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AllergyWatch®

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

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More Diverse Diet in Infancy Linked to Lower Allergy Risk

THERE is ongoing debate over how infant feeding practices may affect the risk of allergic disease. Despite longstanding advice, there is no clear evidence that allergen avoidance or delayed introduction of foods has any beneficial effect. A previous study suggested infants whose diet included a greater diversity of foods during the first year of life were at lower risk of atopic dermatitis. A further study was conducted to assess the relationship between food diversity and other allergic disease risks, as well as associations with T-cell markers.

The study included 856 children from a previously reported European birth cohort, including information on feeding during the first year of life from monthly parental diaries. Regular follow-up questionnaires were used to collect data on environmental factors and the development of asthma, allergic rhinitis, food allergy, and atopic sensitization up to age 6 years. Data analysis included precautions against reverse causation.

Based on a score consisting of six food items, children who had a more diverse diet during the first year of life were at lower risk of allergic diseases. Food diversity score was inversely associated with asthma risk, with a dose-response effect: adjusted odds ratio 0.74 per additional food item introduced.

Similar inverse associations were noted for food allergy. A more diverse diet during the first year of life was also associated with increased expression of forkhead box protein 3, a transcription factor for regulatory T cells; and decreased expression of Cε germline transcript, a marker for antibody isotype switching to IgE.

The results suggest that increased dietary diversity in infancy may lower the risk of asthma, food allergy, and food sensitization later in childhood. While the ➤➤

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underlying mechanism remains unclear, it might involve induction of regulatory T cells. The investigators conclude, "Our findings highlight the role for diversity of environmental exposures on the development of allergic diseases."

COMMENT: *These European researchers extended their analysis of a birth-cohort study, in which they previously found that increased food diversity in the first year of life reduced the development of atopic dermatitis. In this report, the data show that increased food diversity can also reduce asthma and food allergies in children. The researchers also found increased expression of regulatory T-cell marker forkhead box protein 3 in children with increased food diversity. The authors suggest that the theory of a protective effect from a Th1/Th2 balance shift may really be from induction of regulatory T cells. The "hygiene hypothesis" debate continues.*
S.M.F.

Roduit C, Frei R, Depner M, et al: Increased food diversity in the first year of life is inversely associated with allergic diseases.
J Allergy Clin Immunol. 2014;133:1056-1064.

♦♦

FOCUS ON PSYCHOSOCIAL FACTORS

In this issue of *AllergyWatch*, we highlight some new research on psychosocial factors affecting allergic disease.
A.M.

Do Allergy Patients Have More Frequent 'Bad Moods'?

A few studies have provided evidence linking emotional stress to worsening of allergy symptoms. This study looked for associations between perceived emotional stress and allergy flares, including measurement of cortisol as a stress biomarker.

The researchers performed a secondary analysis of data on 179 participants from a study evaluating the effects of mindfulness on health symptoms and inflammation. Before each 2-week study period, subjects provided data on their perceived stress level and depressive symptoms. Online diaries were analyzed to assess same-day allergy flares, stressful events, perceived stress, and mood. The analysis also included measurements of cortisol in daily saliva samples.

Sixty-nine participants reported allergy symptoms. Scores for perceived stress were higher in this "allergy flare" group, compared to subjects without allergy symptoms. During two independent 14-day periods, allergy flares were significantly and positively associated with perceived stress, but not with depressive symptoms. Negative mood scores were also related to allergy flares across the course of the study. Salivary cortisol levels were unrelated to allergy symptoms.

Persistent emotional stress is associated with more frequent allergy flares. The study also suggests that individuals with more allergy flares have more problems with negative mood. Being aware of stress levels might be helpful for some patients with allergies.

COMMENT: *If you have ever thought that your patients were "cranky," you may be on the right track. This study looked at patient perception of stress and symptoms of depression over two periods of 2 weeks within a 3-month time span. The survey excluded patients who regularly participated in exercise. Patients who had flares of allergy had higher scores for perceived stress than those without allergy flares. They also had higher negative mood scores. Acute stress was not associated with allergy flares; rather, stress over time appeared more important. This article reminds us that stress can affect allergy flares.*
V.H.-T.

Patterson AM, Yildiz VO, Klatt MD, Malarkey et al: Perceived stress affects allergy flares.
Ann Allergy Asthma Immunol. 2014;112:317-321.

♦♦

Are Patients with Allergy to Insect Stings at Risk for Depression?

THE effects of Hymenoptera sting allergy on mental health are unclear. Worry about stings and the need for self-injectable medications can contribute to anxiety, which may cause patients to limit their activities, especially outdoors. This study evaluated anxiety and depression symptoms in patients with bee sting allergy.

The survey study included three groups of patients with Hymenoptera sting allergies: 35 using epinephrine only, 11 currently or previously receiving venom immunotherapy (VIT), and 44 receiving neither treatment. On standard questionnaires, patients receiving epinephrine only had higher mean anxiety and depression scores. In contrast, mean and median scores for both anxiety and depression were lower in patients receiving VIT. Of six patients with more than mild anxiety, five were in the epinephrine group and one in the no-treatment group.

Female patients had higher depression scores. Patients in the VIT and epinephrine groups were more likely to have a history of severe anaphylaxis.

Among patients with Hymenoptera sting allergy, VIT may improve quality of life by reducing anxiety and depression. Receiving VIT may lessen the mental health impact of bee sting allergy, compared to either epinephrine only or no treatment.

COMMENT: *As allergists, we know that emotions can affect or exacerbate allergic symptoms. In this survey study, most patients with insect sting allergy reported at least mild anxiety, but no anxiety above mild was reported by patients receiving VIT. These findings support the use of VIT to treat not only the allergic manifestations of insect sting allergy, but also to alleviate anxiety. Of the 20% of patients who reported some depression, half were in the group whose only treatment was epinephrine. Only 11% of the group with depression were on VIT. Overall, VIT patients had lowest scores for anxiety and depression, compared to those with receiving epinephrine only or no treatment. This article reminds us to consider the importance of anxiety and depression in our patients who live with life-threatening allergic disease.*
V.H.-T.
Findeis S, Craig T: The relationship between insect sting allergy treatment and patient anxiety and depression.
Allergy Asthma Proc. 2014;35:260-264, 2014. ♦♦

Depression Affects Adult Asthma Incidence

THERE is a well-documented link between asthma and depression, but the temporal nature of the association is unclear. Data from a large study of adult asthma patients were used to analyze the incidence of asthma associated with depressive symptoms, as well as the incidence of depression associated with asthma.

