AllergyWatch®

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

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FOCUS ON ASTHMA

IN a single issue of the *New England Journal of Medicine*, the treatment of mild persistent asthma turned up in three different articles.

Fluticasone-Salmeterol vs Montelukast for Step-Down Therapy

ONCE persistent asthma is brought under control by inhaled corticosteroids, guidelines call for therapy to be "stepped-down" to the minimal level required for symptom control. Studies of options for step-down therapy have focused on moderate or severe asthma. This randomized trial compared two approaches to step-down therapy in patients with mild persistent asthma.

The multicenter study included 500 patients who achieved "acceptable" asthma control after 4 to 6 weeks of open-label treatment with inhaled fluticasone propionate, 100 µg twice daily. One group continued on the same dose of fluticasone. Another group was switched to montelukast, 5 or 10 mg per night; while a third group was switched to fluticasone 100 µg plus salmeterol 50 µg per night. After 16 weeks, time to treatment failure and other outcomes were assessed in double-blind fashion.

Treatment failure rate was about 20% with continued twice-daily fluticasone and with once-daily fluticasone plus salmeterol. For patients switched to montelukast, the failure rate was 30%--hazard ratio 1.6 compared with the other two groups. Percentage of asthma-free days was around 80% in all three groups. Mean prebronchodilator FEV_1 was higher in the two fluticasone groups than with montelukast.

For patients with mild persistent asthma that is well-controlled with twice-daily inhaled fluticasone, step-down therapy with once-daily fluticasone plus salmeterol provides the same level of asthma control. The treatment failure rate is higher for patients with once-daily montelukast, although this regimen also provides good control for most patients.

COMMENT: *Treatment recommendations for mild persistent asthma have recommended stepping*➤➤

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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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down therapy, especially steroids, to the lowest effective dose. This study examines two optional strategies to step down from twice-daily inhaled fluticasone: daily montelukast or once-daily fluticasone-salmeterol combination inhaler. Both worked for many patients, but the combination inhaler once a day was superior.
R. J. M.
The American Lung Association Asthma Clinical Research Centers: Randomized comparison of strategies for reducing treatment in mild persistent asthma.
N Engl J Med. 2007; 356:2027-2039. ♦♦

As-Needed Beclomethasone/Albuterol for Mild Persistent Asthma

REGULAR inhaled corticosteroids are the recommended treatment for mild persistent asthma. Evidence suggests that inhaled corticosteroids may enhance the effects of β_2-agonists. This trial evaluated the effectiveness of symptom-driven use of beclomethasone dipropionate plus albuterol, in a single inhaler, for control of mild persistent asthma.

The "Beclomethasone plus Salbutamol Treatment" (BEST) study included 455 patients with mild persistent asthma at 25 European centers. Mean FEV_1 was 2.96 L, or 88.36% of predicted. After a 4-week run-in period, patients were randomly assigned to receive as-needed beclomethasone 250 µg plus albuterol 100 µg in a single inhaler; as-needed albuterol only; twice-daily beclomethasone plus as-needed albuterol; or twice-daily beclomethasone/albuterol, plus as-needed albuterol. Treatment continued for 6 months--the main outcome of interest was morning peak expiratory flow rate.

During the last 2 weeks of treatment, morning peak expiratory flow rate was higher for patients taking as-needed beclomethasone/albuterol, compared to as-needed albuterol only. As-needed combination therapy was also associated with a reduced number of exacerbations, compared with albuterol alone. Outcomes in the as-needed beclomethasone/albuterol group were not significantly different from those of patients taking regular beclomethasone, with or without albuterol. Cumulative inhaled beclomethasone dose was 18.48 mg in the as-needed combination group, compared to approximately 77 mg in the two regular beclomethasone groups.

The BEST study results demonstrate the effectiveness of as-needed combination therapy with inhaled beclomethasone 250 mg plus albuterol 100 mg for patients with mild persistent asthma. Outcomes are superior to those of as-needed albuterol only and comparable to those of regular inhaled beclomethasone, with a substantially lower inhaled corticosteroid dose. Symptom-driven combination therapy is a simple approach that may help to overcome the problem of poor compliance with asthma treatment.

COMMENT: *This study examined four step-down options: inhaled albuterol as needed, beclomethasone plus albuterol in a single inhaler (bec-alb MDI) as needed, bec-alb MDI twice a day, and regular twice-a-day beclomethasone. The main finding was that symptom-driven use of the bec-alb combination inhaler as an intermittent rescue treatment was as effective over 6 months as regular twice-a-day beclomethasone and superior to albuterol alone. Previous data tell us that prevention of airway remodeling is not justification for the continuous use of controllers, so each of us should be deciding which of the alternatives has the best risk-benefit profile for clinical outcomes.*
R. J. M.
Papi A, Canonica GW, Maestrelli P, et al: Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma.
N Engl J Med. 2007;356:2040-2052. ♦♦

Mild Persistent Asthma: Treatment Options

RECENT research lends new insights into the management of mild persistent asthma. In an interactive feature, the editors of *NEJM* present a clinical vignette, accompanied by expert commentaries, and invite readers to vote and comment on the most appropriate treatment. The vignette describes a 30-year-old woman with mild asthma that is well-controlled with twice-daily inhaled corticosteroids.

A commentary by Dr. Monica Kraft recommends as-needed inhaled beclomethasone and albuterol. Although intermittent use of inhaled corticosteroids has not yet been approved by the FDA, this form of step-down therapy offers a chance to reduce corticosteroid exposure while maintaining asthma control. Dr. Kraft notes that the patient in the vignette is well-motivated and understands the risks of the as-needed regimen.

Dr. Elliott Israel favors oral montelukast plus as-needed albuterol. Given the availability of several effective options, he bases this choice on the patient's preference for less therapy and fewer side effects. Montelukast will address complaints related to exercised-induced bronchospasm while reducing side effects, including long-term fracture risk. If symptoms or exacerbations are a problem, then the corticosteroid/beta-agonist combination can be used.

Dr. George T. O'Connor would place the patient on once-daily combination therapy, noting that it provides better disease control than montelukast and is more convenient than twice-daily inhaled corticosteroid. He notes that this approach is not included in current guidelines, which are based largely on expert opinion. However, experience suggests that the once-daily combination regimen is effective, simple, and safe.

