

ALLERGYWATCH®

"10th Anniversary Volume"

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

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Airway Inflammation and Epithelial Damage in Elite Swimmers and Skiers

MANY athletes in endurance sports develop exercise-induced asthma. A mixed neutrophilic/eosinophilic airway inflammation has been reported in swimmers and cross-country skiers, but its association with airway hyperresponsiveness (AHR) is unknown. This study evaluated patterns of inflammation and epithelial damage associated with "swimmers' asthma" and "skiers' asthma."

The study included 64 high-level competitive swimmers and cold-air athletes (cross-country skiers, speed skaters, and biathletes). The athletes were studied during a period without recent training; patients with mild asthma and healthy controls were studied for comparison. All groups underwent allergy skin prick testing, methacholine challenge, and induced sputum analysis.

Airway hyperreactivity was found in 69% of swimmers and 28% of cold-air athletes. On sputum analysis, neutrophil count was correlated with training hours in

both groups of athletes. Swimmers had higher eosinophil counts than controls, but lower eosinophil counts than patients with mild asthma. Swimmers were the only group in which eosinophil count was correlated with AHR. Swimmers also had a higher bronchial epithelial cell count than controls or asthma patients, but epithelial damage was not correlated with AHR. Sputum eosinophil count was no higher in cold-air athletes than in healthy controls.

In elite swimmers and cold-air athletes, evidence of airway inflammation is associated with AHR. Most of these high-level athletes--especially swimmers--have epithelial desquamation, which is not seen in patients with mild asthma. This bronchial epithelial damage, combined with training in cold air or chlorinated pools, could play a role in the development of airway remodeling and AHR.

COMMENT: *The mechanism of exercise-induced symptoms is quite variable, depending on the underlying degree of airway inflammation. This study helps us better understand the contribution of airway >>>*

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- 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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inflammation in elite swimmers and cold-air athletes. The role of inflammation has been previously shown in other studies, and highlighted in the JACI issue on the Beijing Olympics in the summer of 2008.

B.E.C.

Bougault V, Turmel J, St-Laurent J, et al: Asthma, airway inflammation and epithelial damage in swimmers and cold-air athletes.

Eur Respir J. 2009;33:740-746. ♦♦

Teen Athletes Don't Have Higher Rates of Sensitization and Asthma

PREVIOUS studies have reported an increased prevalence of allergic disease among athletes. However, most of these studies have focused on elite athletes, with comparison to the general population rather than age-matched controls. This study compared rates of allergic sensitization and allergic disease among young male soccer players, versus age-matched controls.

The study included 194 boys and young men who were members of Italian soccer teams. The participants were classified according to age and competitive level as beginners, age 8 to 11; juniors, age 12 to 16; and under 21, age 17 to 20. Questionnaires were used to assess the prevalence and symptoms of allergic diseases, as well as use of allergy drugs. Skin prick or patch tests were performed in participants with a personal history of allergic disease. Allergic disease prevalence and other findings were compared to those of age-matched student controls.

The 34.5% prevalence of allergic diseases among the young male soccer players in the study was not significantly different from the 31.6% rate in age-matched controls. There was also no difference in the rate of positive tests for skin sensitization among symptomatic subjects: 14.4% in soccer players versus 19.2% in controls. Among participants with allergic dermatitis, the rate of positive patch tests was nonsignificantly higher in soccer players: 35.7% versus 23.0%.

Among soccer players, training intensity was unrelated to allergic disease prevalence. The soccer players had a lower rate of sensitization to perennial allergens and a lower prevalence of asthma, but there was no difference in exercise-induced bronchoconstriction. Nevertheless, the soccer players were more likely to use antiallergy and antiasthma medications. Among subjects with allergic disease, rates of medication use were 75.0% for soccer players versus 42.3% for controls.

This study finds a high prevalence of allergic diseases and allergic symptoms among young male soccer players. However, the prevalence of allergy is no higher than in an age-matched control group; allergic disease prevalence is unaffected by training intensity. Despite the lack of difference in allergies, the study suggests that athletes may be more likely to receive medications for allergies and asthma.

COMMENT: *This study evaluated young soccer players (age 8 to 20) in Italy compared with age-matched controls. The only striking difference between the groups was that the soccer players took twice as much allergy and asthma medication. It is unclear if this difference reflects medication overuse or if it is a sign of more optimal disease management in soccer players.*

S.A.T.

Ventura MT, Cannone A, Sinesi D, et al: Sensitization, asthma and allergic disease in young soccer players. Allergy. 2009;64:556-559. ♦♦

Combined LABA/ICS Has Benefits in Intermittent Asthma

THERE are continued questions regarding the combined use of long-acting β_2 -agonists (LABAs) and inhaled corticosteroids (ICS) in patients with intermittent asthma. Repeated low-dose allergen challenge is a useful way to simulate natural exposure to allergens. This approach was used to test the effects of formoterol alone versus formoterol plus budesonide in patients with intermittent asthma.

The randomized, crossover study included 15 patients with intermittent allergic asthma, currently treated only with as-needed short-acting β_2 -agonist. Three different treatments were compared in double-blind fashion: formoterol 4.5 μ g via Turbuhaler, budesonide 160 μ g/formoterol 4.5 μ g via Turbuhaler; and placebo. All treatments were taken as two puffs 30 minutes after allergen challenge. Outcomes included airway responsiveness to methacholine, pulmonary function, and asthma symptoms, among others.

On placebo, allergen challenge was associated with a significant increase in airway hyperresponsiveness: geometric mean provocative dose of methacholine causing a 20% drop in FEV₁ was 397 μ g before challenge versus 168 μ g afterward. Exhaled nitric oxide increased from 46 to 73 ppb and asthma symptom score from 0.39 to 0.68. All of these effects were avoided during treatment with budesonide/formoterol, which was also associated with improvement in FEV₁. The symptom response to allergen challenge was reduced with formoterol alone, but this treatment did not prevent the increase in airway inflammation.

In patients with intermittent asthma, short-term treatment with a combined LABA/ICS prevents increased airway hyperresponsiveness, airway inflammation, and other responses to allergen challenge. Formoterol alone reduces symptoms, but does not address other signs of asthma deterioration. Using a LABA alone might mask the presence of airway inflammation, which could lead to worsening asthma.