The Coronary Artery Risk Development in Young Adults (CARDIA) study was used to identify 3,614 participants initially free of asthma. At year 5 evaluation, 856 of these patients had elevated depressive symptoms and 2,758 did not. The researchers also identified 3,016 participants initially free of depressive symptoms, of whom 188 did and 2,828 did not have prevalent asthma. Patients were followed up 20 years for assessment of incident asthma and depressive symptoms, respectively.

With adjustment for covariates, there was a 1.26 hazard ratio (HR) for incident asthma among patients with elevated depressive symptoms. In a cumulative exposure model, with depressive symptoms weighted by number of reports, the HR decreased to 1.15, but remained significant. There was no difference in the risk of incident depressive symptoms for patients with and without asthma.

Long-term follow-up shows that patients with greater depressive symptoms are more likely to develop adult-onset asthma. Physicians should be aware that patients with depression are at increased risk of new-onset asthma; controlling depression might have a role to play in asthma prevention strategies.

COMMENT: *Depression is a significant marker for incident adult-onset asthma. This is an important observation in the evaluation of new patients presenting with asthma, as well as in follow-up care for those who have poor asthma control. Validated instruments can be used to diagnose and monitor therapy for depression in selected patients.*
B.E.C.
Brunner WM, Schreiner PJ, Sood A, Jacobs DR Jr: Depression and risk of incident asthma in adults.
Am J Respir Crit Care Med. 2014:189;1044-1051. ♦♦

Central Obesity Predicts Asthma Risk in Children

OVERWEIGHT and obesity have been linked to an increased incidence of asthma. Most studies of this relationship have used body mass index (BMI) as the sole indicator of adiposity. This study evaluated other anthropometric measures, physical fitness, and sedentary behavior as predictors of childhood asthma.

The analysis included data from the nationwide Taiwan Children Health Study, including 2,758 children followed up from fourth to sixth grade. Annual assessments included BMI; anthropometric measures of obesity, including abdominal and hip circumference, skin fold thicknesses and body composition; and physical fitness and sedentary time. The researchers examined the association between central obesity and asthma, as well as interrelationships among central obesity, physical fitness, sedentary time, and asthma.

Central obesity was the most accurate predictor of asthma--especially for active asthma rather than physician-diagnosed asthma. Incidence of active asthma was 2.54 cases per 100 person-years for children at or above the 85th percentile for waist circumference, compared to 1.91 per 100 for those below the 25th percentile. ➤➤

Associations were similar for waist to hip ratio and weight to height ratio.

Low physical fitness and high screen time were also associated with asthma development, via their contributions to central obesity. Obesity-related decreases in pulmonary function were identified as a possible mechanism in the pathway from central obesity to asthma.

Central obesity is a strong predictor of childhood asthma. By increasing central obesity, low physical fitness and high screen time are important contributors to asthma risk in children. The authors believe their findings may have "critical implications" for future asthma-prevention strategies.

COMMENT: *Obesity measured by abdominal girth is a marker of physical fitness and a predictor of sedentary lifestyle. This appears to be a very significant pathway to asthma, associated with physiologic changes that are likely not primarily driven by an inflammatory process. Dr. Thomas Platts-Mills first brought this to the medical community's attention over three decades ago. Also see the accompanying editorial by Dixon and Surratt:*
Am J Respir Crit Care Med. 2014;189:1155.
B.E.C.
Chen Y-C, Tu Y-K, Huang K-C, et al: Pathway from central obesity to childhood asthma: physical fitness and sedentary time are leading factors.
Am J Respir Crit Care Med. 2014;189:1194-1203. ♦♦

Epigenetics, β_2 Receptor and Inner-City Asthma

THERE have been conflicting reports as to how variants of the β_2 adrenergic receptor gene *(ADRB2)* affect asthma severity and control. Epigenetic phenomena affecting *ADRB2*, such as methylation of CpG "islands," may have an important influence on asthma phenotype. This study assessed DNA methylation of *ADRB2* and disease phenotype among inner-city schoolchildren with asthma.

The researchers analyzed DNA methylation of multiple CpG sites in the promoter region of *ADRB2* in samples from 77 school-age, inner-city children with asthma. The average percentage of DNA methylation across sites was analyzed for association with measures of asthma severity and morbidity. For individual CpG sites, methylation ranged from 0% to 6%, with an average of 2.4% across sites.

On univariate analysis, higher percentage methylation was associated with lower asthma severity, based on reported dyspnea. Trends linking increased methylation to lower rescue medication use, nighttime symptoms, school absence, activity limitations, and improved lung function were not significant. The association between methylation and decreased dyspnea remained significant on multivariate analysis: odds ratio 0.20.

Further analysis focused on three clades of highly correlated *ADRB2* methylation sites. Although all three clades were strongly related to decreased dyspnea, the associations were not significant.

Increased *ADRB2* gene methylation is associated with decreased symptom severity, especially dyspnea, in inner-city children with asthma. The results are "an important step in elucidating the relationship between methylation at the *ADRB2* gene and clinical asthma phenotypes,, the researchers write. Further epigenetic studies of *ADRB2* may lead to the discovery of new asthma pathways and pharmacologic targets.

COMMENT: *Epigenetics is a hot area in research, and one that may explain asthma and allergy disease trends that have outpaced genetic mutation rates. In this study, methylation in the promoter region of the β_2 adrenergic receptor gene was strongly associated with milder asthma. Although confirmatory studies are necessary, these findings may be a first step in a process of using epigenetics to identify therapeutic targets. Stay tuned!*
S.A.T.
Gaffin JM, Raby BA, Petty CR, et al: β-$_2$ Adrenergic receptor gene methylation is associated with decreased asthma severity in inner-city schoolchildren.
Clin Exp Allergy. 2014;44:681-689. ♦♦

Does IgE/IgG4 Ratio Predict Uncooked Egg Tolerance?

NEW approaches are needed to predict the natural development of tolerance to egg, cooked as well as uncooked, in children with egg allergy. Specific IgG4 (sIgG4) has been shown to play a protective role during resolution of cow's milk allergy, but its effects on the development of egg tolerance are unclear. This study evaluated ovalbumin-specific IgG4 as a predictor of tolerance in children with egg allergy, including comparison with other immunologic tests.

The prospective study included children and adolescents with IgE-mediated egg allergy who were following an egg-free diet. Patients underwent skin prick testing and measurement of specific IgE (sIgE) to ovalbumin, ovomucoid, and egg white, as well as ovalbumin- and ovomucoid-sIgE. The various tests were compared for their ability to predict tolerance of cooked and uncooked egg. Based on food challenges, the study included 50 children who were allergic and 50 who were tolerant of cooked egg; and 64 who were allergic and 21 tolerant of uncooked egg.