COMMENT: *A regular feature of this journal is called "Clinical Decisions." This section walks a clinician through the three main treatment options for mild persistent asthma as each one is discussed by a different expert.*
R. J. M.
Treatment of mild persistent asthma.
N Engl J Med. 2007;356:2096-2100. ♦♦

FOCUS ON IMMUNOTHERAPY

Immunotherapy: State of the Art

THE scientific basis of allergen immunotherapy is firmly established. Further expansion of this technique requires new approaches to overcoming the disadvantages in terms of safety and convenience. The author reviews the current status of allergen immunotherapy, focusing on the established technique of subcutaneous immunotherapy (SCIT) and the emerging alternative of sublingual immunotherapy (SLIT).

Studies have demonstrated SCIT's effectiveness for sensitivity to *Hymenoptera* venom, allergic rhinitis, and allergic asthma. Questions remain as to the effective doses of allergen extract for SCIT, largely owing to limitations in the use of major allergen content to express potency and dosing. Subcutaneous immunotherapy can reduce additional sensitivities and progression to asthma, and has a lasting effect on symptoms after discontinuation of treatment. More research is needed on SCIT for atopic dermatitis and food allergy, as well as on multiple-allergen SCIT. Recent studies have lent new insights into the risk of systemic and fatal reactions to SCIT, as well as the use of rush or clusters dosing schedules.

Of the proposed alternative approaches to immunotherapy, SLIT is the best established. It is effective in allergic rhinitis, including in children, and allergic asthma. Safety and convenience are the major advantages. No fatal reactions have been reported so far, although other adverse events can occur. Recent studies have investigated the use of SLIT for food allergies. Dosing is a major unresolved question--data suggest a "flat" dose-response curve. In addition, comparative studies have suggested that SLIT does not achieve the same level of clinical effectiveness of SCIT.

Although questions remain, immunotherapy is still the only true disease-modifying approach to treatment of asthma and allergic rhinitis. New approaches under investigation include modified recombinant allergens, peptides, and immunostimulatory DNA sequences bound to allergenic proteins.

COMMENT: *As only he can do, Dr. Nelson distills an enormous amount of data to create a coherent state of the art (and science) of immunotherapy. The most interesting parts are those devoted to experimental modifications of subcutaneous treatment, and the section comparing subcutaneous and sublingual treatments. This is the best "10,000-foot view" you will find.*
R. J. M.
Nelson HS: Allergen immunotherapy: where is it now?
J Allergy Clin Immunol. 2007; 119:769-777. ♦♦

How Does Immunotherapy Work?

IN properly selected patients, allergen-specific immunotherapy (SIT) is a reliably effective treatment for allergic diseases. Recent years have lent new insights into the mechanism of its effectiveness. The authors review the sequence and mechanisms of events in the response to allergen-SIT.

Mast cell and basophil desensitization play a role in the very early effects of SIT. From the first injection, there is evidence of a significant decrease in mast cell and basophil activity for degranulation and systemic anaphylaxis. Induction of T-cell tolerance, characterized by the generation of allergen-specific Treg cells, is a critical step. Upregulation of CD4+CD25+ Treg cells may play an important role; transforming growth factor-β not only suppresses allergen-specific T cells but also contributes to tissue remodeling.

Serum-specific IgE levels gradually decrease after months or years of SIT, but cannot account for the ➤➤

resulting reduction in allergen responsiveness. Immunoglobulin G antibodies--especially IgG_4--may capture allergen before it reaches the IgE, thus preventing mast cell and basophile activation. Immunotherapy also induces secretion of interleukin-10 (IL-10), which suppresses total and allergen-specific IgE and increases IgG_4 production. In addition to SIT's effects in altering thresholds for mast cell and basophil activation and reducing IgE-mediated histamine release, IL-10 downregulates eosinophil function and suppresses production of IL-5. Effects on late-phase reactions in the mucosa or skin are an important part of the long-term effects of SIT.

Recent discoveries suggest that IL-10- and TGF-β-secreting Treg cells and immunosuppressive cytokines are important contributors to the effectiveness of SIT for allergic disease. The findings may be applicable to other conditions involving immune reactions, and could aid in developing safer, more efficient approaches to SIT. The article includes discussions of the mechanisms of sublingual immunotherapy and of novel immunotherapy vaccines and approaches.

COMMENT: *Long gone are the days of explaining the effect of SIT as induction of "blocking antibody." Now we know that T-regulatory cells and suppressive cytokines like IL-10 and TGF-β are likely to be principal actors in this drama, and that allergen tolerance is achieved by a complex interaction of many cellular and humoral elements of the immune system. This review article nicely outlines these events. Good reading.*
R. J. M.

Akdis M, Akdis CA: Mechanisms of allergen-specific immunotherapy.
J Allergy Clin Immunol. 2007;119:780-789. ♦♦

How Long Should Immunotherapy Continue?

SUBCUTANEOUS immunotherapy (SCIT) is of demonstrated efficacy for patients with respiratory allergies. However, in addition to safety concerns, inconvenience and cost are important obstacles to treatment. Despite its clinical importance, few studies have looked at how long SCIT has to be continued for effectiveness. A literature review was performed to analyze data on the duration of clinically effective SCIT, as well as the risk of relapse after treatment discontinuation.

Most data on the duration of effective immunotherapy come from studies of treatment for *Hymenoptera* sensitivity. Long-term follow-up studies have suggested that a 5-year course of treatment is effective for most patients. Nevertheless, up to 15% of patients may relapse in the 10 years after discontinuation of venom immunotherapy. Severe reactions to stings or systemic reactions to immunotherapy are associated with a higher risk of relapse.

Just eight studies providing data on the duration of response after SCIT for inhalant allergies. In a prospective study of 40 patients receiving 12 to 96 months of SCIT for dust mite allergy, the 3-year relapse rate was 55%. The figure was 62% for patients receiving less than 35 months of SCIT, compared to 48% for those treated for more than 36 months. A study of patients receiving 3 years of immunotherapy for cat or dog allergen found increased allergen-induced bronchial sensitivity at 5 years' follow-up.

Several studies have provided data on the duration of efficacy for pollen SCIT. One reported a 30% relapse rate within the first 3 years after the end of treatment. Thereafter, the risk of relapse was small. A study of children receiving grass pollen immunotherapy reported good persistence of effect, although most patients still required medications for symptoms during pollen season. In one study, duration of efficacy was linked to decreased skin test reactivity.

The limited available data suggest a significant risk of relapse after the end of SCIT in patients with various types of allergies. Factors affecting the duration of clinical remission include the length of immunotherapy and the type of allergen--ie, perennial versus seasonal. In the absence of specific tests or clinical markers of relapse risk, decisions as to duration of immunotherapy must be individualized.