COMMENT: *This study again supports the role of combination LABA-ICS in the treatment of allergen-mediated airway inflammation. It also reinforces as-needed budesonide and formoterol as a strategy to relieve symptoms associated with intermittent allergen exposure.*

B.E.C.

Dahlén B, Lantz AS, Ihre E, et al: Effect of formoterol with or without budesonide in repeated low-dose allergen challenge.

Eur Respir J. 2009;33:747-753. ◆◆

Respiratory Infections in Childhood Affect Respiratory Health in Adulthood

CHILDHOOD respiratory infections have known effects on childhood asthma and pulmonary function. However, few longitudinal studies have evaluated the possible long-term effects of childhood infections on

adult respiratory health. Nine-year follow-up data were used to determine whether severe childhood respiratory infections predict asthma and lung function in young adulthood.

The analysis included 9,175 participants from the European Respiratory Health Survey. In 1992-94, at age 20 to 44, subjects completed baseline evaluations including questionnaires and lung function testing. Similar evaluations were performed at an average follow-up of 8.9 years. Mixed effects models were used to examine associations between childhood respiratory infections and the prevalence, incidence, and persistence of asthma and the level of and changes in lung function.

Serious respiratory infections (SRI) before age 5 were reported by 10.9% of participants, while 2.8% reported being hospitalized for lung disease (HLD) before age 2. Subjects with childhood SRI had higher rates of current wheezing, odds ratio (OR) 1.9; and asthma, OR 2.5. Childhood SRI was also associated with an 89 mL reduction in FEV₁, a 49 mL reduction in forced vital capacity (FVC), and a 1.2% reduction in FEV₁/FVC ratio.

History of childhood SRI was also associated with increased rates of new asthma and new wheezing, OR 1.5 for both; and of persistent wheezing, OR 2.2. There was no association between SRI and declines in lung function. Similar associations were noted with HLD, and the patterns were consistent across the 29 research centers. The association between SRI and lower FEV₁ remained significant after exclusion of patients with a history of asthma and those with current wheezing. There was an interactive effect of exposure to maternal or active smoking with childhood respiratory infections.

Severe respiratory infections in early childhood are associated with reduced pulmonary function and increased rates of respiratory morbidity in adulthood. More research into these associations is needed; meanwhile, the authors emphasize the need for prevention through childhood immunizations and avoidance of maternal and personal smoking.

COMMENT: *Early airway injury from viral infections predisposes to recurrent symptoms, as has been shown in the COAST study. The new results reinforce those findings, and also that having a previous exacerbation is the strongest predictor for subsequent exacerbations.*

B.E.C.

Damage SC, Eras B, Jarvis D, et al: Do childhood respiratory infections continue to influence adult respiratory morbidity?

Eur Respir J. 2009;33:237-244. ◆◆

Does Athlete's Foot Affect Asthma Severity?

ALLERGY to molds has been linked to increased asthma exacerbations and severity. Previous studies have suggested that sensitization to the dermatophyte *Trichophyton* is associated with asthma, and that antifungal treatment may improve patient outcomes. ►►

The specific IgE response to *Trichophyton* was evaluated in a large sample of Japanese patients with asthma.

Specific IgE titers to *Trichophyton rubrum*, the major cause of dermatophyte infection in Japan, were measured in 258 patients with asthma ranging from mild to severe. One hundred fourteen healthy controls were studied as well; sensitization to other common allergens was also evaluated in both groups. Associations between *Trichophyton* sensitization and asthma severity were assessed.

Rates of positivity for *Trichophyton*-specific IgE were 32.4% in patients with severe asthma, 15.8% in those with moderate asthma, 4.9% in those with mild asthma, and 7.0% in controls. The differences were significant for patients with severe or moderate asthma versus controls and for patients with mild versus moderate asthma. Positivity rates for other allergens—including mixed molds and dog and cat dander—were higher in asthma patients than in controls, but not significantly different between the three asthma severity groups.

A similar pattern emerged on exclusion of 53 patients who also tested positive for mixed molds, suggesting that the findings were not influenced by cross-reactivity. On multivariate analysis, a specific IgE response to *Trichophyton* was independently associated with asthma severity.

In this Japanese study, positive IgE results for *Trichophyton* are associated with increased asthma severity. Sensitization to *Trichophyton* may be associated with the development of severe asthma, and should be considered in evaluation of patients with refractory asthma.

COMMENT: *The association of Trichophyton sensitization and colonization in patients with asthma has been demonstrated in Venezuela, Turkey, and now Japan. Mean data clearly demonstrated correlations between Trichophyton IgE and severity of moderate and severe asthma. Importantly, these mean data were generated by a subgroup of 16% and 32% of IgE Trichophyton-positive asthmatics. Antifungal treatment of these patients who also have been colonized demonstrated benefit. Time to examine the feet of our patients with severe asthma.*

S.F.W.

Matsuoka H, Niimi A, Matsumoto H, et al: *Specific IgE response to Trichophyton and asthma severity.*

Chest. 2009;35;898-903. ◆◆

New Data on OSA Risk among Asthma Patients

PREVIOUS studies have reported high rates of obstructive sleep apnea (OSA) symptoms among patients with asthma. Factors associated with snoring and OSA risk were evaluated in a referral population of asthma patients.

The study included 244 patients seen at pulmonary and asthma clinics. Risk of OSA was assessed using the Sleep Apnea scale of the Sleep Disorders Questionnaire-

-risk of OSA was considered high at a cutoff score of 36 for men and 32 for women. Asthma severity was categorized using the National Asthma Education and Prevention Program guidelines. Factors associated with habitual snoring and high OSA risk were assessed by logistic regression.

Thirty-seven percent of the patients were habitual snorers, while 40% were considered at high OSA risk: 28% of men and 45% of women. Factors independently associated with habitual snoring were gastroesophageal reflux disease, odds ratio (OR) 2.19; and inhaled corticosteroid (ICS) use, OR 2.66. Patients with more severe asthma were more likely to have high OSA risk: OR 1.59 for each one-step increase in asthma severity. For ICS use, the OR was 4.05—ICS use was associated with both habitual snoring and high OSA risk in linear, dose-dependent fashion. After controlling for covariates, high OSA risk was twice as common among women with asthma: OR 2.11, compared to men.