Ovalbumin-sIgG4 had an independent protective effect against uncooked egg allergy. The ovalbumin-sIgE/sIgG4 ratio better identified children likely to tolerate uncooked egg compared to sIgE and prick testing especially for patients with ovalbumin-sIgE less than 1.9 kU/L and ovomucoid-sIgE less than 2.12 kU/L.

For making challenge recommendations, the most accurate ovalbumin-sIgE/IgG4 cutoff points were less than 2.46 for cooked egg and 1.45 for uncooked egg. These thresholds were associated with 89.5% and 80% probabilities of tolerance, with negative likelihood ratios 0.08 and 0.06, respectively. Compared to sIgE, the ovalbumin-sIgE/IgG4 cutoffs identified an additional 23% and 14% of children as tolerant of cooked and uncooked egg, respectively. Compared to sIgE alone, skin prick testing better predicted tolerance of cooked and ➤➤

uncooked egg at an ovomucoid sIgE of less than 0.92 kU/L and ovalbumin sIgE of less than 1.37 kU/L.

The ovalbumin-specific IgG4 level is an independent predictor of the development of uncooked egg tolerance in egg-allergic children. The ovalbumin-sIgE/sIgG4 ratio, in combination with skin prick testing, is of higher value than sIgE in identifying children likely to become tolerant to cooked and uncooked egg.

COMMENT: *In contrast to our naturopathic colleagues, we generally think of specific IgG4 as a marker of tolerance whose primary utility is in studying mechanisms of immunotherapy efficacy. In this study, ovalbumin-specific IgG4 appears to be a predictor of natural tolerance development to uncooked egg in children allergic to eggs. With the food allergy epidemic in full swing, and with our "tolerant but sensitized" patients outnumbering the truly food allergic, we need more sensitive and specific tests. Until then, perhaps sIgE/IgG4 ratios will be useful in deciding whether to reintroduce the food in question.*
S.A.T.

Vazquez-Ortiz M, Pascal M, Jimenez-Feijoo R, et al: Ovalbumin-specific IgE/IgG4 ratio might improve the prediction of cooked and uncooked egg tolerance development in egg-allergic children.
Clin Exp Allergy. 2014;44:579-588. ♦♦

Omalizumab Helps Some Atopic Dermatitis Patients

ANTI-IgE therapy with omalizumab is an established treatment for severe allergic asthma and has shown activity against chronic spontaneous urticaria. Based on conflicting studies, it appears that omalizumab is beneficial only for a subgroup of patients with atopic dermatitis (AD). This study sought to identify markers of response to omalizumab in AD.

The prospective study included 20 adults with moderate to severe AD: 11 women and 9 men, aged 23 to 76 years. All received open-label treatment with omalizumab, given on a fixed schedule of 14 cycles of omalizumab 150 mg at 2-week intervals. Biomarkers potentially associated with a clinical response to omalizumab were analyzed.

As in previous studies, some patients had a good response: 4 had a SCORAD reduction of 50% or greater, and 4 had reductions of 25% to 50%. None of 7 patients with filaggrin mutations responded to omalizumab, while all 8 responders were not filaggrin mutation carriers. On quantitative serum metabolite studies, responders had higher baseline levels of three glycerophospholipid levels (PC.ae.C38:1, lysoPC a C28:0, and lysoPC a C26:1), along with lower total sphingomyelin (SM)/total phosphatidylcholine (PC) and total SM/total SM + PC ratios. Reductions in free IgE and the Th2 cell-attracting thymus and activation-related chemokine (TARC) were similar for omalizumab responders and nonresponders.

This pilot study suggests criteria associated with a response to omalizumab therapy for AD. Responders are free of filaggrin mutations, and thus have immunodysregulation rather than a primary skin barrier deficiency; and have increased PC species in serum. Further study is needed to confirm these findings and to address the underlying mechanisms.

COMMENT: *Allergists have long understood that using omalizumab only in patients with refractory allergic asthma is probably missing the boat when it comes to the total unmet need of "anti-IgE responsive" diseases. Prior studies of omalizumab for atopic dermatitis have reported conflicting results, though it has been remarkably effective in some patients. This study advances our understanding by identifying a subgroup of atopic dermatitis patients who respond to this anti-IgE therapy.*
S.A.T.

Hotse M, Baurecht H, Rodriguez E, et al: Increased efficacy of omalizumab in atopic dermatitis patients with wild-type filaggrin status and higher serum levels of phosphatidylcholines.
Allergy. 2014;69:132-135. ♦♦

Grandmothers' Smoking Affects Grandchildren's Asthma Risk

IT has been suggested the epigenetic changes may play a role in the "environment-driven epidemic of asthma," and that cigarette smoke may be a key environmental factor. Transgenerational effects of cigarette exposure during pregnancy in animals are supported by one study suggesting that that childhood asthma risk is affected not only by the mother's smoking, but by in utero exposure to the grandmother's smoking. The effects of grandmothers' smoking on childhood asthma risk were assessed using data from a large population study.

From the Avon Longitudinal Study of Parents and Children, the researchers identified four groups of grandchildren whose grandmothers did and did not smoke during the pregnancy resulting in their parent. The grandchildren's asthma and respiratory outcomes were assessed, including comparison of those whose mothers did and did not smoke.

Prenatal exposure of the mother or father to cigarette smoke did not affect the grandchildren's risk of being diagnosed with asthma. However, paternal prenatal exposure to their own mothers' smoking was associated with an increased risk of persistent wheezing in girls: adjusted odds ratio 1.42. Parental prenatal exposure did not appear to affect bronchial responsiveness or other objective lung function measures.

The study does not replicate a previously reported link between maternal prenatal tobacco exposure and the risk of respiratory symptoms in that mother's offspring. However, it does report a higher risk of persistent wheezing among girls whose fathers were exposed to maternal smoking during pregnancy. The authors discuss the implications for further research to understand epigenetic factors affecting asthma development.