COMMENT: *This transparent review summarizes the medical literature and emphasizes the variability in results. The need for individualization is emphasized, recognizing the lack of evidence to provide accurate direction. The 3- to 5-year duration recommendation--with payers focusing on the low end for financial reasons--is based upon some data and much inference. Flexibility should be an option. This article would be useful if a clinician is writing a letter of appeal to a conservative, restrictive payer who is denying flexibility and individualization. Guidelines are not paylines.*
D. K. L.

Cox L, Cohn JR. Duration of allergen immunotherapy in respiratory allergy: when is enough, enough?
Ann Allergy Asthma Immunol. 2007;98:416-426. ♦♦

Families Show No Increase in Allergies after Getting a New Pet

MANY recent studies have evaluated the effects of exposure to furred animals on the risk of sensitization and allergic symptoms in children and adults. The results have been conflicting, with some studies reporting a protective effect. The effects of extensive, new exposure to furred animals on the risk of developing new allergies were prospectively examined.

Through newspaper advertisements, the investigators recruited 68 families who were planning to buy a dog or cat, or in which at least one child was going to start riding a horse. Family members were evaluated before exposure to the new pet and each year for 5 years thereafter. Evaluations included an allergy symptom questionnaire, measurement of specific IgE antibodies, and measurement of allergen in dust samples.

The analysis included 158 children and 128 parents: mean age 7.8 and 36.2 years, respectively. Of these, 15 children and 22 adults showed evidence of allergic sensitization at baseline, a rate of 15%. Of children ➤➤

with baseline sensitization, 11% became sensitized to the newly introduced allergen while 16% became sensitized to another animal. Of subjects who were not previously sensitized, only 1 adult became sensitized to the new animal--a rate of 0.4%. None of these subjects developed sensitization to a different animal. Allergic symptom scores were higher for subjects who were sensitized at baseline. However, there was no significant increase in symptom scores over time.

For adults and children over age 1, extensive exposure to a new furred animal does not appear to increase the rate of allergic symptoms or sensitization over 5 years. This is so regardless of baseline sensitization status. Even when there is a history of allergies, there appears to be no strong scientific basis for the recommendation to avoid new exposure to furred animals to prevent new allergies.

COMMENTS: *The question of whether furry pets in the home protect against developing pet allergy or asthma is provocative and the results of previous studies are conflicting. The strengths of this study are its large size and prospective design. The results suggest that, after the first year of life, introducing a pet into the home will likely not increase allergy symptoms in the family.*
S. A. T.
Millqvist E, Johansson Å, Månsson T, Bende M: A prospective study of allergy development in 158 children and 128 adults with new extensive exposure to furred animals.
Clin Exp Allergy. 2007;37:948-953. ♦♦

Smoking Linked to Reduced Bronchial Dendritic Cells in Asthma

FOR patients with asthma, cigarette smoking is associated with increased symptoms and other severity indicators, as well as an impaired response to corticosteroids. Little is known about smoking's effects on bronchial inflammation. The current study evaluated the effects of smoking on bronchial dendritic cells.

Endobronchial biopsy specimens were obtained from 21 asthmatic patients who had never smoked, 6 of whom were steroid-naive; 24 asthmatic patients who were current smokers, 9 steroid-naive; and 10 healthy never-smokers. Immunostaining was performed to identify CD83+ mature DCs, CD1a+ Langerhans cells, and CD20+ B lymphocytes, as well helper T-cell types 1 and 2, expressing interferon-γ (IFN-γ) and interleukin-4 (IL-4), respectively.

The asthmatic smokers had a median of 37/mm^3 mature DCs, compared with 76/mm^3 in the asthmatic never-smokers, whether or not they were steroid-naive; and 85/mm^3 in the control group. Median B-cell count was 26/mm^3 in the asthmatic smokers, compared with 45/mm^3 in the asthmatic never-smokers. For steroid-naive smokers, B-cell count was 23/mm^3, compared with 34/mm^3 in the control group. The asthmatic smokers also tended to have fewer IFN-γ-expressing cells than steroid-naive, never-smokers with asthma: 70/mm^3 versus 144/mm^3, respectively.

Among patients with asthma, current smokers show evidence of altered bronchial mucosal immunity. Smoking is associated with reduced numbers of mature DCs and B cells. These changes may help to explain the reduced corticosteroid responsiveness in asthmatic smokers, as well as their increased susceptibility to infection.

COMMENT: *Cigarette smoking has many adverse effects on the lower airway. The downregulation of mucosal dendritic cells may be an important factor in the response to corticosteroids and the propensity to develop respiratory infections.*
B. E. C.
Tsoumakidou M, Elston W, Zhu J, et al: Cigarette smoking alters bronchial mucosal immunity in asthma.
Am J Respir Crit Care Med. 2007;175: 919-925. ♦♦

Overweight Girls Are at Increased Risk of Adult-Onset Asthma

CROSS-sectional data suggest an association between the rising rates of asthma and obesity. There are conflicting data as to whether this link is affected by sex. Data from a prospective birth cohort study were used to assess childhood obesity as a risk factor for later asthma, including the effects of sex and other potential modifying factors.

The analysis was based on the Tasmanian Asthma Survey, which included 8,583 children first studied in 1968 at age 7. Evaluations at that time included height and weight measurement and pulmonary function testing. In 1991-93, a random sample of 2,000 subjects, stratified for childhood asthma status, were re-evaulated. The association between body mass index (BMI) at age 7 and the subsequent development of asthma was assessed, including the possible impact of sex, childhood lung function, and age at menarche.

Based on BMI z-score quartiles, adiposity at age 7 was related to the presence of asthma at age 32 that had developed after age 21 in females, but not in males. For females classified as overweight at age 7, the odds ratio for asthma onset after age 21 was 3.05. This relationship was unaffected by pulmonary function test results at age 7 or by age at menarche. In both females and males, adiposity at age 7 was unrelated to asthma that developed later but was in remission at age 32.

Girls at higher levels of BMI at age 7 are at increased risk of adult asthma, with onset after age 21. Efforts to address the problem of overweight and obesity should include a focus on children, especially girls, to reduce the later risk of asthma. Because of the rising prevalence of overweight, the risk of asthma in young women today is probably even higher than in this birth cohort.

COMMENT: *This article continues to strengthen the association between obesity and the subsequent development of asthma--especially in women in the third decade of life.*
B. E. C.
Burgess JA, Walters EH, Byrnes GB, et al: Childhood adiposity predicts adult-onset current asthma in females: a 25-yr prospective study.
Eur Respir J. 2007;29:688-675. ♦♦

Smokers Are Less Sensitive to Steroids--Should They Get Montelukast?