Among patients with asthma, high OSA risk is associated with asthma severity, GERD, and ICS use. In contrast to the usual male predominance, female asthma patients are at higher risk. More research is needed to explain this and other characteristics of the link between OSA and asthma.

COMMENT: *Obstructive sleep apnea is a common finding especially in patients with asthma. This questionnaire-based study found that 40% of asthmatics had high OSA risk. Noteworthy was a dose-response association with ICS. We should be aware of comorbid OSA in our asthma patients and look for further clarification on the role of ICS in its pathogenesis.*

S.F.W.

Teodorescu M, Consens FB, Bria WF, et al: *Predictors of habitual snoring and obstructive sleep apnea risk in patients with asthma.*

Chest. 2009;135;1125-1132. ◆◆

Specific/Total IgE Ratio Predicts Response to Immunotherapy

THERE is currently no test capable of predicting the clinical response to allergen specific immunotherapy (ASI). A wide range of baseline parameters were evaluated as predictors of the response to ASI.

The retrospective study included 279 monosensitized adult patients receiving 4 years of ASI for allergic rhinitis with or without asthma. Immunotherapy was administered sublingually in 203 patients and subcutaneously in 76. Diagnostic information on serum specific and total IgE levels, blood eosinophil counts, and specific/total IgE ratio was evaluated for correlations with the clinical response to ASI, based on at least a 30% reduction in symptom scores.

The clinical response rate was 52.0% overall, 55.2% with subcutaneous ASI, and 50.7% with sublingual ASI. The serum specific/total IgE ratio was significantly correlated with clinical response. Diagnostic performance was best at a ratio of greater than 16.2%: sensitivity was 96.7% and specificity 88.1%. The specific/total IgE >>>

ratio offered better performance than either IgE value alone.

The serum specific/total IgE ratio is a potentially useful predictor of the clinical response to ASI. The authors note some important limitations, including the fact that the study included only patients monosensitized to grass, *Parietaria judaica*, *Olea europea*, or house dust mite.

COMMENT: When patients ask about the effectiveness of specific immunotherapy, the answer usually involves references to statistics and probabilities. These Italian researchers report that the ratio of s-IgE/total IgE has a sensitivity of 97% and a specificity of 88% in predicting a good clinical response to immunotherapy in allergic patients. Limitations include a small sample size, subjective assessment for clinical response, and retrospective design. It would be nice to have a tool that accurately predicts clinical response to therapies.

S.M.F.

Di Lorenzo G, Mansueto P, Pacor ML, et al: Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen-specific immunotherapy.

J Allergy Clin Immunol. 2009;123:1103-1119. ♦♦

Bronchiolitis Severity Affects Childhood Asthma Risk and Morbidity

BRONCHIOLITIS during infancy is a risk factor for asthma during early childhood. However, it is unclear whether the risk and morbidity of early childhood asthma depend on the severity of bronchiolitis. This study sought evidence of a "dose-dependent" relationship between the severity of bronchiolitis and early childhood asthma.

The researchers analyzed data on healthy term infants born between 1995 and 2000 and enrolled in the Tennessee's statewide TennCare Medicaid program. Infants with bronchiolitis were identified, and bronchiolitis severity classified according to the highest level of health care required. Prevalent asthma was assessed at age 4 to 5.5 years using Medicaid and linked vital records data. Asthma morbidity between age 4.5 and 5.5 was rated using information on hospitalizations, emergency department visits, and oral corticosteroid use.

Of 90,341 children in the retrospective birth cohort study, 18% had a visit for bronchiolitis during infancy. This group accounted for 31% of children with asthma between age 4 and 5.5 years. The more severe the bronchiolitis, the greater the risk of asthma: adjusted odds ratios were 1.86 for bronchiolitis treated on an outpatient basis, 2.41 for bronchiolitis leading to an emergency room visit, and 2.82 for bronchiolitis with hospitalization. The associations were strongest for children with a maternal history of asthma. Bronchiolitis severity was also related to the risk of asthma morbidity.

Among infants with bronchiolitis, the risk of early childhood asthma increases with the severity of bronchiolitis. There is also a "dose-response" relationship between bronchiolitis severity and asthma-specific morbidity. Nearly one-third of cases of early childhood asthma

occur in patients with a history of bronchiolitis in infancy, the new results suggest.

COMMENT: In this study of infants with bronchiolitis, those with the most severe morbidity had an increased risk of more severe asthma by age 4 to 5.5 years. Another interesting finding was that in the subset of bronchiolitic infants whose mothers had asthma, there was an even greater risk to develop asthma with a similar severity-dependent pattern. The data suggest that there is a dose-response relationship between the severity of bronchiolitis in infancy and the severity of asthma in childhood.

S.M.F.

Carroll KN, Wu P, Gebretsadik T, et al: The severity-dependent relationship of infant bronchiolitis on the risk and morbidity of early childhood asthma.

J Allergy Clin Immunol. 2009;123:1055-1061. ♦♦

Maternal Farm Exposure Affects Cord Blood Treg Cells

THE offspring of mothers exposed to farm environments are at reduced risk of allergic diseases. One possible explanation is that farm exposure reflects microbial exposure, with a less allergic anti-Th2 phenotype developing through an innate immune mechanism. This study evaluated the possible effect of maternal farm exposure on regulatory T (Treg) cells in cord blood.

Specific farm exposures were assessed in two groups of pregnant mothers in a rural area of Germany: 22 farming and 60 nonfarming women. Cord blood samples were tested to seek quantitative and qualitative differences in Treg cells between the two groups of offspring. In vitro stimulations were performed to determine whether the Treg cell differences would lead to differences in Th1/Th2 effector cell responses and lymphocyte proliferation.

Both unstimulated and after stimulation with PHA mitogen, cord blood Treg cell counts increased with maternal farming exposure. Treg cell counts were associated with increased forkhead/winged-helix family transcriptional repressor p3 (FOXP3) expression, a key Treg cell characteristic. There was also a trendwise increase in lymphocyte activation gene 3 (Ppg) expression. Levels of the Th2 cytokine interleukin-5 were decreased in association with decreased lymphoproliferation and increased levels of interleukin-6.

Greater maternal exposure to farm animals and stables had discrete effects on Treg cells and/or Th1/Th2 cells. There was also evidence of increased FOXP3 demethylation in offspring of mothers exposed to farm milk.