COMMENT: *Epigenetics refers to heritable changes in gene activity that are not caused by changes in the DNA sequence and are a mechanism for environmental* ➤➤

influences on gene expression. Animal studies suggest that epigenetic factors can explain harmful effects of in utero exposure to nicotine on the airways, which can be passed on to the next generation without these animals having in utero nicotine exposure. A smaller prior human study indicated that exposure of the mother in utero to her own mother's smoking increased risk of asthma in the child. This study evaluated data from the Avon Longitudinal Study of Parents and Children, including 966 cases of asthma and 5,915 controls without asthma. In contrast to prior studies, there was no association with asthma risk and maternal exposure in utero. However, paternal exposure to their mothers' smoking during pregnancy was associated with a higher risk of asthma in the daughters of those fathers. While these results are intriguing, the authors caution that the results are "hypothesis-generating only" and are based on reported symptoms, without corroborating biologic evidence. How often do you get a smoking history about the grandmother?
D.A.K.
Miller LL, Henderson J, Northstone K, et al: Do grandmaternal smoking patterns influence the etiology of childhood asthma?
Chest. 145;1213:1218. ♦♦

Pregnancy and Asthma: Opportunities for Intervention

PREGNANT women with uncontrolled asthma face increased health risks to themselves and their child. Contrary to asthma guidelines, physicians may be hesitant to prescribe asthma medications during pregnancy. This study evaluated a pharmacist-led, multidisciplinary intervention to improve asthma control in pregnant women.

A randomized trial enrolled 60 pregnant women at less than 20 weeks' gestation who had used asthma medications in the previous year. One group was assigned to the pharmacist-led intervention, which included asthma education, monitoring, feedback, and follow-up. Patients were provided with a portable electronic spirometer; asthma control was assessed at monthly telephone calls or visits. The pharmacist and family physician collaborated on decisions regarding step-up therapy. Asthma action plans were developed with involvement of a respiratory physician, at the discretion of the family physician. Controls received usual care.

The study intervention was associated with larger reductions in Asthma Control Questionnaire (ACQ) scores: mean 0.46 versus 0.15 at 3 months and 0.89 versus 0.18 at 6 months. Only the 6-month difference was significant. All intervention patients had adequate asthma control, with an ACQ score less than 1.5, compared to 69% of the usual care group. During the study, no patient in either group had asthma related oral corticosteroid use, hospital admission, emergency department visits, or missed work days.

This multidisciplinary management approach improves asthma control in pregnant women. Empowering and supporting women in controlling their asthma during pregnancy can reduce the burden of disease, and may lead to improved health outcomes. Although the study intervention was led by pharmacists, the researchers note it could potentially be delivered by any member of the health care team.

COMMENT: *Few studies have attempted to evaluate asthma interventions in pregnant women. This small study from Australia randomized 60 pregnant women with asthma to receive usual care or a pharmacist-led intervention involving a single asthma education session, home spirometry, and monthly monitoring with phone calls to determine if asthma control had changed. Of interest, 70% of women were unaware of the hazards of poorly controlled asthma and one-third stopped or reduced asthma medications without physician approval. The intervention group showed "statistically and clinically significant" improvement in asthma control. While it is unclear which of these interventions contributed to improvement in outcomes, the intervention was fairly simple and could be replicated in an office setting.*
D.A.K.
Lim AS, Stewart K, Abramson MJ, et al: Multidisciplinary approach to management of maternal asthma (MAMMA): a randomized controlled trial.
Chest. 2014;145:1046-1054. ♦♦

Can We Predict Who Will Fail Venom Immunotherapy?

VARIOUS factors have been suggested as being associated with an increased risk of treatment failure during venom immunotherapy (VIT) for Hymenoptera allergy. Mastocytosis is one possible risk factor, but diagnosis poses a challenge. This study evaluated evidence of mastocytosis and other potential risk factors for clinical failure of VIT.

The retrospective study included 1,532 patients who underwent VIT for established honeybee or vespid venom allergy, The patients were drawn from a study designed to detect a twofold increase in the risk of an objective systemic reaction during in-hospital sting challenge. Including patients tested twice, the analysis included the results of 1,609 sting challenges. Putative risk factors for failed VIT were analyzed, including clinical indicators of systemic mastocytosis: adult-onset mastocytosis in the skin and/or a baseline serum tryptase (BST) concentration of greater than 20.0 μg/L.

Evidence of systemic mastocytosis was present in 6.4% of patients. There was a 6.5% rate of objective generalized symptoms in response to sting challenge, indicating VIT failure.

In patients without mastocytosis of the skin, a BST concentration greater than 20.0 μg/L was not associated with an increased risk of VIT failure. However, several significant risk factors were identified, including angiotensin-converting enzyme (ACE) inhibitor use, odds ratio (OR) 5.24; honeybee venom allergy, OR 5.09; systemic allergic reaction during VIT, OR 3.07; and "substantial likelihood" of systemic mastocytosis, OR 2.74. Factors associated with a lower failure rate were double VIT, OR 0.51; and longer duration of VIT, OR 0.68 per month of treatment. ➤➤

Several factors affect the likelihood of successful VIT, including type of venom allergy and the dose and duration of therapy. Indicators of mastocytosis are a significant risk factor for VIT failure, but not the most important one. Use of an ACE inhibitor may have a greater impact on the success or failure of VIT.

COMMENT: *Venom immunotherapy is the most successful form of immunotherapy we have, yet it is not 100% effective. This study from Germany evaluated a huge number of patients treated with VIT, of whom 6.5% had objective symptoms after intentional sting challenge. After adjusting for many variables, factors associated with a higher failure rate included BST greater than 20 ng/mL, allergy to honeybee, and systemic reactions during VIT. Use of an ACE inhibitor at the time of sting challenge was also associated with higher failure, although only 30 patients fell into this group. The study protocol called for discontinuation of ACE inhibitors before sting challenge if possible, implying that these patients may have had higher cardiovascular morbidity accounting for their higher risk. Higher VIT dose (200 mcg) and longer VIT duration reduced the risk of VIT failure. Although the data regarding ACE inhibitors add fuel to the controversy, the other findings reconfirm prior observations regarding VIT outcomes.*
D.A.K.

Ruëff F, Vos B, Elberink JO, et al: Predictors of clinical effectiveness of Hymenoptera venom immunotherapy. **Clin Exp Allergy**. 2014;44:736-746. ♦♦

Do ACE Inhibitors Increase Risk of Reactions during VIT Build-Up?

SOME reports have linked angiotensin-converting enzyme (ACE) inhibitors to an increased rate of systemic reactions during Hymenoptera venom immunotherapy (VIT). Despite a lack of strong supporting evidence, recent guidelines have suggested discontinuation or substitution of ACE inhibitor therapy before starting VIT. The effects of ACE inhibitors on the rate of systemic reactions during the build-up phase of VIT were evaluated in a large clinical experience.