DESPITE the fact that smoking aggravates their condition, the percentage of asthma patients who smoke is about the same as in the population. Smoking has been linked to reduced sensitivity or oral and inhaled corticosteroids--questions remain about the optimal treatment for this group of patients. A randomized trial compared the effects of an inhaled corticosteroid and a leukotriene receptor antagonist in asthmatic smokers.

The "Smoking Modulates Outcomes of Glucocorticoid Therapy" (SMOG) study included two groups of patients with mild asthma: 39 light smokers (2 to 15 pack-years) and 44 nonsmokers. In randomized, crossover fashion, patients received 8 weeks of treatment with twice-daily inhaled beclomethasone and 8 weeks of once-daily oral montelukast, with a 6-week washout period. The primary outcome measure was change in prebronchodilator FEV_1.

The two groups of patients had similar baseline characteristics, including FEV_1, bronchodilator responsiveness, and methacholine sensitivity. Nevertheless, asthma symptoms were significantly increased for smokers, who also had decreased quality of life and daily peak flow. There were no differences in treatment adherence between treatments or for smokers vs nonsmokers.

In the nonsmoking patients, inhaled beclomethasone yielded a 170 mL increase in FEV_1, compared to no change in asthma patients who smoked. In both groups, inhaled corticosteroid was associated with a reduction in sputum eosinophils and eosinophil cationic protein. In contrast, montelukast was associated with a significant 12.6 L/min increase in morning peak expiratory flow only in smokers--not in nonsmokers.

This randomized trial confirms that asthma patients who smoke have a reduced response to inhaled corticosteroid, compared to asthmatic nonsmokers. For smokers, certain outcomes appear better with oral montelukast, suggesting that leukotriene synthesis or sensitivity may be increased in this group. The authors call for further investigation of montelukast or other treatment alternatives for asthma patients who continue to smoke.

COMMENT: *This study confirms that asthmatics who smoke are particularly insensitive to inhaled corticosteroid, and that there may be an evolving role for anti-leukotriene drugs in smokers. A larger study is definitely needed to confirm this observation.*
B. E. C.

Lazarus SC, Chinchilli VM, Rollings NJ, et al: Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma.
Am J Respir Crit Care Med. 2007;175:783-790. ♦♦

ADAM Gene Expression Increases with Asthma Severity

PREVIOUS studies have reported that the "a distintegrin and metalloproteinase 33" gene (*ADAM33*) is a risk factor for asthma and bronchial hyperresponsiveness, and may play a pathophysiologic role in airway remodeling. Animal studies have suggested that *ADAM8*--another gene in the same family, which has been little studied in human asthma--may play a role in allergic lung inflammation. Expression of these two ADAM genes was evaluated in well-characterized patients with asthma, including their relationship to disease severity.

The investigators measured mRNA and protein expression of *ADAM33* and *ADAM8* in bronchial biopsy specimens from patients with known mild, moderate, or severe asthma and from healthy controls. The patients with moderate and severe asthma has significantly greater expression of *ADAM33* mRNA than the mild asthma patients or controls. On immunostaining, severe asthma was associated with increased staining for *ADAM33* in the epithelium, submucosa cells, and smooth muscle. Expression of *ADAM8* mRNA was higher in all three asthma groups than in controls. Inflammatory cell staining for *ADAM8* was greater in moderate and severe disease than in mild asthma.

In patients with asthma, bronchial expression of *ADAM33* mRNA and protein increase along with disease severity. Expression of *ADAM8* mRNA is higher in asthma patients than controls, while protein expression is higher in patients with more severe disease. Both genes may be involved in airway remodeling associated with progressive asthma; further study may lead to the identification of new therapeutic targets.

COMMENT: *The ADAM family of proteins have been identified as possible "asthma susceptibility genes," since polymorphisms are associated with bronchial hyperresponsiveness and inflammation in asthmatics.* ADAM33 *mRNA staining was found in epithelium from 80% of patients with moderate and severe asthma compared to controls and patients with mild asthma. Increased expression of mRNA of* ADAM8 *was also found in all asthmatics, but there was increased inflammatory cell expression for* ADAM8 *in the patients with moderate and severe asthma. It has been suggested that these genes contribute to the remodeling process important in asthma progression. These researchers demonstrated that there is increased expression of both* ADAM8 *and* ADAM33 *with increasing disease severity.*
S. M. F.

Foley SC, Mogas AK, Olivenstein R, et al: Increased expression of ADAM33 *and* ADAM8 *with disease progression in asthma.*
J Allergy Clin Immunol. 2007;119:863-871. ♦♦

Airflow Obstruction Sites Are Relatively Stable in Asthma

IMAGING studies have shown airflow obstruction is unevenly distributed in the lungs of patients with asthma. It is unknown whether the locations of these obstructions vary over time or with repeated episodes of bronchoconstriction, or whether some sites are more often affected than others. This issue was addressed by performing MRI with hyperpolarized helium-3 ➤➤

(H^3He), a new technique that provides high-resolution images of the air spaces within the lung.

Ten young adult patients with asthma underwent H^3He MRI before and immediately after methacholine challenge. The same technique was performed a mean of 6 months later. The images were reviewed by consensus of three radiologists, with focal areas of airflow obstruction recorded as ventilation defects. Changes in the location and size of ventilation defects from before to after methacholine challenge and between study days were assessed.

On comparison of premethacholine scans taken on different days, 41% of defects were in the same location. Comparison of day 1 and 2 postmethacholine scans showed no change in location for 69% of defects. Of these, there was no change in size for 69% and 43% of defects, respectively. On comparison of the before- and after-methacholine images, 58% of defects were in the same location on day 1 and 73% on day 2. The percentage increase in number of ventilation defects from before to after methacholine was substantially greater than the percentage reduction in lung function parameters.

This H^3He MRI study finds that many ventilation defects in the lungs of asthma patients remain or recur in the same location over time or in response to repeated bronchoconstriction. The results suggest that asthma-related regional changes in airflow obstruction are relatively fixed. This could be an effect of airway remodeling, but might also reflect stability of the chronic inflammatory process in asthma.

COMMENT: *Using a new technology which involves MRI imaging, these researchers report that ventilation defects in the lungs of asthmatic patients tended to be in the same location even after repeated methacholine challenges. This suggests that the inflammatory defect with resulting obstruction seems to be clustered in specific regions of the lung. The futurists will suggest that the next step would be to determine how to direct our therapy at the particularly affected areas.*
S. M. F.

de Lange E, Altes TA, Patrie JT, et al: The variability of regional airflow obstruction within the lungs of patients with asthma: assessment with hyperpolarized helium-3 magnetic resonance imaging.
J Allergy Clin Immunol. 2007;119:1072-1078. ♦♦

SLIT Redux

SUBLINGUAL immunotherapy (SLIT) seems particularly advantageous for the treatment of allergic diseases in children. With its good safety profile, SLIT might be prescribed in primary care settings. So far, however, all clinical trials of SLIT in children have been performed at referral centers. This randomized controlled trial evaluated the efficacy of SLIT delivered in primary care for pediatric patients with grass pollen allergy.

