegh A, et al: Critical role of kallikrein in hereditary angioedema pathogenesis: ➤➤

a clinical trial of ecallantide, a novel kallikrein inhibitor.
J Allergy Clin Immunol. 2007;120:416-422. ♦♦

CLINICAL TIDBITS

Maintenance Venom Immunotherapy: How Far Can You Go?

THERE have been several attempts to extend treatment intervals in patients undergoing maintenance venom immunotherapy (MVIT). However, there are few published data on the effects of intervals longer than 3 months.

In a series of 47 patients, the investigators gradually extended the interval between MVIT treatments from 3 to 6 months. One patient had a systemic reaction after being treated at a 4-month interval. Two field stings occurred in two patients, one of whom had a mild systemic reaction. After the 6-month interval was reached, deliberate sting challenges were performed in 14 patients allergic to bee venom, producing systemic reactions in 3 patients. After resuming regular monthly MVIT, these patients all tolerated repeated sting challenges.

Extending the MVIT interval from 3 to 6 months does not provide adequate protection. Patients allergic to bee venom should continue to be treated at the standard interval of 1 to 3 months.

COMMENT: *How far can you go? Apparently 3-month intervals are a consideration for maintenance venom immunotherapy, but 6-month intervals are not. I doubt many of us would have considered extending the interval beyond 3 months, but you now have data showing that is not a good idea. Venom immunotherapy can only go so far.*
D. K. L.
Goldberg A, Confino-Cohen R: Effectiveness of maintenance bee venom immunotherapy administered at 6-month intervals.
Ann Allergy Asthma Immunol. 2007:99:352-357. ♦♦

Omalizumab May Help in Chronic Urticaria

UP to half of patients with chronic urticaria have an autoimmune profile. Good responses to omalizumab are described in 3 patients with chronic, refractory urticaria. All patients had longstanding chronic urticaria that failed to respond to maximal therapy with antihistamines, antileukotrienes, and H2 blockers. In each case, systemic steroids yielded only temporary improvement.

All patients were started on omalizumab therapy, given every 2 weeks. Urticaria resolved completely within 1 week after starting treatment in 2 patients, and within 6 weeks in the third patient. One patient had an elevated anti-IgE receptor antibody level, which normalized after the start of omalizumab therapy.

Treatment with omalizumab may help patients with chronic refractory urticaria. Further study is needed to evaluate the effectiveness and mechanisms of this treatment.

COMMENT: *This small case series adds additional evidence supporting the use of omalizumab for refractory urticaria. The rapid improvement in two subjects, within 1 week, is surprising if the mechanism of action is down regulation of the high affinity IgE receptor. Time will tell, but any reasonably safe treatment is welcome for these patients who are frustrated and looking for help.*
D. K. L.
Spector SL, Tan RA: Effect of omalizumab on patients with chronic urticaria.
Ann Allergy Asthma Immunol. 2007;99:190-193. ♦♦

Zileuton CR Now Available

A new controlled-release (CR) formulation of the leukotriene inhibitor zileuton allows twice-daily administration. The effectiveness of treatment with zileuton CR was evaluated in a randomized trial of 613 asthma patients who were receiving short-acting beta-agonists only. One group received zileuton CR, 1,200 mg twice daily, while another group received twice-daily placebo. Two smaller groups received zileuton immediate release (IR), 600 mg four times daily, or placebo four times daily.

By 12 weeks, FEV_1 improved by a mean of 0.39 L (28.0%) in the zileuton CR group, compared to 0.27 L (12.7%) in the corresponding placebo group. Treatment with zileuton CR was associated with significant reductions in beta-agonist use and asthma exacerbations. There were no differences in adverse events. Threefold elevations in alanine aminotransferse occurred in 2.5% of patients receiving zileuton CR.

Zileuton CR offers a new twice-daily option for treatment of moderate persistent asthma. Safety and efficacy appear similar to zileuton IR given four times daily.

COMMENT: *As specialists, we frequently encounter patients who do not respond to standard pharmacologic therapy for asthma--generally inhaled corticosteroids with long-acting beta-agonists and leukotriene receptor antagonists. Having an alternative is attractive, and making zileuton a twice-a-day option is a step forward. The problem is that we do not have a body of data to compare the efficacy of zileuton in these challenging patients, or in subjects with inadequate response to leukotriene receptor antagonists. This study comparing zileuton to placebo does not answer the question, but at least we will have it in the clinic to try.*
D. K. L.
Nelson H, Kemp J, Berger W, et al: Efficacy of zileuton controlled-release tablets administered twice daily in the treatment of moderate persistent asthma: a 3-month randomized controlled study.
Ann Allergy Asthma Immunol. 2007;99:178-184. ♦♦

Latex Allergy Persists at Long-Term Follow-up

HEALTH care workers (HCWs) with occupational allergy to natural rubber latex (NRL) are advised to avoid exposure to Hev b NRL allergens. The authors report a 5-year follow-up study of 34 HCWs with latex allergy, including changes in percutaneous reactivity to NRL and non-ammoniated latex (NAL) allergens.