The analysis included 775 consecutive cycles of VIT build-up administered to 743 patients between 2004 and 2012. Factors potentially affecting the rate of systemic reactions were analyzed, including cardiovascular medications, patient age and sex, type of venom allergy, reactivity in diagnostic tests, severity of anaphylaxis episodes, comorbid conditions, time to VIT initiation, and treatment protocols.

During VIT initiation, 24.5% of patients were receiving some type of cardiovascular medication, including ACE inhibitors in 11.6% and beta-blockers in 3.0%. Treatment with ACE inhibitors was routinely continued, while beta-blockers were replaced if appropriate.

There was an 11.7% rate of any documented VIT-related reaction, including subjective symptoms, and a 3.0% rate of reactions meeting objective criteria for anaphylaxis. There was no increase in systemic reactions with either ACE inhibitors or beta-blockers. On multivariate analysis, any use of cardiovascular drugs was not a significant factor. Risk was significantly increased for patients with a prolonged latency before VIT initiation, odds ratio 1.010 per month; and those undergoing a 5-day rather than a 3-day rush protocol, odds ratio 3.522.

These findings in a large and homogeneous group of patients show no evidence of an increased risk of systemic reactions during the VIT build-up phase in patients taking ACE inhibitors. ACE inhibitor therapy "may therefore be maintained during VIT," the investigators conclude. They add that "no definite statement" can made regarding beta-blocker use during VIT.

COMMENT: *Venom immunotherapy is associated with a higher risk of systemic reactions than aeroallergen immunotherapy. ACE inhibitors have been associated with increased systemic reactions during VIT, but the evidence is largely anecdotal. This study from Germany evaluated a large number of rush VIT procedures and found only a 3% rate of objective systemic reactions. ACE inhibitors, used by 11.6% of patients, were not associated with an increased risk of VIT reactions. Incidentally, the researchers also noted that a 3-day RIT procedure was safer than a 5-day procedure. This study will not end the debate, but it provides additional evidence that ACE inhibitors may not need to be stopped during VIT build-up.*
D.A.K.

Stoevesandt J, Hain J, Stoltze I, et al: Angiotensin-converting enzyme inhibitors do not impair the safety of Hymenoptera venom immunotherapy build-up phase. **Clin Exp Allergy**. 2014;44:747-755. ♦♦

Anti-TSLP Antibody-- Novel Treatment for Asthma?

THE epithelial cell-derived cytokine thymic stromal lymphopoietin (TSLP), produced in response to proinflammatory stimuli, is thought to be an important driver of allergic inflammatory responses. The fully human anti-TSLP monoclonal immunoglobulin G2γ AMG 157 specifically binds TSLP, preventing interaction with its receptor. The effects of AMG 157 on allergen-induced airway responses were studied in patients with mild allergic asthma.

The proof-of-concept study included 31 adults with mild allergic asthma. Patients were assigned to receive three monthly intravenous treatments with AMG-157, 700 mg, or placebo. The FEV_1 responses to allergen challenge were assessed before treatment and after the second and third doses: Exhaled nitric oxide level, blood and sputum eosinophil counts, and airway hyperresponsiveness were evaluated as well.

The AMG 157 group showed significant reduction in early and late responses to allergen. During the late phase (3 to 7 hours), the maximum percentage decrease in FEV_1 was 34.0% after the second dose and 45.9% after the third dose. Anti-TSLP therapy was also associated with reduced blood and sputum eosinophil levels, before and after allergen challenge, and reduced exhaled NO. Adverse events were slightly higher in the ➤➤

AMG 157 group, with no serious events.

The anti-TSLP antibody AMG 157 appears to reduce allergen-induced bronchoconstriction and inflammation in patients with mild allergic asthma. The findings support the role of TSLP in airway allergic responses and inflammatory changes. The authors propose further studies of the mechanism of action of AMG 157, and its clinical value for patients with poorly controlled asthma.

COMMENT: *In an exciting study by Gauvreau et al, the researchers demonstrated that treatment (5 to 12 weeks) with a humanized monoclonal antibody (AMG 157) against TSLP attenuated asthma attacks evoked by allergen bronchoprovocation--the most predictive model for the evaluation of drug effects in asthma. As pointed out by Dahlén in an accompanying editorial (N Engl J Med. 2014;370:2144-2155), the magnitude of the impact may be comparable to that achieved by blocking asthma mediators such as the cysteinyl leukotrienes. The clinical role of anti-TSLP therapeutics needs to be studied further.*
C.D.
Gauvreau GM, O'Byrne PM, Boulet L-P, et al: Effects of an anti-TSLP antibody on allergen-induced asthmatic responses.
N Engl J Med. 2014;370:2102-2110. ♦♦

What's the Best Approach to Preventing Severe Asthma Exacerbations?

INHALED corticosteroids (ICS) are the mainstay of treatment to prevent asthma exacerbations. However, other approaches have been studied, including the combination of ICS with long-acting β agonists (LABAs). A network meta-analysis was performed to compare the available evidence on existing strategies to prevent asthma exacerbations.

A literature review identified 64 randomized trials evaluating 15 medication strategies for maintenance therapy of chronic asthma in adult patients. Eligible studies evaluated interventions of at least 24 weeks' duration and reported data on asthma exacerbations, with a total of 59,622 patient-years of follow-up. The rate of severe asthma exacerbations, based on American Thoracic Society/European Respiratory Society criteria, was assessed for the various strategies versus low-dose ICS as the reference strategy.

The greatest reduction in severe exacerbations was achieved with ICS/LABA combinations, whether used as maintenance/reliever therapy or in a fixed daily dose. There was no difference in effectiveness between these two dosing strategies: compared to low-dose ICS, rate ratios were 0.44 for combined maintenance and reliever treatment and 0.51 for combined fixed-dose treatment. None of the other combination therapies evaluated was superior to ICS; all single-drug strategies were inferior to a single low-dose ICS. A secondary composite outcome of moderate or severe exacerbations showed similar results. Safety outcomes were best with treatment based on current guidelines and combined maintenance/reliever therapy.

The results support ICS/LABA combinations as the most effective approach to preventing severe asthma exacerbations. Outcomes are similar using maintenance/reliever and fixed-dose strategies. "These two strategies seem preferred when low dose inhaled corticosteroids are not sufficient, and step-up of treatment is warranted," the researchers conclude.