The study included 204 children and adolescents with hay fever, aged 6 to 18 years, seen in Dutch general practices. One group received 2 years of SLIT using a mix of five grass pollen species, while controls received placebo SLIT. The main outcome measure was daily total symptom score (on a 0-to-15 scale) during pollen season of the second year of treatment.

Outcomes analysis included 168 patients: 91 assigned to active SLIT and 77 to placebo. In the summer of year 2, there was no significant difference in mean daily total symptom score; the between-group difference was only 0.08. Other outcomes were also similar between groups, including days free of rescue medications, disease-specific quality of life, and ratings of overall treatment effect. The active SLIT group had a higher rate of local side effects: 39% vs 17%.

Delivered in primary care, grass pollen SLIT does not appear effective for the treatment of hay fever in children and adolescents. More research would be needed before SLIT could be recommended for treatment of grass pollen allergy in primary care practice.

COMMENT: *Since SLIT is considered safe, it has been suggested that it can be a successful therapy for patients even in a primary care clinic. These Dutch researchers used grass allergen SLIT in 91 children with moderate seasonal allergic rhinitis and compared their 2-year clinical results with those of 77 controls. Although the main reasons for the lack of clinical response were not clear, polysensitization, compliance issues, and specific allergen immunologic changes were not specifically addressed. The authors conclude that SLIT was not effective in a primary care setting.*
S. M. F.

Röder E, Berger MY, Hop WCJ, et al: Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care.
J Allergy Clin Immunol. 2007;119:892-898. ♦♦

MANY patients with birch pollen allergy also have food hypersensivity reactions to apples, the result of cross-reactivity between the birch pollen allergen Bet v 1 and the apple protein Mal d 1. Sublingual immunotherapy (SLIT) with birch pollen allergen might be especially appropriate for patients with this oral allergy syndrome (OAS). The effects of birch pollen SLIT on concomitant food allergy to apple were evaluated.

Fifteen adult patients with sensitization to Bet v 1 plus OAS to apple received 1 year of birch pollen SLIT. Before and after treatment, the patients underwent nasal challenge with birch pollen and double-blind placebo-controlled food challenges with apple. Specific antibody levels to both allergens were measured, and proliferation in peripheral blood mononuclear cells and allergen-specific T-cell lines were assessed.

Birch pollen SLIT reduced the reaction to nasal allergen challenge, as well as seasonal allergic symptoms, in 9 of the 15 patients. However, there was no change in the reaction to oral challenge with apple. In SLIT responders, Bet v 1-reactive IgE and IgG_4 were significantly increased, but Mal d 1-specific antibodies were unaffected. Bet v 1-specific T-cell responses were reduced, while Mal d 1-induced T-cell proliferation was unchanged. In contrast, after SLIT, Mal d 1-spe- ➤➤

cific T-cell lines showed an increased response to restimulation with apple protein and lost cross-reactivity to birch pollen allergen.

For patients with birch pollen allergy and OAS to apple, successful SLIT using Bet v 1 does not affect immune responses or reactions to Mal d 1. Combined immunotherapy using pollen and related food allergens might be a more effective strategy for this group of patients. Despite their cross-reactivity, Mal d 1 may have a T-cell response that is independent of Bet v 1.

COMMENT: *The symptoms of OAS frequently improve in patients receiving standard subcutaneous immunotherapy. Patients with birch tree pollinosis and OAS who received higher doses of SLIT with Bet v 1 (birch allergen) all had impressive immunologic and clinical responses to Bet v 1 challenge. Interestingly, their responses to Mal d 1 (apple allergen) didn't change even after 1 year of SLIT with Bet v 1. The authors suggest combining inhalant and food allergens in SLIT vaccine for patients with OAS.*

S. M. F.

Kinaciyan T, Jahn-Schmid B, Radakovics A, et al: Successful sublingual immunotherapy with birch pollen has limited effects on concomitant food allergy to apple and the immune response to Bet v 1 homolog Mal d 1. **J Allergy Clin Immunol**. 2007;119:937-943. ♦♦

IN Northern Europe as elsewhere, the prevalence of allergic rhinoconjunctivitis has risen sharply. The grass allergen tablet (GRAZAX) represents a potentially valuable new approach to allergen-specific immunotherapy for this large patient population. Data from a large clinical trial were used to assess the cost-effectiveness of the grass allergen tablet for patients with grass pollen-induced rhinoconjunctivitis.

The pharmacoeconomic analysis was conducted alongside a double-blind, placebo-controlled trial that included 634 patients in eight Northern European countries. The cost-utility analysis used data from seven countries, including prospectively collected data on patient-specific resource utilization and quality of life. The analysis used a societal perspective with a 9-year time horizon, focusing on quality-adjusted life years (QALYs) gained.

Efficacy analysis strongly favored grass allergen tablet therapy over symptomatic medications, including a 30% reduction in symptom score and a 38% reduction in medication score. Mean number of QALYs gained was 0.976 with the grass allergen tablet vs 0.947 with placebo. In addition to using more loratadine and budesonide, patients assigned to placebo had greater loss of productivity at work. With an annual cost of 1,500 euros for the grass allergen tablet, cost per QALY gained ranged from 12,930 euros to 18,263 euros in the seven countries studied. Treatment was considered cost-effective as long as the annual cost was less than 2,200 euros.

The data support the cost-effectiveness of grass allergen tablet therapy for grass pollen induced rhinoconjunctivitis in Northern Europe. Cost-effectiveness is based on a tablet price of less than 6 euros, as well as a sustained effect of 6 years.

COMMENT: *Sublingual immunotherapy appears to be here to stay, and its cost effectiveness may well dictate the size of its niche. The results of this study suggest that sublingual grass immunotherapy may be cost effective for monosensitized patients in Northern Europe. However, there are several study design issues that should be noted. Reliance on quality of life as the primary outcome in an immunotherapy study may not be an adequate marker of efficacy. Also, the assumption that the efficacy of sublingual immunotherapy persists for years following its discontinuation remains unproven. Stay tuned for further cost-effectiveness studies, including comparisons of sublingual and subcutaneous immunotherapy.*

S. A. T.

Bachert C, Vestenbæk U, Christensen J, et al: Cost-effectiveness of grass allergen tablet (GRAZAX®) for the prevention of seasonal grass pollen induced rhinoconjunctivits--a Northern European perspective. **Clin Exp Allergy**. 2007;37:772-779. ♦♦

In Persistent Rhinitis, Diagnosis Predicts Airway Inflammation and Asthma

ACCUMULATING data suggest that rhinitis and asthma are the upper and lower airway manifestations of a single syndrome that varies widely in severity. In clinical practice, the presence of airway inflammation and the diagnosis of asthma may more likely be associated with allergic rhinitis (AR) and chronic rhinosinusitis (CRS) than with nonallergic rhinitis (NAR). The presence of lower airway symptoms and airway inflammation were assessed in a series of patients evaluated for persistent rhinitis.