Maternal farm exposures during pregnancy are associated with increased numbers and functioning of Treg cells in cord blood. The increase in Treg cells is associated with reductions in secretion of Th2 cytokines and lymphocyte proliferation. Maternal farm exposure might be "a natural model of immunotherapy," affecting the child's immune system very early in life. ►►

COMMENT: *In this well-designed study, cord blood from infants of mothers with farm exposure had increased Treg cells associated with lower Th2 responses, compared to a cohort of infants from nonfarming mothers. The authors speculate that farm exposure might reflect a natural model of immunomodulation altering the child's immune system and reducing allergic potential.*

S.M.F.

Schaub B, Liu J, Höppler S, et al: Maternal farm exposure modulates neonatal immune mechanisms through regulatory T cells.

J Allergy Clin Immunol. 2009;123:774-782. ♦♦

Low Parental Support Linked to Reduced Cortisol Sensitivity

HIGH stress, especially family stress, is associated with worse asthma outcomes. Paradoxically, stress induces secretion of cortisol, which suppresses inflammation and may thus reduce asthma symptoms. This study evaluated the effects of a specific type of family stress on glucocorticoid resistance in children with asthma.

Sixty-seven children with asthma and 76 healthy controls, mean age 13, completed a questionnaire regarding their perceived levels of support and understanding from their parents. This parental support variable was compared with in vitro measures of lymphocyte resistance to glucocorticoids, as well as eosinophil mobilization and activation parameters.

Asthma patients and controls had the same mean level of family support: 2.5 on a 1-to-4 scale. In the in vitro studies, asthmatic children who perceived low parental support showed increased resistance to the anti-inflammatory effects of hydrocortisone on interleukin-5 and interferon- γ . Circulating levels of eosinophil cationic protein were also higher among asthmatic children with low parental support. The associations remained significant after adjustment for socioeconomic status, exposure to smoking, asthma severity, and medication use.

Strained family relationships, and possibly stress in general, appear to be associated with reduced glucocorticoid sensitivity in children with asthma. Low parental support is associated with reduced regulation of cytokine activity by cortisol, which may lead to increased airway inflammation. Although further research is needed, interventions to address strained family relationships might help to improve outcomes in children with asthma.

COMMENT: *It is well known that stress has a detrimental effect on patients with chronic diseases such as asthma. These Canadian researchers report that the stress from strained parent-child relationships can have a detrimental effect on the ability of cortisol to regulate the cytokines that enhance inflammation in childhood asthmatics. Could there have been an immunologic basis for long-term hospitalization or the "parentectomy" that was recommended years ago for*

resistant childhood asthma?

S.M.F.

Miller G, Gaudin A, Zysk E, Chen E, et al: Parental support and cytokine activity in childhood asthma: the role of glucocorticoid sensitivity.

J Allergy Clin Immunol. 2009;123:824-830. ♦♦

Pediatric Chronic Rhinosinusitis Pathology Differs from Adults

IN adults, chronic rhinosinusitis (CRS) is characterized by eosinophilic inflammation. Although a similar process has been assumed in children with CRS, previous reports have described a predominantly lymphocytic pattern of inflammation. This study compared the immunohistopathologic findings of children and adults with CRS.

Biopsy specimens of maxillary mucosa were obtained from 19 young children (median age 3 years) with CRS. Immunohistochemical techniques were used to compare the cellular immune responses of this group of children with those in a sample of adults with CRS.

Specimens from children with CRS showed more positive epithelial staining for cytotoxic T lymphocytes (CD8), neutrophils (myeloperoxidase), and monocytes/macrophages (CD68), compared to specimens from adults. The pediatric specimens also showed a trend toward increased staining for T lymphocytes (CD3) and helper T lymphocytes (CD4) in the epithelium. In the submucosa, specimens from children showed increased staining for B lymphocytes (CD20), plasma cells (κ and λ), neutrophils, and monocytes/macrophages, as well as a trend toward increased staining for helper T lymphocytes. Aside from increased staining for neutrophils in the submucosa, the results were similar for CRS children with negative versus positive sinus cultures.

In young children with CRS, the inflammatory pattern is characterized by a mix of lymphocytes, macrophages, and neutrophils. The immunopathologic differences between pediatric and adult CRS may reflect differences in pathogenesis or in the progressive inflammatory response in patients with a protracted course of disease. Different approaches to treatment may be appropriate.

COMMENT: *Numerous examples of how young children are not "little adults" exist in the medical literature. Here is yet another study showing that extrapolation from adult data is misleading--notably the impression that CRS is an eosinophilic disease. Perhaps the etiology for cellular immunopathologic findings is entirely unique between children and adults, or alternatively the findings represent early pathology in evolution. Quite interestingly, these results have significant parallels to findings in pulmonary tissue in pediatric asthma.*

K.R.M.

Coffinet J, Chan KH, Abzug MJ, et al: Immunopathology of chronic rhinosinusitis in young children.

Pediatrics. 2009;154:754-758. ♦♦

Coming Clean (with Bleach)

IN children with atopic dermatitis (AD), antibiotics against *Staphylococcus aureus* are an important part of treatment. The emergence of community-acquired methicillin-resistant *S. aureus* raises new concerns in this patient population. This study assessed the prevalence of community-acquired MRSA in children with AD, and evaluated the benefits of two forms of anti-staphylococcal therapy.

The randomized trial included 31 children, from infancy to adolescence, with moderate to severe AD and clinical evidence of secondary bacterial infection. All patients received 2 weeks of antibiotic therapy with cephalexin. They were then assigned to combination therapy with intranasal muciprocin ointment plus sodium hypochlorite (bleach) baths with; or placebo ointment/plain water baths. The bleach baths were prepared by adding one-half cup of 6% bleach to a full tub of water; both treatments continued for 3 months. Responses were assessed using the Eczema Area and Severity Index Score.

This sample of children with AD had a low prevalence of community-acquired MRSA: 7.4% of *S. aureus* skin cultures and 4% of positive nasal cultures. This compared to rates of 75% to 85% in a children's hospital population.

Bleach baths plus intranasal muciprocin was associated with significant reductions in eczema severity compared to the placebo group. The difference was significant at both 1 and 3 months. The improvements were noted in areas submerged in the bath—not on the head and neck. The bleach baths were well tolerated.

