AllergyWatch®

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

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A New Therapy for Chronic Idiopathic Urticaria...

MANY patients with chronic idiopathic urticaria (CIU) do not have a good clinical response even to high doses of H_1 antihistamines. In phase 2 clinical trials, anti-IgE therapy with omalizumab has shown symptomatic benefits. This randomized, phase 3 trial evaluated the use of omalizumab for moderate to severe CIU.

The study included 323 adult and adolescent patients with moderate to severe CIU who did not respond to treatment with recommended doses of H_1 antihistamines. About three-fourths of patients were women; the mean age was 42.5 years. Three groups received omalizumab, 75, 150, or 300 mg, in three subcutaneous doses given 4 weeks apart. Controls received placebo; all treatments continued for 16 weeks. The main outcome of interest was a weekly itch severity score.

At baseline, mean itch severity score (on a 0-to-21 scale) was about 14 points. The two higher doses of omalizumab were associated with greater reductions in itch severity, compared to placebo. At 12 weeks, the mean reduction was 5.1 points with placebo, 5.9 points with omalizumab 75 mg, 8.1 points with omalizumab 150 mg, and 9.8 points with omalizumab 300 mg.

Overall adverse event rates were similar with omalizumab and placebo. Patients receiving omalizumab 300 mg had a 6% rate of serious adverse events, compared to 3% with placebo and 1% with omalizumab 150 and 75 mg.

This trial shows that omalizumab can reduce itch severity in patients with CIU who don't improve with H_1 antihistamines. Omalizumab produces good clinical responses with both the 150 mg and 300 mg doses, although serious adverse events are more frequent at the higher dose. The researchers call for further studies to delineate the role of omalizumab in treatment of chronic or spontaneous urticaria.

COMMENT: *This multicenter, randomized, double-blind study evaluated the efficacy and safety of omalizumab in patients with moderate-to-severe CIU* ➤➤

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The following journals have been selected as the primary focus of review in the preparation of materials within "AllergyWatch®".

- Annals of Allergy, Asthma and Immunology
- Journal of Allergy and Clinical Immunology
- American Journal of Respiratory and Critical Care Medicine
- Chest
- Clinical Experimental Allergy
- Allergy
- International Archives of Allergy and Immunology
- Annals of Internal Medicine
- Pediatrics
- Journal of Pediatrics
- Thorax
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- European Respiratory Journal
- Pediatric Allergy and Immunology

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who remained symptomatic despite licensed doses of H_1 antihistamines. Omalizumab, in doses of 150 or 300 mg in three subcutaneous injections at 4-week intervals, resulted in significant improvement in weekly itch-severity score compared to a 75 mg dose or placebo. Of note, there was no significant change in the proportion of angioedema-free days during week 4 through week 12 in the group receiving 150 mg of omalizumab. The frequency of adverse events was similar across groups.
C.D.
Maurer M, Rosén K, Hsieh H-J, et al: Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria.
N Engl J Med. 2013;368:924-935. ♦♦

...With Long-Term Remission for Many Patients

RECENT studies have reported short-term benefits of omalizumab for patients with chronic urticaria who either do not respond or experience adverse effects with conventional treatment. This study reports short- and long-term outcomes of fixed-dose omalizumab in a small group of patients with severe chronic urticaria.

The experience included 16 patients with severe, chronic spontaneous urticaria. All received omalizumab, 150 mg every 2 to 4 weeks; treatment duration was adjusted to individual responses. Retrospective outcome analysis included number of treatments to achieve remission and the sustainability of remission over time.

Urticaria went into remission after the first dose in 10 patients--a rate of 62%. Another 4 patients achieved remission after two to six doses; the remaining 2 patients discontinued omalizumab after two treatments. More than 9 months after their last treatment, 4 out of 14 patients were still in remission. Another 7 patients remained in remission on maintenance omalizumab, with treatment frequency individualized to their duration of remission. Three patients stopped responding to omalizumab.

This single-center experience supports the short- and long-term efficacy of omalizumab for patients with severe chronic urticaria. The authors note the variability in time to remission and duration of response, with some patients requiring maintenance therapy for sustained remission.

COMMENT: *This experience demonstrates that omalizumab is effective therapy for induction and maintenance of chronic remission in patients with severe chronic urticaria. The onset of remission is rapid, with 10 of 16 patients responding to the first dose. Maintenance therapy may be individualized to between 4 and 8 weeks. The study is limited by its small sample size, retrospective nature, and lack of controls. However, the practicing allergist should know that omalizumab is soon to receive FDA approval for this indication, since the favorable randomized trial results reported by Maurer et al.*
C.C.R.
Song CH, Stern S, Giruparajah M, et al: Long-term efficacy of fixed-dose omalizumab for patients with severe chronic spontaneous urticaria.
Ann Allergy Asthma Immunol. 2013;110;113-117. ♦♦

FOCUS ON RISK FACTORS

This issue we focus on several recent papers reporting on risk factors for asthma and atopy.
A.M.