Allergic symptoms were significantly reduced with avoidance of NRL. On serial skin tests, the chances of more than a 100-fold reduction in sensitivity to Hev b 2 and Hev b 7 were reduced for workers who had a history of systemic reactions to NRL, cross-reaction to foods, continued local reactions to NRL gloves, or continued high exposure to NRL gloves. Measurement of latex-specific IgE had a sensitivity of 54% and specificity of 87.5%, compared to NAL skin tests. Adding recombinant Hev b 5-enriched allergosorbent improved the diagnostic performance of the ImmunoCAP assay.

Even though symptoms improve with NRL avoidance, latex-allergic HCWs show evidence of continued sensitization at long-term follow-up. They should be advised to continue avoidance.

COMMENT: *Although the epidemic of new latex allergy cases has subsided, little is known about the long term immunologic fate of latex allergy patients. This study evaluated HCWs with latex allergy 5 years after their initial evaluation, including titrated prick skin tests and in vitro specific IgE testing. Not surprisingly, 70% of the subjects retained their skin test reactivity. However, their reactivity threshold improved dramatically in most cases. This study also exposes the deficiencies of in vitro latex IgE testing products that are not enriched with recombinant Hev B5.*
S. A. T.
Smith AM, Amin HS, Biagini RE, et al: Percutaneous reactivity to natural rubber latex proteins persists in health-care workers following avoidance of natural rubber latex.
Clin Exp Allergy. 2007;37:1349-1356. ♦♦

Early Childhood IgG_2 Subclass Deficiency May Be Transient

LOW levels of IgG_2 have been thought to increase the risk of infection, although recent reports have questioned this assumption. The natural history of low serum IgG_2 was studied in 13 children. All were found to have low IgG_2 at referral for evaluation of recurrent infections. The children were referred at a median age of 3.7 years.

During a median follow-up of 1.5 years, IgG_2 levels normalized in all patients. All children had an adequate immunologic response to immunizations, such as tetanus, polio, and pneumococcal vaccine. Four patients had a history of transient hypogammaglobulinemia.

Low serum IgG_2 in infants and young children resolves over a period of months to years. The findings suggest that low IgG_2 may represent the "tail end" of transient hypogammaglobulinemia.

COMMENT: *This small but important study supports the idea that IgG_2 subclass deficiency in infancy is a transient phenomenon, and may be the last vestige of transient hypogammaglobulinemia of infancy. Reassuring are the data showing resolution of the deficiency in all 13 study subjects, and the absence of invasive disease during follow-up.*
K. R. M.
Atkinson AR, Roifman CM: Low serum immunoglobulin G_2 levels in infancy can be transient.
Pediatrics. 2007;120:e543-e547. ♦♦

REVIEWS OF NOTE

COMMENT: *This is a very nice review of what will become state-of-the-art management of pediatric patients with HAE, once a C1 esterase inhibitor concentrate is widely available for use in the United States.*
K. R. M.
Farkas H, Varga L, Széplaki G, et al: Management of hereditary angioedema in pediatric patients.
Pediatrics. 2007;120:e713-e722. ♦♦

COMMENT: *This is an excellent review of a tough clinical problem. The bottom line is we remain limited to optimizing current therapy, looking for cofactors or alternative diagnoses, and resorting to systemic corticosteroids when necessary. Corticosteroid-sparing agents are out there, but it is very difficult to assess their value. Furthermore, most of these agents have significant risk. What is a clinician to do?*
D. K. L.
Randhawa I, Klaustermeyer WB: Oral corticosteroid-dependent asthma: a 30-year review.
Ann Allergy Asthma Immunol. 2007;99:291-303. ♦♦

COMMENT: *This is an excellent, readable summary of role of T regulatory cells in immune dysregulation, with clinical applications.*
S. F. W.
Larché M: Regulatory T cells in allergy and asthma.
Chest. 2007;132:1007-1014 ♦♦

COMMENT: *This is an important summary of T cell involvement in the allergic reaction.*
B. E. C.
Beler KC, Kallinch T, Hamelmann E: T-cell co-stimulatory molecules: novel targets for the treatment of allergic airway disease.
Eur Respir J. 30:383-390. ♦♦

COMMENT: *This review does not support a clear association between early exposure to indoor allergens and the acquisition or persistence of asthma. This* ➤➤

is not consistent with the results reported by Illi et al (Lancet. 2006;368:763-770). It should also be noted that this article is not referenced in the discussion.
B. E. C.
Torrent M, Sunyet J, Garcia R, et al: Early-life allergen exposure and atopy, asthma, and wheeze up to 6 years of age.
Am J Respir Crit Care Med. 2007;176:446-453. ♦♦

COMMENT: *This review helps to put in perspective the clinical presentation and ramifications of chronic structural changes secondary to persistent asthma.*
B. E. C.
James AL, Wenzel S: Clinical relevance of airway remodeling in airway diseases.
Eur Respir J. 2007;30:134-155. ♦♦

COMMENT: *Along with the "hygiene hypothesis" for the increasing prevalence of allergy worldwide came the notion that introducing benign gram-negative bacteria into the gastrointestinal tract might have a salutary effect on the prevention of allergy. These bacterial preparations have become known as probiotics and have strong lay proponents. However, the scientific research into their clinical effects has been disappointing. To date, the only benefit in some (but not all) studies has been on atopic dermatitis. This article is a review of the data on probiotics for those who haven't already made up their minds.*
R. J. M.
Prescott SL, Björkstén B: Probiotics for the prevention or treatment of allergic diseases.
J Allergy Clin Immunol. 2007;120:255-262. ♦♦

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