Children with AD do not appear to be particularly vulnerable to infection or colonization with community-acquired MRSA. For patients with AD and secondary bacterial infections, the combination of dilute bleach baths and intranasal muciprocin is associated with reductions in AD severity. More study is needed to establish the efficacy and safety of bleach baths.

COMMENT: *Staphylococcal colonization has long been known to be associated with AD severity. What has not been known is the extent to which children with this disorder are colonized with MRSA—an increasing problem in most communities. Thus far, we are thankfully reassured from an MRSA standpoint.*

The objective clinical improvement with use of bleach baths in a placebo-controlled, blinded setting reaffirms this treatment as part of our armamentarium for AD control. It would have been helpful to know whether or not the bleach baths actually reduced staphylococcal colony counts—not investigated here but hopefully a focus of future research. What also remains is convincing skeptical parents that this treatment will be beneficial, and without significant adverse effects.

K.R.M.

Huang JT, Abrams M, Tiougan B, et al: Treatment of Staphylococcus aureus colonization in atopic dermatitis decreases disease severity.

Pediatrics. 2009;123:e808-e814. ◆◆

CAMP Shows No Long-Lasting Benefit from ICS, Once Discontinued

THE Childhood Asthma Management Program (CAMP) study showed improved asthma control in children receiving inhaled anti-inflammatory therapy. However, questions remain regarding the long-term safety and benefits of these medications, especially inhaled corticosteroids. A post-trial follow-up study was performed to assess asthma control and other outcomes after discontinuation of anti-inflammatory medications.

The study included 941 children with mild to moderate asthma who received 4.3 years of twice daily budesonide, nedocromil, or placebo during the CAMP trial. The patients were followed up for 4.8 years after the end of the trial, during which their care was managed by their primary care physicians. The three treatments were compared for asthma control and a wide range of other outcomes.

Nearly 5 years after the end of the CAMP trial, asthma control and pulmonary function measures were no different for the budesonide and nedocromil groups versus the placebo group. Psychologic status was similar as well. Children in the budesonide group had a significant reduction in mean height, compared to the placebo group: mean difference 1.1 cm at the end of the trial and 0.9 cm at the end of post-trial follow-up. The difference was more pronounced in girls than boys, 1.7 versus 0.3 cm, respectively. In all three groups, patients were receiving inhaled corticosteroids during approximately 30% of follow-up.

Long-term follow-up of young asthma patients enrolled in the CAMP trial shows that the benefits of continuous inhaled corticosteroids are not maintained after treatment is discontinued. Neither form of anti-inflammatory therapy tested has a persistent modifying effect on the course of asthma. Inhaled corticosteroid therapy has a small but significant effect on growth in asthmatic children.

COMMENT: *The landmark CAMP prospective study has provided our field with a wealth of important data since its inception over 15 years ago. This latest post-CAMP trial yields useful information about the course of asthma once inhaled corticosteroids are discontinued. While the post-discontinuation results are not surprising, our collective disappointment remains regarding the impact of our current therapies on asthma disease progression, despite ongoing treatment. After all, wouldn't we agree that an ideal asthma therapy would improve the natural course of asthma—in addition to controlling current symptoms—at least while it is being used?*

K.R.M.

Strunk RC, Sternberg AL, Szefler SJ, et al: Long-term budesonide or nedocromil treatment, once discontinued, does not alter the course of mild to moderate asthma in children and adolescents.

J Pediatrics. 2009;154:682-687. ◆◆

No Benefit of PPIs in Asthma Patients without GERD Symptoms

GASTROESOPHAGEAL reflux disease (GERD) is frequently found in patients with asthma, but often causes mild or no symptoms. The effects of proton-pump inhibitor (PPI) therapy on asthma outcomes in this group of patients are unknown. The asthma control benefits of PPI therapy were evaluated in patients with poorly controlled asthma and no symptoms of GERD.

The study included 412 patients with poorly controlled asthma despite inhaled corticosteroid therapy, and with no more than minimal symptoms of GERD. They were randomly assigned to receive 24 weeks of treatment with esomeprazole, 40 mg twice daily, or placebo. Asthma control was assessed using patient diaries; ambulatory pH monitoring was used to determine the presence or absence of GERD.

The frequency of episodes of poor asthma control was not significantly different between groups: 2.5 versus 2.3 events per person-year with esomeprazole versus placebo, respectively. Secondary outcomes were similar as well, including pulmonary function, airway reactivity, asthma control and symptoms, and quality of life. Esomeprazole did not improve asthma outcomes in the 40% of patients who had positive results on esophageal pH monitoring. There were 11 serious adverse events in the esomeprazole group versus 17 in the placebo group.

Esomeprazole does not improve asthma outcomes in patients with poorly controlled asthma who are free of GERD symptoms. This is so even for patients with reflux documented by esophageal pH monitoring. Asymptomatic gastroesophageal reflux does not appear to be a major contributor to inadequate asthma control.

COMMENT: *We are taught that frequent contributors to unstable asthma include chronic sinusitis, uncontrolled allergies, and GERD. Acid reflux can be asymptomatic. In this study, subjects with poorly controlled asthma and no heartburn were studied for the presence of asymptomatic acid reflux, and randomized to high-dose esomeprazole or placebo. Treatment did not improve asthma control. However, the results might have been different if the patients had symptomatic reflux. Also, reflux of non-acid irritants might need other forms of treatment.*

R.J.M.

The American Lung Association Clinical Research Centers: Efficacy of esomeprazole for treatment of poorly controlled asthma.

N Engl J Med. 2009;360:1487-1499. ♦♦

High Rate of Accidental Allergic Reactions to Cow's Milk

ACCIDENTAL allergic reactions to cow's milk protein are common in milk-allergic children. Most previous studies of accidental allergic reactions have focused on peanut allergy. This study analyzed the frequency and characteristics of accidental allergic reac-

tions among children allergic to cow's milk.

The study included 88 children with cow's milk allergy, median age 32.5 months. Accidental exposures over the previous 12 months were assessed using a standardized questionnaire. Reactions were classified as to severity, and cow's milk and casein-specific antibody titers were measured.