New Findings on Asthma Risks in Infants and Children

MANY low-income children with persistent wheezing have a history of recurrent asthma symptoms since infancy. Questions remain ➤➤

about the risk factors for early-onset asthma symptoms in this group of patients. Data from the Childhood Asthma Prevention Study (CAPS) were used to analyze factors associated with increased risk of asthma at school age in low-income children.

The analysis included 177 low-income children with frequent wheezing, enrolled at age 9 to 24 months. About half of infants in the multiethnic sample were Hispanic. When the children were 7 years old, caregiver reports of physician-diagnosed asthma were assessed, with confirmation by bronchial hyperresponsiveness (BHR) testing. The study sought to identify baseline factors associated with asthma and BHR at age 7.

Forty-nine percent of caregivers reported that their child had physician-diagnosed asthma at age 7, while 60% of children tested positive for BHR. Maternal reports of wheezing severity at baseline were strongly associated with physician-diagnosed asthma at age 7, and spirometric lung function results were significantly different for BHR-positive versus BHR-negative children. On univariate analysis, higher maternal psychologic resources were significantly associated with physician-diagnosed asthma, but not positive results for BHR.

Among children with a history of frequent wheezing, just 39% met conservative criteria for asthma at age 7. Maternal psychologic resources, baseline symptom severity, and low birthweight were significant predictors for this group of patients.

Low-income infants with wheezing appear to be a unique population with unique characteristics and risks for persistent asthma. In addition to caregiver reports of physician-diagnosed asthma, BHR testing is needed to confirm the presence of asthma at school age. Maternal psychologic resources may be an important determinant of which children receive asthma diagnosis and treatment.

PRETERM birth can affect lung development, leading to increased morbidity in the newborn period. Prematurity is regarded as a risk factor for asthma and other childhood respiratory problems, but little is known about the development of pulmonary function in healthy, late-preterm infants. The authors performed follow-up respiratory tests in a group of infants born at 33 to 36 weeks' gestation.

The prospective study included 31 late preterm infants: mean gestational age 34.1 weeks and mean birthweight 2,150 g. The infants were all free of clinical respiratory disease when studied at term corrected age. A race- and sex-matched comparison group of term infants were studied within 72 hours after delivery. Both groups underwent pulmonary function testing, including respiratory compliance (Crs), measured by the single-breath occlusion technique; and time to peak tidal expiratory flow to expiratory time (TPTEF:TE), estimated in at least 50 flow-volume loops.

Respiratory compliance was significantly reduced in the late preterm infants, compared to the term group: 1.14 versus 1.32 mL/cm H_2O/kg. There were also significant differences in TPTEF:TE, 0.308 versus 0.423; and respiratory resistance, 0.064 versus 0.043 cm H_2O/mL/s. The difference in Crs associated with late-preterm birth was greater after adjustment for socioeconomic status.

Late preterm infants with no clinical respiratory disease, studied at term corrected age, have significant differences in pulmonary function compared to term infants. Delayed or abnormal pulmonary development may place these infants at increased risk of pulmonary problems later in childhood.

COMMENT: *Predicting risk factors for asthma is important in order to identify children or newborns at risk and intervene to prevent and treat the disease. These two studies have interesting lessons. First, premature infants need long-term follow-up to see if their airway obstruction becomes clinically manifested as phenotypic asthma. Low birth weight appears to be a risk factor for low-income children, which has been noted in previous studies not corrected for economic status. Second, newer, non-effort-dependent tests may be very helpful for early diagnosis. Finally, we should be cognizant of the mental state of the mothers of wheezing infants and use noninvasive tests to measure airway resistance, function and reactivity.*
S.F.W.

Tamesis GP, Covar RA, Strand M, et al: Predictors for asthma at age 7 years for low-income children enrolled in the childhood asthma prevention study.
J Pediatr. 2013;162:536-542.
McEvoy C, Venigalla S, Schilling D, et al: Respiratory function in healthy late preterm infants delivered at 33-36 weeks of gestation.
J Pediatr. 2013;162:464-469. ♦♦

How Do Asthma, Smoking, and Atopy Contribute to Fixed Airflow Obstruction?

THERE are continued questions about the role of asthma in the development of fixed airflow obstruction (AO)--especially combined with other factors such as smoking and atopic sensitization. This long-term follow-up study analyzed the relative contributions of these three factors to the fixed AO in middle-aged adults.