The study included 108 of a consecutive series of 590 patients referred to an allergy clinic with symptoms of chronic persistent (more than 4 weeks) rhinitis. All were investigated using a stepwise approach, according to the Allergic Rhinitis and Its Impact on Asthma (ARIA) recommendations. Diagnostic criteria for asthma included symptoms plus a positive result on bronchodilation testing and/or measurement of methacholine hyperresponsiveness. Exhaled nitric oxide (FENO) was measured as an indicator of airway inflammation.

Thirty-nine percent of patients were diagnosed with AR, 21% with NAR, and 40% with CRS. A diagnosis of asthma was made in 33% of AR patients and 42% of CRS patients, compared with 8.7% of NAR patients. Mean FENO values were 44.3 ppb in the AR group and 53 ppb in the CRS group, compared with 22 ppb in the NAR group. Patients with asthma had a mean FENO of 64 ppb, compared to 33.3 ppb for those without asthma.

Among patients with persistent rhinitis, the results of clinical investigation can help to predict the presence of lower airway inflammation and asthma. Patients diagnosed with AR or CRS have higher FENO values and a higher prevalence of asthma than those diagnosed with NAR. The results support the ARIA recommendation of testing for asthma in patients with AR and asthma-like symptoms, and suggest that the same should apply to patients with CRS and lower airway symptoms. ➤➤

COMMENT: *It is important to note that this Italian study included subjects referred to allergy specialists rather than a cross-section of the general population. It appears that for this population, the various ARIA guideline subclassifications do not differ with respect to predicting the presence of asthma.*
S. A. T.
Rolla G, Guida G, Heffler E, et al: Diagnostic classification of persistent rhinitis and its relationship to exhaled nitric oxide and asthma: a clinical study of a consecutive series of patients.
Chest. 2007;131:1345-1352. ♦♦

How Are Allergic Reactions Managed in the ED?

FEW studies have focused on the frequency and management of anaphylaxis in the emergency department (ED), despite evidence that most patients with anaphylaxis are treated in the ED. A nationally representative sample of ED visits was analyzed to gain insights into the number, characteristics, and management of visits for anaphylaxis in the United States.

Combined data from the National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1993 to 2004 were used to identify 12.4 million ED visits for allergy-related causes. These visits accounted for 1.03 million visits per year, or 1.0% of all U.S. ED visits. The rate of allergy-related visits remained stable during the period studied, at around 3.8 per 1,000 population per year.

"Unspecified allergy" accounted for 57% of all acute allergic reactions treated, "unspecified adverse effect of drug, medicinal, and biological substance" for 35%, and angioneurotic edema for 8%. Just 0.9% of visits were coded as anaphylactic shock and 0.2% as anaphylactic shock due to food reaction. Sixty-three percent of allergy-related visits were coded as urgent, but only 4% of patients were admitted.

Medications were prescribed in the ED for 87% of visits--most commonly H_1 blockers. The rate of prescriptions for many medications increased during the period studied, including corticosteroids, from 22% of visits in 1993 to 50% in 2004; H_2 blockers, from 7% to 18%; and inhaled β-agonists, from 2% to 6%. At the same time, prescription of epinephrine decreased from 19% to 7%.

The data suggest significant variations in the management of acute allergic reactions at U.S. EDs. Only about 1% of allergy-related ED visits are coded as anaphylaxis, and the use of epinephrine appears to be low and decreasing. The authors call for measures to improve guidelines for the management of allergic reactions and anaphylaxis in the ED.

COMMENT: *The surprising results of this national survey are that only 1% of "allergic reactions" seen at U.S. emergency departments are coded as anaphylaxis and that the use of epinephrine is declining as a treatment choice. These data should inspire allergists/immunologists in all localities to become more involved with ED physicians in correcting misperceptions.*
D. K. L.
Gaeta TJ, Clark S, Pelletier AJ, Camargo CA: National study of US emergency department visits for acute allergic reactions, 1993 to 2004.
Ann Allergy Asthma Immunol. 2007;98:360-365. ♦♦

Adult-Onset Wheezing: Rates and Risk Factors

THERE are few data on adult-onset wheezing, largely because of problems with recall in establishing the presence of asthma or wheezing during childhood. Data from a British birth cohort study were used to assess risk factors for the onset and recurrence of wheezing in adulthood.

The initial birth cohort included 18,558 British children born during 1 week in 1958. Assessments included interviews regarding the presence of wheezing, conducted with parents at age 7, 11, and 16 with the cohort members at age 23, 33, and 42. At age 44 to 45 years, 12,069 subjects were still available for a biomedical survey, including total and specific IgE measurement and responses to grass, cat, and dust mite allergens.

A total of 9,377 subjects participated in the biomedical survey, for a response rate of 78%. The overall incidence of wheezing increased from 18% at age 7, to 24% at age 16%, to nearly 50% by age 42. The incidence of wheezing in adulthood--both from 17 to 33 years and from 34 to 42 years--was positively related to atopy, defined as any specific IgE level of 0.3 kU/L or higher. Smoking was also a significant risk factor.

With adjustment for sex and smoking, atopy was estimated to account for 34% of incident asthma and 5% of incident wheezing without asthma. In contrast, with adjustment for sex and atopy, smoking accounted for about 13% of incident asthma and 34% of incident wheezing without asthma. For subjects without wheezing earlier during adulthood, the prevalence of wheezing at age 42 was related to the presence of wheezing in childhood.

In this British birth cohort, about half of subjects report wheezing by middle age, with about half of these cases representing true adult-onset wheezing. Allergy and smoking are the main risk factors, perhaps especially in subjects with a history of childhood symptoms. These factors may have differing effects on the risk of asthma vs wheezing without asthma.