COMMENT: *This meta-analysis confirms the use of ICS/LABA for prevention of severe exacerbations. Combination therapy as maintenance and reliever was equally effective as daily combination therapy. Overall, exacerbation rates were low (less than one every 2 years), which makes it difficult for an individual practitioner to conclude which treatment is actually effective. Increased costs of combination treatment add to the equation. This might be another reason to consider combination ICS/LABA as maintenance and reliever therapy.*
S.F.W.
Loymans RJB, Gemperli A, Cohen J, et al: Comparative effectiveness of long term drug treatment strategies to prevent asthma exacerbations: network meta-analysis.
BMJ. 2014;348:g3009. ♦♦

CLINICAL TIDBITS

When Cat Owners Go to College, Antibodies Change

FOR patients with cat allergy, there is little evidence for the effectiveness of avoidance, including removing cats from the home. It may be that skin test-positive patients who live with cats are "desensitized" by exposure to cat allergen. This study evaluated immune responses to cat allergen in a "natural model of cat avoidance"--college students who move away from home.

Ninety-seven college students underwent skin prick testing and serum IgE and IgG measurement at the beginning and end of one academic year. Thirty-three percent of students had IgG antibodies to Fel d 1 but no evidence of sensitization, while 25% had a positive skin-prick test and/or IgE antibodies. The remaining 42% had negative skin tests and no detectable antibodies.

At the end of the academic year, the nonsensitized subjects with IgG antibodies showed a significant decrease in both IgG antibodies and IgG4 to Fel d 1. The sensitized students had no change in IgE, but a significant decrease in Fel d 1-specific IgG.

Thus elimination of cat exposure leads to a significant decrease in the ratio of IgG to IgE, with no new-onset sensitization. The findings may explain why cat-allergic students have increased symptoms on returning home. The study raises questions about advice to avoid cats and probably other domestic animals as well.

COMMENT: *This study evaluated college students who owned cats at home but were not permitted pets at school, and thus had decreased exposure to cat. Over 8 months' follow-up, there was decrease in the IgG:IgE ratio, with no new-onset sensitization. Increased* ➤➤

symptoms in skin test-positive college students returning home may reflect a decline in IgG. The allergen "dose" associated with having a cat at home may act in a way similar to immunotherapy.
C.C.R.
Erwin EA, Woodfolk JA, James HR, et al: Changes in cat-specific IgE and IgG antibodies with decreased cat exposure.
Ann Allergy Asthma Immunol. 2014;112:545-551. ♦♦

Vitamin D-Binding Protein Gene Affects Asthma Risk

ALTHOUGH debate continues, vitamin D insufficiency has been linked to increased asthma morbidity. Single-nucleotide polymorphisms of the *GC* gene, which encodes vitamin D-binding protein, affect circulating vitamin D levels in healthy infants and young children. This study evaluated the effects of *GC* SNPs on childhood asthma risk.

The retrospective analysis included medical records of 463 children who had available data on *GC* genotype, vitamin D-binding protein level, and circulating 25-hydroxyvitamin D at age 6 to 36 months. To minimize confounding due to ethnicity, the analysis was limited to 334 Hispanic children, 87 of whom developed asthma.

Children with the ET/ET *GC* genotype (Gc1s/Gc1s variant) had lower asthma risk than those with the DT/DT genotype (Gc1f/Gc1f variant). The proportion of children with asthma decreased with each copy of the D allele replaced by the E allele. Adjusted for obesity, odds ratios were 0.38 with the ET/ET genotype and 0.62 with the ET/DT genotype. Other *GC* SNPs were unrelated to asthma risk.

The ET/ET genotype of the vitamin D-binding protein gene is associated with decreased asthma risk among inner-city Hispanic children. The mechanism of this protective effect and its presence in other populations warrant further study.

COMMENT: *This study demonstrates that, at least in the Hispanic population of New Haven, the ET/ET vitamin D-binding protein genotype may protect against the development of asthma in a gene dose-response pattern, compared to wild-type DT/DT. There is no correlation with serum vitamin D levels. The vitamin D-binding protein genotype may protect against childhood asthma by some as yet poorly understood immune mechanism, such as macrophage activation or tissue availability of vitamin D. Generalizability to other populations requires further study.*
C.C.R.
Navas-Nazario A, Li FY, Shabanova V, et al: Effect of vitamin D-binding protein genotype on the development of asthma in children.
Ann Allergy Asthma Immunol. 2014;112:519-525. ♦♦

Children with 22q11 Deletion Can Receive Live Viral Vaccines Safely

THE congenital disorder DiGeorge syndrome (DGS) causes cellular immune deficiency. Although live vaccines are generally contraindicated in patients with severe cell-mediated immunodeficiency, little is known about vaccine use and safety among children with DGS.

This issue was addressed in a multicenter cohort of 194 patients with DGS. All had chromosome 22q11.2 microdeletion, confirmed by fluorescence in situ hybridization. Analysis of retrospective data showed that 77% of patients received measles-mumps-rubella (MMR) vaccine and 75% received varicella vaccine. At age 18 to 35 months, 58% of children had received recommended vaccines. Adverse event rates were 14% after MMR doses and 20% after varicella vaccine doses; there were few serious events and no major events or deaths within the 56-day window after live vaccination.

Early diagnosis was associated with decreased live vaccine coverage and timeliness, but baseline CD4 percentage was similar for children who did and did not receive live vaccines by age 12 to 18 months. The CD4 percentage in children who received varicella vaccine was lower in those with adverse events: 24.8% versus 35.5%. Fourteen patients developed illnesses that could have been prevented by live vaccines.

The study suggests that live vaccines are commonly given and generally well-tolerated in children with DGS and mild to moderate immunosuppression. The researchers call for prospective studies to confirm their findings; they note the study included few children with severe immunosuppression.

COMMENT: *This large, retrospective study of 194 subjects with confirmed 22q11 deletion and mild to moderate immune deficiency (representative of partial DGS) confirms smaller reports that such children tolerate live viral vaccines well. Adverse events following live immunizations were typically minor and self-limited. Since the degree of immune sufficiency varies over time, lymphocyte screening of all patients with partial DGS before vaccine administration is necessary.*
C.D.
Hofstetter Am, Jakob K, Klein NP, et al: Live vaccine use and safety in DiGeorge syndrome.
Pediatrics. 2014;133:e946-e954. ♦♦

Once-Daily Combination Shows Promise in Persistent Asthma

A combination of the inhaled corticosteroid fluticasone furoate (FF) and the long-acting β_2-agonist vilanterol (VI) is being developed for once-daily treatment of asthma and chronic obstructive pulmonary disease. This study evaluated the safety and efficacy of once-daily FF/VI in patients with persistent asthma.