The analysis included data on members of the Tasmanian Longitudinal Health Study cohort, who were born in 1961 and underwent prebronchodilator spirometry in 1968. Follow-up surveys from 2002 to 2005 were available for 5,729 participants. Further studies--including pre- and post-bronchodilator spirometry, skin prick testing, and measurements of lung volumes and diffusing capacity--were obtained in a sample of 1,389 participants enriched for asthma and chronic bronchitis cases. Main effects and interactions of asthma, smoking, and atopy on fixed AO were assessed.

For the entire cohort, the prevalence of fixed AO at follow-up was 6.0%. There was a multiplicative effect between the effects of active smoking and asthma on the postbronchodilator FEV_1/FVC ratio, which was significant only for subjects with atopic sensitization. The effects of early-onset, current clinical asthma on ➤➤

fixed AO were equivalent to those of a 33-year pack-year smoking history: odds ratio 3.7. The effects of late-onset, current clinical asthma were equivalent to a 24 pack-year history: odds ratio 2.6.

The results show a significant three-way interaction between asthma, active smoking, and atopic sensitization on the presence of fixed AO. This synergistic effect is mainly apparent in atopic adults who have ever smoked and who have current asthma. The findings support a role of asthma in the development of chronic obstructive pulmonary disease, and again highlight the importance of smoking cessation for patients with asthma.

COMMENT: *A long-term study with a very high retention rate supports the "Dutch hypothesis" and the role of Th2 mechanisms as factors for fixed AO. The study describes a group of patients who are poorly responsive to currently available guideline-based therapy and who need a personalized care plan for their asthma management.*
B.E.C.
Perret JL, Dharmage SC, Matheson MC, et al: The interplay between the effects of lifetime asthma, smoking, and atopy on fixed airflow obstruction in middle age.
Am J Respir Crit Care Med. 2013;187:42-48. ♦♦

Early Life Exposures and Asthma: Hygiene and Now Pollen, Too?

LITTLE is known about how pollen exposure affects the development of childhood asthma. This study evaluated persistent pollen exposure in infancy as a contributor to allergic sensitization and asthma in childhood.

The analysis included 620 participants from the Melbourne Atopy Cohort Study--all with a family history of allergic disease and born between 1960 and 1964. Birth during pollen season and cumulative exposure to pollen in the first 3 to 6 months of life were assessed. Persistent pollen exposure was analyzed as a risk factor for sensitization to common foods and aeroallergens at age 2 years and for asthma or hay fever at age 6 to 7 years.

Level of exposure to pollen through age 6 months was significantly associated with aeroallergen sensitization at 2 years. The strongest association was noted for greater cumulative pollen exposure up to 3 months: adjusted odds ratio (OR) 1.34. Risk of hay fever was associated with pollen exposure up to 3 months: OR 1.14. Pollen exposure between 4 and 6 months was associated with the risk of asthma at school age: OR 1.35. For children without a parental history of asthma, birth during pollen season was associated with an increased risk of allergic disease later in childhood.

Persistent exposure to pollen during infancy is associated with an increased risk of asthma and hay fever at age 6 to 7 years. The results are consistent with a "critical window of opportunity" to modify the risk of allergic outcomes during early development.

COMMENT: *The hygiene hypothesis, including a lack of diversity in the gut microbiome in the first year of life, has become a dominant focus of researchers attempting to explain the increase in atopic diseases over the past few decades. The authors of this Australian birth cohort study took a different approach to early-life exposures. Instead of examining bacterial or other infectious exposures, they looked at the association of hay fever and asthma with higher levels of pollen exposure in the first year of life. Indeed, infants with 3 to 6 months of cumulative pollen exposure in their first year were more likely to develop allergic rhinitis and asthma. These results add to the intrigue regarding how early-life exposures influence allergic disease phenotypes.*
S.A.T.
Erbas B, Lowe AJ, Lodge CJ, et al: Persistent pollen exposure during infancy is associated with increased risk of subsequent childhood asthma and hayfever.
Clin Exp Allergy. 2013;43:337-343. ♦♦

How Does Menstrual Cycle Affect Respiratory Symptoms?

A growing body of evidence suggests that sex hormones affect respiratory health throughout a woman's lifespan. Most studies of menstrual cycle variations in respiratory health have focused on asthmatic women. This study evaluated menstrual patterns of respiratory symptoms throughout the menstrual cycle in a general population of women.

The researchers analyzed population-based survey data from 3,926 Northern European women who had regular menstrual cycles of 28 days or less and were not taking exogenous sex hormone. Chronobiologic methods were used to examine changes in respiratory symptoms at different times throughout the menstrual cycle. Associations were stratified for differences in body mass index, smoking, and asthma status.