COMMENT: *Epidemiologic studies are often limited by the use of recall data or self-reported diagnoses. Both are the case in this long-term cohort study. However, the duration and the size of this study make me interested. An association of atopy and cigarette smoking with asthma at any age suggests the importance of chronic airway inflammation in the development of the disease. An occurrence of wheezing in over 50% of the population is most likely due to self-report and the transient wheeze associated with respiratory infection. These data support the idea that all subjects with persistent wheeze should have an allergy evaluation at least once.*
D. K. L. ➤➤

Butland BK, Strachan DP: Asthma onset and relapse in adult life: the British 1958 birth cohort study.
Ann Allergy Asthma Immunol. 2007;98:337-343. ♦♦

Tiotropium Plus Fluticasone-Salmeterol for Moderate to Severe COPD

PATIENTS with moderate or severe chronic obstructive pulmonary disease (COPD) have chronic dyspnea that does not adequately respond to short-acting bronchodilators. Many of these patients receive combination therapies including an inhaled corticosteroid (ICS), long-acting β-agonist (LABA), and long-acting cholinergic drug, such as tiotropium. Although this combination approach seems reasonable, its safety and efficacy have not been documented. The combination of tiotropium and salmeterol or fluticasone-salmeterol was evaluated for patients with COPD.

The randomized trial included 449 patients with moderate or severe COPD at 27 Canadian centers. All patients received tiotropium, along with placebo, salmeterol, or fluticasone-salmeterol. Clinical outcomes were compared between groups, focusing on the risk of a COPD exacerbation requiring systemic steroid or antibiotic therapy.

Dropout rates were high in the tiotropium plus placebo and tiotropium plus salmeterol groups--many patients switched to open-label treatment with ICS or LABAs. Exacerbation rates were not significantly different between the three assigned groups: 62.8% with tiotropium plus placebo, 64.8% with tiotropium plus salmeterol, and 60.0% with tiotropium plus fluticasone-salmeterol. The differences remained significant in sensitivity analyses, although point estimates and 95% confidence bounds shifted in favor of the combination therapies.

Several secondary outcomes were better with tiotropium plus fluticasone-salmeterol, including lung function and disease-specific quality of life. The three-drug combination also brought significant reductions in COPD exacerbations requiring hospitalization and all-cause hospitalization--incidence rate ratio 0.53 and 0.67, respectively--compared to tiotropium plus placebo. Tiotropium plus salmeterol did not significantly improve lung function or hospitalization risk, compared with tiotropium plus placebo.

For patients with moderate or severe COPD, the exacerbation rate is not decreased by adding fluticasone-salmeterol to treatment with tiotropium. However, the three-drug combination does improve other outcomes, including lung function, quality of life, and hospitalization rates. Additional large studies will be needed to establish the true benefits of this combination therapy for COPD.

COMMENT: *Allergists/immunologists care for patients with mixed reversible and irreversible airflow limitation or subjects with asthma who smoke. The optimal treatment of such patients is difficult to determine, since the clinical trials recruit patients exclusively with asthma or COPD but not features of both. This is a large COPD study funded without pharmaceutical support. The conclusion is that ICS with LABA and tiotropium is no more effective than tiotropium alone in reducing exacerbations, although there was a non-significant reduction in the combination treatment arm. Moreover, the combination of ICS/LABA/tiotropium reduced hospitalizations, improved quality of life, and increased lung function. What would be the results with a higher dose of ICS? Should we consider tiotropium in subjects with asthma and irreversible airflow limitation?*
D. K. L.

Aaron SD, Vandemheen KL, Fergusson D, et al: Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease.
Ann Intern Med. 2007;146:545-555. ♦♦

Exposure to Mold Component Linked to Reduced Wheezing Risk in Infants

THE biologically active molecule (1-3)-β-D-glucan is a major component of the cell wall of molds and certain soil bacteria and plants. It has been linked to respiratory symptoms in adults, particularly in occupational settings, but there are few data on its potential health effects in infants. Exposure to (1-3)-β-D-glucan was evaluated as a risk factor for allergic sensitization and wheezing in infants.

Dust samples were obtained from the homes of 574 infants who had at least one parent with a history of allergic symptoms. House dust concentrations of (1-3)-β-D-glucan and endotoxin were measured. The main outcomes of interest were rates of recurrent wheezing at age 1, as reported by parents; and sensitization to common aeroallergens, milk, and egg white.

Infants in the highest quartile of exposure to (1-3)-β-D-glucan were at lower risk of recurrent wheezing, adjusted odds ratio (OR) 0.39; and of recurrent wheezing plus allergic sensitization, OR 0.57. Conversely, these outcomes were more common for infants in the lowest quartile of (1-3)-β-D-glucan exposure: OR 3.04 for recurrent wheezing, with or without sensitization. Endotoxin exposure had no effect on either outcome.

For infants of atopic parents, high indoor exposure to (1-3)-β-D-glucan is associated with a lower risk of recurrent wheezing. This protective effect may be especially strong in infants with allergic sensitization. Long-term follow-up is needed to see if (1-3)-β-D-glucan exposure affects allergic disease outcomes later in childhood.

COMMENT: *This is the first report of a potential association of this molecule with infantile wheezing. We have classically considered this constituent of fungal and bacterial cell walls to be associated with workplace-induced asthma and flulike complaints. More work is needed to delineate the mechanisms involved, but it appears that atopy is an important predisposing factor.*
A. M. ➤➤

Iossifova YY, Reponen T, Bernstein DI, et al: House dust (1-3)-β-D-glucan and wheezing in infants.
Allergy. 2007;62:504-513. ♦♦

Penicillin Skin Testing Is Safe, Experience Suggests

MANY patients reporting past penicillin allergy are treated with vancomycin or fluoroquinolones. The authors review their experience with penicillin skin testing (PST) in patients with a history of penicillin allergy.

The retrospective analysis included 596 patients with a history of penicillin allergy who underwent PST from 1999 to 2004. About one-half were inpatients, one-fourth were ICU patients, and one-fourth were outpatients. Penicillin skin testing was performed according to standard techniques, including the use of benzylpenicilloyl-polysine, penicillin G, and histamine and saline controls.

At the time of PST, the main antibiotics used were vancomycin and fluoroquinolones. The PST results were positive in 8.2% of patients, indeterminate in 3.4%, and negative in the remaining 88.4%. There was one case of urticaria developing immediately after PST, a rate of 0.17%. When the PST results were negative, 55% of patients were switched to a β-lactam drug. This was done in 70.3% of ICU patients, compared with 8.6% of outpatients; and in 58.6% of adults, compared with 8.1% of patients under age 18.

Adverse reactions occurred in 5 of 290 patients who received a β-lactam antibiotic after a negative PST, a rate of 1.7%. These included 2 patients who developed hives after 16 to 20 days of treatment; 1 patient who developed a nonspecific rash after 17 days; 1 patient who developed flushing and urticaria 3 hours after a test dose of piperacillin-tazobactam; and 1 patient who developed a rash with pruritus after 12 hours.