Thirty-five children had a total of 53 accidental allergic reactions to cow's milk protein during the 1-year study period. Fifty-three percent of the reactions were mild, 32% moderate, and 15% severe. Forty-seven percent occurred at home and 85% under daily life circumstances. Eighty-three percent of reactions were attributable to foods, with a wide range of food products implicated. Median cow's milk-specific IgE levels were 37.70 kUA/L in children with severe reactions, 7.71 kUA/L in those with moderate reactions, and 3.37 kUA/L in those with mild reactions. Children with asthma were 10 times more likely to have severe reactions.

Over 1 year, 40% of children with cow's milk allergy will have accidental allergic reactions, the new results suggest. Fifteen percent of such reactions are severe; severe reactions are more common in children with asthma and high specific IgE levels. Co-operative efforts, including physicians, parents, and food manufacturers, will be needed to decrease the rate and severity of accidental allergic reactions to milk products.

COMMENT: *Cow's milk causes more childhood food allergies than any other food. What are the data on accidental reactions? Over only 1 year of study, 40% of children had reactions; 47% of the reactions were moderate or severe. Half of them occurred at home. I found fascinating the sources of exposure, including cosmetics, cold cuts, baked goods, and a commercial vegetable puree. Such studies allow us to address parents' anxieties by providing real data. Knowledge is power.*

R.J.M.

Boyano-Martínez T, García-Ara C, Pedrosa M, et al: Accidental allergic reactions in children allergic to cow's milk proteins.

J Allergy Clin Immunol. 2009;123:883-888. ♦♦

Blood Tests Predict Adult-Onset Allergic Asthma

PATIENTS with allergic rhinitis are at risk of developing asthma. Currently, monitoring of disease activity is based mainly on symptoms. Recent reports suggest that eosinophil cationic protein (ECP) and eosinophil peroxidase (EPO) reflect disease activity in allergic rhinitis. These markers of eosinophil activity were evaluated as predictors of asthma risk in patients with allergic rhinitis.

The study included 44 patients with seasonal allergic rhinitis who had participated in a previous study 6 years earlier. That study included measurement of blood eosinophils, as well as levels of ECP and EPO in serum and nasal lavage specimens. The current study included re-evaluation of current rhinitis and asthma symptoms, as well as skin prick testing for common aeroaller-▶▶

gens. The eosinophil markers were evaluated as predictors of new allergies, worsening rhinitis, and development of asthma.

At follow-up, 4 patients had worsened seasonal rhinitis symptoms, 10 had perennial rhinitis, 14 had asthma-like symptoms, and 7 had been diagnosed with asthma. Skin tests showed new sensitizations in 13 patients. In serum, both eosinophil markers were higher in patients who had developed asthma-like symptoms: 16.7 versus 8.2 $\mu\text{g/L}$ for serum ECP and 17.8 versus 8.8 $\mu\text{g/L}$ for serum EPO. The eosinophil markers in nasal lavage were not significant predictors; nor was blood eosinophil level. None of the eosinophil parameters predicting worsening rhinitis or new sensitizations.

In patients with seasonal allergic rhinitis, serum ECP and EPO may be useful predictors of the later development of asthma. The availability of these blood tests may allow patients to be targeted for preventive measures, which should be evaluated in randomized controlled trials.

COMMENT: *In this study, serum ECP and EPO levels were twice as high among adult allergic rhinitis patients who later had asthma than those who did not develop asthma. These findings may be the beginning of the end of the guesswork involved with predicting which allergic rhinitis patients will later have asthma.*

S.A.T.

Nielsen LP, Peterson CGB, Dahl R: Serum eosinophil granule proteins predict asthma risk in allergic rhinitis. *Allergy*. 2009;64:733-737. ◆◆

Maternal Vitamin D Intake Affects Childhood Asthma Risk

VITAMIN D has recently been shown to have various immunologic effects. Some studies have found that a higher vitamin D intake during pregnancy is associated with a lower rate of early childhood wheezing, although another study reached a contradictory conclusion. The relationship between maternal vitamin D intake and allergic disease outcomes in children was assessed in a Finnish population.

The population-based study included 1,669 children who were members of a Finnish birth cohort. (The children had increased susceptibility to type 1 diabetes associated with HLA-DQB1.) Maternal vitamin D intake was assessed using a food frequency questionnaire. Outcomes of interest were allergic diseases developing by age 5, including asthma, allergic rhinitis, and atopic eczema.

The mothers had a mean vitamin D intake of 5.1 μg from food and 1.4 μg from supplements. Less than one-third of the women were taking vitamin D supplements; only 15% met the recommended vitamin D intake of 10 $\mu\text{g/d}$. On adjusted analysis, children whose mothers had a higher intake of vitamin D from food were at lower risk of asthma and allergic rhinitis: hazard ratio 0.80 and 0.85, respectively. Use of vitamin D supplements did not affect the allergic disease outcomes. The protective effects of high vitamin D intake were unaffected by

adjustment for other dietary factors.

High maternal intake of vitamin D from foods is associated with a reduced risk of early childhood asthma and allergic rhinitis in offspring. This and other findings highlight the need for an intervention trial of maternal vitamin D intake during pregnancy (with close attention to potential toxicity of vitamin D).

COMMENT: *The relationship between maternal vitamin D intake during pregnancy and atopy has become a hot topic, particularly because of the conflicting conclusions thus far reported. This Finnish cohort study found that a higher maternal vitamin D intake during pregnancy was associated with a reduced risk of both asthma and allergic rhinitis at age 5. Although the jury is still out whether to advise vitamin D supplementation during pregnancy, this may be a "cleaner" way to study this phenomenon because Finland is a place with generally low vitamin D intake, low sunlight exposure, and a high prevalence of asthma.*

S.A.T.

Erkkola M, Kaila M, Nwaru BI, et al: Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clin Exp Allergy*. 2009;39:875-882. ◆◆

New Data on Mechanisms of Immune Effects of Probiotics

THE role of probiotics has recently been reviewed by several authors. However, the immunomodulatory mechanisms for their antiallergic effects are still unclear. In vivo and in vitro experiments were performed to evaluate the immunomodulatory effects of a combined probiotic preparation.

The study looked at responses to the VSL#3 probiotic preparation, a high-concentration combination of eight species. In vitro experiments were performed using bone-marrow dendritic cells (BM-DCs) and spleen cells isolated from control mice and from animals sensitized to Par j 1—the major allergen of *Parietaria judaica*. Maturation and cytokine production by BM-DCs was stimulated by both live and sonicated VSL#3. In spleen cells, the VSL#3 preparations modulated cytokine production toward a Treg/Th0 profile, with increased production of interleukin-10 and interferon- γ .