The randomized trial included 586 patients aged 12 years or older with moderate to severe, persistent asthma. They were assigned to 24 weeks of treatment with FF/VI 200/25 μg, FF 200 μg once daily in the ►►

evening, or fluticasone proprionate (FP) 500 µg twice daily.

The FF/VI combination was associated with significant improvement in the co-primary endpoints of trough FEV_1, with differences of 193 mL compared to FF and 210 compared to FP; and weighted mean 0 to 24 h serial FEV_1, with differences of 136 and 206 mL, respectively. The combination was associated with more rescue-free days and symptom-free periods than FF, but there were no differences in asthma-related quality of life. Adverse events were similar between treatments.

The once-daily FF/VI combination produces greater improvement in lung function and symptoms in patients with mild to moderate, persistent asthma, compared to once-daily FF. Adverse events and safety outcomes are encouraging as well.

COMMENT: *This FF/VI combination produces a significant increase in FEV_1 compared to inhaled corticosteroid monotherapy. This may be related to the addition of a long-acting β_2-agonist and is not unexpected. The percentage of withdrawals due to exacerbations is dramatically lower with the once-daily combination product. Taken together, these data suggest that the FF/VI combination will be an important contribution to long-term asthma management.*
B.E.C.

O'Byrne PM, Bleecker ER, Bateman ED, et al: Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma.
Eur Respir J. 2014;43:773-781. ♦♦

Other Adiposity Markers Linked to Asthma in Children

PREVIOUS studies of the association between obesity and asthma have focused on body mass index (BMI) as a marker of obesity and overweight. This study evaluated other indicators of adiposity for association with asthma in Puerto Rican children, including the potential mediating role of atopy.

The study included 351 Puerto Rican children with asthma and 327 nonasthmatic controls. The odds of asthma were increased not only with increased BMI, but also at higher values for percentage body fat and waist circumference. Significant associations were also noted for lung function, asthma severity and control, and atopy, although these varied for the different markers of adiposity.

Atopy was a strong mediator of the association between adiposity and asthma. Allergic rhinitis explained 22% to 53% of the association with asthma, while cockroach sensitization explained 13% to 20% of the association with forced vital capacity and 29% to 42% of the association with asthma emergency department visits.

Other adiposity markers besides BMI are associated with asthma in Puerto Rican children, and atopy appears to be an important mediator. Follow-up studies would be needed to identify a causal role of adiposity distribution and atopy on "obese asthma" in children.

COMMENT: *Obesity is a well-known risk factor for asthma, particularly in children. This report from Puerto Rico examined several indicators of adiposity to improve our understanding of "obese asthma." Body mass index continues to show statistically significant associations with asthma and FEV_1, although percentage body fat also was associated with increased urgent care visits. Waist circumference was correlated with increased total IgE and allergic rhinitis, whereas BMI, percentage body fat, and waist circumference were all associated with allergy and skin test reactivity. The authors suggest that using other measures of adiposity in addition to BMI could help our understanding of the asthma-obesity link.*
S.M.F.

Forno E, Acosta-Pérez E, Brehm JM, et al: Obesity and adiposity indicators, asthma, and atopy in Puerto Rican children.
J Allergy Clin Immunol. 2014;133:1308-1314. ♦♦

No Benefit of Anti-IL-13 in Severe Asthma

INTERLEUKIN-13 may play a role in asthma pathology and corticosteroid resistance in some patients. This study evaluated GSK679586, a humanized monoclonal antibody that blocks IL-13 binding to both IL-13 receptor α1 and α2, in patients with refractory asthma.

The study included 199 patients with severe asthma that persisted after upward titration to a fluticasone propionate dose of 1,000 µg/d or higher. They were randomly assigned to three once-monthly treatments with GSK679586, 10 mg/kg IV, or placebo. At 12 weeks, the anti-IL-13 and placebo groups showed no significant difference in Asthma Control Questionnaire score, the primary outcome; or in FEV_1. There was no difference on subgroup analysis of patients with increased serum IgE and/or blood eosinophil counts.

The two groups had similar exacerbation rates. Two patients had serious adverse events (lethargy and supraventricular extrasystoles) related to GSK679586 treatment.

Anti-IL-13 treatment with GSK679586 does not improve disease control or other outcomes in patients with severe refractory asthma. Further study is needed to determine whether there is any group of patients who can benefit from treatments targeting IL-13 and/or IL-4.

COMMENT: *The patients in this study all had severe persistent asthma and remained symptomatic in spite of high-dose inhaled corticosteroids. That's one of the reasons the authors give for not showing statistically significant improvement with this new anti-IL-13 product. The IL-13/IL-4 signaling mechanism is complex and the patients were already on corticosteroids, which can inhibit this pathway. That could also help to explain why patients receiving anti-IL-13 treatment had only a modest improvement on nighttime awakenings and wheezing compared to controls. Identification of the proper phenotypes for these types of new targeted therapies will be critical for their success.* ►►

S.M.F.
De Boever EH, Ashman C, Cahn AP, et al: Efficacy and safety of an anti-IL-13 mAb in patients with severe asthma: a randomized trial.
J Allergy Clin Immunol. 2014;133:989-996. ♦♦

Statins Don't Prevent COPD Exacerbations

OBSERVATIONAL data have suggested a lower exacerbation rate and other improvements in clinical outcomes for patients with chronic obstructive pulmonary disease (COPD) who take cholesterol-lowering statin drugs. Simvastatin's effects on COPD exacerbations were evaluated in a randomized trial.

Eight hundred eighty-five patients with COPD were randomly assigned to 2 years of treatment with simvastatin, 40 mg/d, or placebo. The patients had a mean FEV_1 of 41.6% of predicted and smoking history of 50.6 pack-years. All had a history of COPD hospitalization or emergency department visit in the past year.

Simvastatin reduced low-density lipoprotein cholesterol levels. However, there was no difference in exacerbation rate: 1.36 per person-year with simvastatin versus 1.39 with placebo. Median time to first exacerbation was similar between groups, as was the rate of nonfatal serious adverse events.

Simvastatin does not reduce exacerbations in high-risk patients with COPD. Another report in the same issue (N Engl J Med. 2014;370: 2191-2200) shows a lack of benefit with rosuvastatin for patients with sepsis-related acute respiratory distress syndrome.