Penicillin skin testing is safe and informative in patients with a history of penicillin allergy, the authors' experience suggest. When the PST results are negative, the patient can safely be switched to a β-lactam drug.

COMMENT: *The commercial absence of both minor and major penicillin determinants for skin testing limits what allergists/immunologists can offer in consultation for antibiotic reactions. The majority of people labeled "penicillin allergy" do not have IgE-mediated reactions, and identifying these patients is our charge. Using penicillin for testing without major or minor determinants does not detect 45% to 60% of patients with penicillin allergy, leading most clinicians to abandon testing and use a challenge/desensitization approach. Meanwhile, we wait and hope and wait and hope for the determinants.*
D. K. L.
Alvarez del Real G, Rose ME, Ramierez-Atamoros MT, et al: Penicillin skin testing in patients with a history of β-lactam allergy.
Ann Allergy Asthma Immunol. 2007;93:335-359. ♦♦

CLINICAL TIDBITS

Differing Responses in Clinically Reactive vs Tolerized CMA

REPORTS of increased lymphocyte proliferative responses in cow's milk allergy (CMA) may reflect lipopolysaccharide (LPS) contamination of commercial cow's milk protein. In addition, peripheral blood mononuclear cells (PBMCs) contain not only B cells, CD45RA+ naive T cells, and CD25+ regulatory T cells (Tregs), but also antigen-specific CD45RA- memory T cells. In the current study, PBMCs from patients with IgE- and non-IgE-mediated CMA were depleted of CD45RA+ T cells and putative CD25+ Tregs. The memory T-cell-enriched, Treg-depleted PBMCs and bulk PBMCs were compared in terms of proliferative index to LPS-depleted α-, β-, and κ-casein and β-lactoglobulin.

Patients with clinically reactive IgE-mediated CMA showed increased responses to caseins only. In contrast, tolerized patients--especially those with atopic dermatitis--had decreased responses to κ-casein, which re-emerged after Treg depletion. Patients with reactive and tolerant delayed non-IgE-mediated CMA were similar to each other.

Only patients with clinically reactive IgE-mediated CMA show proliferative responses to casein -- but not to b-lactoglobulin. The findings in patients with tolerized, IgE-mediated CMA suggest that κ-casein may play a role in tolerance induction. No proliferative responses to any milk proteins are noted in patients with non-IgE-mediated CMA.

COMMENT: *Cow's milk allergy reactions have been divided into immediate IgE-mediated reactions, intermediate reactions occurring within 45 minutes up to 20 hours, or slow-reacting T-cell-mediated reactions with diarrhea, asthma, or eczema occurring more than 20 hours after ingestion. In a study of CMA in atopic children with eczema, the percentage of CD45RA+ 62 ligand + cells with casein was elevated compared to healthy controls. (See Frieri M, et al: Ann Allergy Asthma Immunol. 2004;92:565-572, 2004.) In this study, PBMCs from clinically reactive and tolerized patients with IgE and non-IgE mediated CMA were depleted of CD45RA+ T cells and CD25+ Tregs. Patients with clinically reactive IgE-mediated CMA were noted to have increased responses only to casein. However, tolerized patients especially with eczema had decreased responses to κ casein, restored after Treg depletion. The authors suggest a possible role for κ casein in CMA-sensitive eczema, and that casein but not β-lactoglobulin Tregs may be involved in tolerance development in patients with IgE-mediated CMA.*
M. F.
Sletten GBG, Halvorsen R, Egaas E, Halstensen TS: Memory T cell proliferation in cowís milk allergy after CD25+ regulatory T cell removal suggests a role for casein-specific cellular immunity in IgE-mediated but not in nonIgE-mediated cowís milk allergy. Int Arch **Allergy Immunol**. 2007;142:190-198. ♦♦

REVIEWS OF NOTE

COMMENT: *New insights into the immunopathogenesis of human rhinoviruses (HRV) have suggested that reduced local immunocompetence may predispose certain atopic individuals to asthma and even autoimmune diseases. This review illustrates the potential immune escape mechanisms used by HRV in targeting dendritic cells, interference with the interferon pathway, modulation of leukocyte interactions, and monocyte cytokine production. Of interest, the bronchial epithelial cells of asthmatics have impaired apoptotic responses to HRV, which can also directly interact with leukocyte biology on intercellular adhesion molecule-1 with retention at the infected site. The authors discuss the role of HRV-stimulated monocytes in producing increased interleukin-10, which could be the "missing link" to explain viral infection and asthma exacerbation. Upregulation of inhibiting accessory molecules on dendritic cells could represent an efficient viral mechanism in suppressing antigen-specific immune responses leading to sinusitis, otitis, bronchitis and pneumonia in predisposed individuals.*
M. F.
Kirchberger S, Majdic O, Stöckl J: Modulation of the immune system by human rhinoviruses.
Int Arch Allergy Immunol. 2007;142:1-10. ♦♦

COMMENT: *Neonatal necrotizing enterocolitis could be due to hypoxia, colonization with pathogenic microbes, sepsis, or an immature gut predisposing to an inflammatory cascade. Probiotics as live microbial supplements could enhance mucosal IgA responses with increased production of anti-inflammatory cytokines. This systematic review and meta-analysis of 7 of 12 randomized controlled trials concludes that probiotics might reduce the risk of necrotizing enterocolitis in preterm neonates with less than 33 weeks gestation. Safety needs to be addressed in larger trials--especially in immunocompromised hosts, since sepsis has been reported. Also, caution is needed because of the variation in patient demographics, age, duration type of probiotic (species, strain, single or combined, live or killed), and maturity of the host.*
M. F.
Deshpande G, Rao S, Patole S: Probiotics for prevention of necrotizing enterocolitis in preterm neonates with very low birthweight: a systematic review of randomized controlled trials.
Lancet. 2007;369:1614-1620. ♦♦

COMMENT: *This important review gives insight regarding the factors that promote persistence of airway inflammation and structural changes in the airway.*
B. E. C.
Holgate ST, Davies DE, Powell RM, et al: Local genetic and environmental factors in asthma disease pathogenesis: chronicity and persistence mechanisms.
Eur Respir J. 2007;29:793-803. ♦♦

COMMENT: *This is an outstanding reference with several clinically useful tables for clinicians evaluating intraoperative anaphylaxis.*
A. M.
Ebo DG, Fisher MM, Hagendorens MM, et al: Anaphylaxis during anaesthesia: diagnostic approach.
Allergy. 2007;62:471-487. ♦♦

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