In an in vivo study, mice underwent intranasal administration of a sonicated preparation of VSL#3, then were immunized with rPar j1. Animals treated with VSL#3 had a significant reduction in serum specific IgG1. Studies of lung tissue showed sharp reductions in expression of interleukin (IL)-13 and IL-4 mRNA expression, along with increased expression of IL-10.

These experimental findings suggest that a high-concentration probiotic preparation can modulate factors involved in the development of a Th2-type response to inhaled allergens. The effect largely involves local anti-inflammatory cytokines, without up-regulation of Th1 responses. The findings may aid in understanding >>>

the mechanisms by which probiotics may be useful in the prevention and treatment of type I allergy.

COMMENT: Probiotic bacteria as single bacterial species or in mixtures of multiple bacteria can affect the innate and adaptive immune system and have been studied in various gastrointestinal, allergic, and autoimmune conditions, both *in vitro* and *in vivo*. These authors believe that, in their lung experiments, VSL#3 biased primary immune responses toward a Treg/Th0-type profile and modified the functional characteristics of established *in vitro* Th2 responses. They also believe that prophylactic intranasal treatment with probiotic bacteria modulated the development of Th2-biased responses *in vivo*.

M.F.

Mastrangeli G, Corinti S, Butroni C, et al: Effects of live and inactivated VSL#3 probiotic preparations in the modulation of *in vitro* and *in vivo* allergen-induced Th2 responses.

Int Arch Allergy Immunol. 2009;150:133-143. ◆◆

Differences in Cytokine Genotypes Associated with CVID

COMMON variable immunodeficiency (CVID) refers to a heterogeneous group of immune disorders associated with hypogammaglobulinemia and high rates of recurrent infections, autoimmune disorders, and cancers. There are conflicting data regarding cytokine profiles in patients with CVID. The authors assessed genotype frequencies of various polymorphic genes coding for cytokines in patients with CVID.

The Iranian study included 30 unselected patients with CVID and 140 healthy controls. Genetic profiles for a number of cytokines were analyzed, including interleukin (IL)-2, IL-12, interferon (IFN)- γ , and transforming growth factor (TGF)- β .

The genotype TGF- β CG at position +915 was over-represented among the patients with CVID. In contrast, the genotypes TGF- β TT at +869 and GG at +915 were less frequent among the patients compared to controls. The most frequent haplotypes in CVID patients were TGF- β TC and IL-2 GT, while the TGF- β TG haplotype was less frequent in patients versus controls. The two groups were similar in terms of allele and genotype frequencies of IFN- γ at position UTR +5644 and of IL-12 at position -1188.

The study presents new data on the genotypes of polymorphic genes encoding various cytokines in patients with CVID. The findings suggest that low production of TGF- β might be found in some CVID patients. Additional research is needed to demonstrate associations between these gene polymorphisms and the immunologic manifestations of CVID.

COMMENT: Cytokine profiling of CVID patients can be useful. The results show some differences in TGF- β and IL-2 genes among patients with CVID, compared to controls. The lack of difference in IFN- γ and IL-12 gene polymorphisms could support the concept that Th1 type

responses are normal in at least some CVID patients. Single-nucleotide polymorphisms affecting cytokines could play a pathophysiologic role in CVID.

M.F.

Rezaei N, Aghamohammadi A, Shakiba Y, et al: Cytokine gene polymorphisms in common variable immunodeficiency.

Int Arch Allergy Immunol. 2009;150:1-7. ◆◆

CLINICAL TIDBITS

Omega 3 and 6 Oils Don't Prevent Clinical Allergies

THERE is high interest in the use of essential fatty acids—especially omega and omega 6 oils—for the prevention and treatment of allergic disease. Previous studies of this issue have yielded conflicting results.

A systematic review of the literature identified 10 papers, reporting on 6 randomized, double-blind trials, of omega 3 and omega 6 oils for primary prevention of allergic disease. Neither fatty acid had any consistent effect on risk of allergic sensitization or other immunologic parameters. On meta-analysis, there was no significant effect of omega 3 or omega 6 oil in preventing asthma, allergic rhinitis, food allergy, or atopic eczema.

Available evidence from randomized trials does not support the effectiveness of omega 3 or 6 oil supplementation for primary prevention of sensitization or allergic disease. The findings contrast with the positive results of previous basic science and epidemiologic studies.

COMMENT: There have been provocative epidemiologic observations identifying an association between dietary omega 3 and omega 6 oils and a lower incidence of allergic disease. However, this meta-analysis found that dietary supplementation with these fats does not appear to be an effective primary prevention strategy. S.A.T.

Anandan C, Nurmatov U, Sheikh A: Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis.

Allergy. 2009;64:840-848. ◆◆

What Acute and Maintenance Doses for Nasal Polyposis?

THERE is a long history of debate over the management of nasal polyposis (NP). A randomized trial was performed to evaluate the safety and efficacy of fluticasone propionate aqueous nasal spray (FPANS) for acute and maintenance therapy of NP.

Two hundred forty-six patients with NP were randomly assigned to three groups. Group 1 received FPANS 200 μ g bid during a 1-month acute period, a 1-month maintenance period, and a 6-month follow-up period. Group 2 received FPANS 200 μ g bid during the acute period and 200 μ g qd during the mainte- ➤➤

nance and follow-up periods. Group 3 received placebo during the acute and maintenance periods and FPANS 200 µg bid during the follow-up period. Outcomes included clinic and evening peak nasal inspiratory flow.

The 200 µg bid dose of FPANS was more effective than placebo after the acute and maintenance periods on all outcomes. After the maintenance period, 200 µg bid was more effective than 200 µg qd on most outcomes. After the follow-up period, all efficacy outcomes were similar between groups. There were no unexpected adverse events.

For patients with NP, FPANS 200 µg bid is an effective acute treatment. A 200 µg qd dose provides good maintenance of long-term efficacy over 6 months' follow-up.

COMMENT: *The use of nasal corticosteroids at approved doses is well accepted as a safe, effective, and—with the availability of generic fluticasone propionate—inexpensive treatment for allergic rhinitis. More controversial questions include whether this therapy is effective for nasal polyps and whether there is a dose response for its efficacy and side effects. This study on nasal polyposis demonstrated that twice-daily long-term dosing is more effective and does not increase the incidence of local side effects.*

S.A.T.