COMMENT: *Retrospective studies have suggested that statins may decrease the rate and severity of exacerbations in COPD. But in this prospective, multicenter randomized trial, adding simvastatin 40 mg to usual care neither reduced the exacerbation rate nor prolonged the time to the first exacerbation. There was also no therapeutic benefit on lung function or quality of life.*
C.D.
Criner GJ, Connett JE, Aaron SD, et al: Simvastatin for the prevention of exacerbations in moderate-to-severe COPD.
N Engl J Med. 2014;370:2201-2209. ♦♦

Does Early Antibiotic Use Really Increase Asthma Risk?

THE use of antibiotics during infancy, through their effects on the diversity and composition of the intestinal microbiota, might contribute to the rising prevalence of childhood asthma. Data from a large population of US children were analyzed to determine the association between antibiotic exposure in the first year of life and the risk of asthma later in childhood.

A nationwide health insurance database was used to identify 62,576 U.S. children enrolled from birth through age 5 from 1999 through 2006. Antibiotic exposure during the first year of life was evaluated for association with the development of three asthma phenotypes: transient wheezing (starting and ending by 3 years), late-onset asthma (starting after 3 years), and late-onset asthma (starting by 3 years and continuing to 4 to 7 years).

Children exposed to antibiotics during the first year of life were more likely to develop transient wheezing, odds ratio (OR) 2.0; and persistent asthma, OR 1.6. There was a significant dose-response effect--in children receiving at least 5 courses of antibiotics, the OR for persistent asthma was 2.0. Early-life antibiotic exposure was unrelated to late-onset asthma. For all three phenotypes, risk was significantly higher for children with lower or upper respiratory infection during the first year of life.

This analysis of population-level data suggests that antibiotic exposure during the first year of life is associated with an increased risk of asthma during the first 3 years of life. The findings support the theory that effects on microbiota during early life might affect asthma risk. Although no causal association can be proved, the investigators conclude, "[C]aution should be taken to avoid unnecessary use of antibiotics in asthma."

COMMENT: *Studies have suggested increased risk of asthma when infants are treated with antibiotics. This retrospective study of a large, national cohort of children took place over an 8-year period. The authors studied effects of antibiotic use and early respiratory infections on the risk of transient wheezing, late-onset asthma, and persistent asthma. Almost 20% of children developed wheezing or asthma between infancy and 7 years. Almost half of children had at least one course of antibiotic during the first year of life. With each course of antibiotic exposure, there was an increased risk of developing asthma. There was also a significant association between early-life upper respiratory infections and each type of asthma phenotype. One limitation of the study was that patients were insured by a single private insurance plan, and thus it may not be generalizable to the entire population. If we did not have concerns about antibiotic overuse before, this study is yet another warning about the importance of judicious use of antibiotics in children.*
V.H.-T.
Ong M-S, Umetsu DT, Mandl KD: Consequences of antibiotics and infections in infancy: bugs, drugs, and wheezing.
Ann Allergy Asthma Immunol. 2014;112:441-445. ♦♦

New Patient-Reported Outcome Tool for Urticaria Control

CHRONIC urticaria is a common skin disorder that can have a major impact on patients' lives. Because of daily fluctuations in symptoms, it can be challenging to assess disease control in patients with urticaria. The authors report the development and validation of a new Urticaria Control Test (UCT).

Using established methods, the researchers developed and evaluated items for potential use in evaluating urticaria control. The resulting four-item UCT ➤➤

included questions related to physical symptoms, quality of life, adequacy of treatment to control symptoms, and perceived overall control over the past 4 weeks.

In a validation study in 120 patients with chronic urticaria, the mean UCT score was 8.8, with a possible range of 0 to 16. Scores varied considerably within all groups of patients, consistent in varying degrees of urticaria control. The UCT showed good convergent and known-groups validity, along with excellent test-retest reliability. It also showed good accuracy as a screening test for identifying patients with inadequately controlled urticaria.

The four-question UCT is the first valid and reliable instrument for assessment of disease control in patients with chronic urticaria. The authors believe it will provide a simple and valuable tool for the management of patients with chronic urticaria in routine practice, as well as in clinical trials. The UCT may also prove useful in patient screening, monitoring disease status, and treatment decision-making.

COMMENT: *Our patients with chronic urticaria frequently present with narratives of how their hives are debilitating to their daily activities. This report presents a four-question Urticaria Control Test that has been validated as a means for patients to self-report the impact of their urticaria over the past 4 weeks. Much like the ACT Asthma Control Test, the UCT is a patient-reported outcome analysis that can help quantify subjective symptoms and could potentially be used to monitor disease severity and impact of treatment. We'll have to try it with our patients and see if it helps with their management.*
S.M.F.

Weller K, Groffik A, Church MK, et al: Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control.
J Allergy Clin Immunol. 2014;133:1365-1372. ♦♦

REVIEWS OF NOTE

COMMENT: *This is the second in a series of two review articles from* The Lancet. *It accurately summarizes what is known about wheezing in preschoolers, as well as gaps in implementation. Specifically, the authors recommend inhaled corticosteroid therapy for persistent preschool wheezers, especially those with a high asthma predictive index. Intermittent, high-dose inhaled corticosteroids may be used for moderately severe viral-induced wheezing.*
S.F.W.

Ducharme FM, Tse SM, Chauhan B: Asthma 2: Diagnosis, management, and prognosis of preschool wheeze.
Lancet. 2014;383:1593-1604. ♦♦

COMMENT: *This is a novel case report of a child presenting with leukocyte adhesion deficiency I type symptoms. The patient had failure of separation of the umbilical cord and recurrent bacterial infections, but with hyperadhesive integrin ligands rather than adhesion deficiency. The findings suggest a novel lesion in a pathway regulating integrin adhesion that may need further exploration.*
C.D.

Simpson BN, Hogg N, Svensson LM, et al: A new leukocyte hyperadhesion syndrome of delayed cord separation, skin infection, and nephrosis.
Pediatrics. 2014;133:e257-e262. ♦♦

COMMENT: *Here is an excellent review of "bronchiolitis obliterans." It focuses on the recognition of this condition as an occupational disease, its increased occurrence following allogeneic hematopoietic stem-cell or lung transplantation, diagnostic challenges, and current therapeutic options.*
C.D.

Barker AF, Bergeron A, Rom WN, Hertz MI: Obliterative bronchiolitis.
N Engl J Med. 2014;370:1820-1828. ♦♦

COMMENT: *This is an important review article covering the spectrum of allergic aspergillosis in patients with chronic upper and lower airway disease that is refractory to therapy.*
B.E.C.

Shah A, Panjabi C: Allergic aspergillosis of the respiratory tract.
Eur Respir Rev. 2014;23:8-29. ♦♦