Jankowski R, Klossek J-M, Attali V, et al: Long-term study of fluticasone propionate aqueous nasal spray in acute and maintenance therapy of nasal polyposis. Allergy. 2009;64:945-950. ♦♦

Exercise Avoids Immune Effects of Prolonged Bed Rest

SPACEFLIGHT could have adverse effects on human immune function. Previous studies using a bed-rest model to assess potential health effects of spaceflight have been limited to men. This study evaluated the effects of prolonged bed rest on immune responses in women.

Twenty-four healthy women were maintained in supine head-down bed-rest (HDBR) position for 60 days. After immunization with bacteriophage φX-174, antibody responses were more rapid and greater for women assigned to HDBR plus regular muscular exercise, compared to those on HDBR alone or HDBR plus dietary protein supplementation. Levels of tumor necrosis factor (TNF)-α increased progressively in the HDBR alone and HDBR plus diet groups, compared to no change with HDBR plus exercise. Women assigned to HDBR plus exercise also had increases in interleukin (IL)-1 receptor antagonist and in RANTES.

Exercise appears to avoid the adverse immune system effects of prolonged bed rest, as a model of spaceflight, in women. In addition to better antibody responses, the addition of exercise avoids increases in TNF-α levels, possibly via activation of the anti-inflammatory cytokine IL-1 receptor antagonist and the chemotactic factor RANTES.

COMMENT: *Running can increase anti-inflammatory cytokines. Enhanced immunologic responses to antigen were found in those women who incorporated an exercise program during simulated weightlessness. Interestingly, exercise also helped reverse the detrimental effects of microgravity on cardiovascular parameters.*

S.M.F.

Shearer WT, Ochs H, Lee B-N, et al: Immune responses in adult female volunteers during the bed-rest model of spaceflight: antibodies and cytokines.

J Allergy Clin Immunol. 2009;123:900-905. ♦♦

No Benefit of Golimumab in Severe Persistent Asthma

TUMOR necrosis factor (TNF)-α could be a useful target for asthma treatment. Golimumab, an anti-TNF-α antibody, was evaluated for safety and efficacy in the treatment of severe persistent asthma.

The randomized trial included 309 patients with severe persistent asthma. Patients received 1 year of monthly subcutaneous injections with golimumab, 50, 100, or 200 mg; or placebo. Change in percent-predicted FEV₁ was not significantly different among groups. Through 24 weeks, the mean number of severe exacerbations was 0.5 across groups. Nearly 20% of patients assigned to golimumab discontinued treatment, compared to 3% of the placebo group. The study was halted early because of the high rate of infections and other serious adverse events with golimumab. Adverse events included 8 malignancies and 1 death.

Anti-TNF-α therapy with golimumab does not have a favorable risk-benefit profile in patients with severe persistent asthma. There is no improvement in pulmonary function or exacerbations, and a high rate of serious adverse events.

COMMENT: *The search for a treatment strategy to control airway inflammation in the patients with less than optimal response to conventional therapy continues. This study does not lend support to the two initial small trials suggesting anti-TNF therapy is helpful in patients with severe asthma. It is not likely that this anti-inflammatory intervention will be a viable option in the treatment of patients with asthma.*

B.E.C.

Wenzel SE, Barnes PJ, Bleecker ER, et al: A randomized, double-blind, placebo-controlled study of tumor necrosis factor-α blockade in severe persistent asthma. Am J Respir Crit Care Med. 2009;179:549-558. ♦♦

REVIEWS OF NOTE

COMMENT: All mothers are concerned about taking medications during pregnancy, as they should be. However, we know that asthma itself is a serious disease that can adversely affect both mother and fetus. A risk-benefit determination favors good control of the asthma along the well-established guidelines for use of medications. This review is one that you could provide to your pregnant patients with asthma.

R.J.M.

Schatz M, Dombrowski MP: Asthma in pregnancy.

N Engl J Med. 2009;360:1862-1869. ◆◆

COMMENT: An issue of great importance to those who treat asthma is the questioned safety of long-acting beta agonists (LABA). This review walks us through the FDA review committee processes that have addressed these drugs. Salmeterol and formoterol remain on the market for combination with inhaled steroids, even though we know the risk of death is slightly but measurably greater than in patients not using LABAs. What must be considered, however, are the benefits on quality of life and measures of control other than death. In these areas, LABAs are effective. Various committees disagree on whether those benefits outweigh the risks. This unseemly standoff will only be resolved by a large prospective trial.

R.J.M.

Kramer JM: Balancing the benefits and risks of inhaled long-acting beta-agonists--the influence of values.

N Engl J Med. 2009;360:1592-1595. ◆◆

COMMENT: This is an excellent review of the current thinking on the pathogenesis of chronic urticaria. The authors acknowledge that we still lack proof of cause and effect that autoantibodies are responsible for hives within the autoimmune subgroup.

S.A.T.

Kaplan AP, Greaves M: Pathogenesis of chronic urticaria.

Clin Exp Allergy. 2009;39:777-787. ◆◆

COMMENT: Immunologic features typical of CHARGE syndrome are summarized in this small study, including phenotypic differentiation from chromosome 22q11.2 deletion disorders. The importance of immunologic evaluation in all patients suspected of having CHARGE syndrome is emphasized, as heretofore potential for immunodeficiency in these patients was not well recognized.

K.R.M.

Jyonouchi S, McDonald-McGinn DM, Bale S, et al: CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness) syndrome and chromosome 22q11.2 deletion syndrome: a comparison of immunologic and nonimmunologic phenotypic features. Pediatrics. 2009;123:e871-e877. ◆◆

COMMENT: Clinicians should have updated knowledge of hereditary angioedema, as the number of treatment options is growing. This article will help.

D.K.L.

Craig T, Riedl M, Dykewicz MS, et al: When is prophylaxis for hereditary angioedema necessary?

Ann Allergy Asthma Immunol. 2009;102:366-372. ◆◆

COMMENT: This is an excellent review of the comorbid conditions associated with asthma, including an excellent reference list.

B.E.C.

Boulet L-P: Influence of comorbid conditions on asthma.

Eur Respir J. 2009;33:897-906. ◆◆

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