For the overall sample and in various subgroups, rhythmic variations across the menstrual cycle were noted for all respiratory symptoms studied. Wheezing was greater between cycle days 10 and 22, with most subgroups showing a midcycle dip around the time of ovulation--about days 14 to 16. Shortness of breath was greater between days 7 and 21, with some subgroups showing a dip just before midcycle. For women with asthma, higher BMI (23 and up), and smokers, cough was greater during the days just after ovulation. In women with low levels of respiratory symptoms, cough was greater just before ovulation and just before the onset of menses.

This study shows rhythmic patterns in respiratory symptoms at different times of the menstrual cycle in a general population of women. Symptoms appear most frequent between the midluteal and midfollicular phases, tending to decrease around the time of ovulation. These findings--along with differences in subgroups defined by asthma, BMI, and smoking--raise the possibility of "individualized chronotherapy" for respiratory diseases.

COMMENT: *This study gives a better understanding of the temporal relationship of symptoms of asthma and hormonal changes. The severity of asthma symp-* ➤➤

toms in this female population is increased with elevated BMI and a history of smoking. This is a group of patients who often have a less predictable response to standard therapy, along with high levels of healthcare utilization.
B.E.C.
Macsali F, Svanes C, Sothern RB, et al: Menstrual cycle and respiratory symptoms in a general Nordic-Baltic population.
Am J Respir Crit Care Med. 2013:187;366-373. ♦♦

Perimenstrual Asthma: Another Phenotype of More-Severe Asthma

SOME women report worsening of asthma symptoms related to menstruation. Based on limited data, perimenstrual asthma (PMA) may be a more severe and difficult-to-control phenotype. The clinical, demographic, and inflammatory findings in a well-characterized sample of women with PMA were analyzed.

From the National Heart, Lung, and Blood Institute's Severe Asthma Research Program (SARP), the investigators identified 92 women reporting PMA symptoms on a screening questionnaire. The demographic, clinical, immunologic/inflammatory measures, and physiologic parameters of women with PMA were compared to those of non-PMA groups. The study also sought to develop a severity-adjusted model for predicting PMA along with further models evaluating the impact of PMA on asthma control.

The 92 women reporting PMA represented 17% of female SARP patients aged 12 to 50 years who responded to a question regarding menses as a trigger for asthma symptoms. Women with self-reported PMA were older, had a higher body mass index, and a higher rate of severe asthma: 52% versus 30%. Perimenstrual asthma was also associated with a lower forced vital capacity (FVC), 84.2% versus 92.1% of predicted; and a higher rate of gastroesophageal reflux disease, 41% versus 23%.

In a multivariate model controlling for severity, factors associated with PMA were aspirin sensitivity and lower FVC % predicted. After further controlling for confounders, PMA was still associated with more severe asthma symptoms and increased urgent health care use.

This study documents a substantial rate of PMA among women with severe asthma. The results suggest that women with PMA tend to have more severe asthma symptoms. The associations with aspirin sensitivity and lower FVC % predicted are consistent with a role of prostaglandins.

COMMENT: *Multiple phenotypes exist in asthma and identification of "newer" phenotypes continues. Perimenstrual asthma has been described in several reports but this study from the SARP is the largest study to evaluate this phenotype. Perimenstrual asthma was associated with more severe disease, aspirin sensitivity, less atopy, and lower FVC. One of the primary study limitations is that the diagnosis of perimenstrual asthma was based on patient self-report. Further studies are required to determine optimal therapy. Nevertheless, questioning about menses as a trigger for asthma is a simple way to identify this phenotype.*
D.A.K.
Rao CK, Moore CG, Bleecker E, et al: Characteristics of perimenstrual asthma and its relation to asthma severity and control: Data from the Severe Asthma Research Program.
Chest. 2012;143:984-992. ♦♦

Tropomyosin Allergen in Tilapia--Link to Ulcerative Colitis?

TILAPIA, one of most commonly farmed freshwater fish, can cause allergic reactions. Tropomyosin is the major allergen in shellfish allergen and is responsible for cross-reactivity to inhaled allergens, but vertebrate tropomyosins are generally considered nonallergenic. This study identifies tropomyosin as an important tilapia allergen.

Allergens were purified, identified, and characterized in serum samples from 10 patients with confirmed allergy to Mozambique tilapia, *Oreochronis mossambicus*. Immunoblotting identified several allergens with apparent molecular weights of 114 to 17 kD. All sera reacted with a 32 kD allergen, Ore m 4, which was identified as tropomyosin on mass spectrometry. Immunoblotting, enzyme-linked immunosorbent assay (ELISA), and ELISA inhibition studies all confirmed IgE binding of the purified protein.

In cDNA sequencing studies, tilapia tropomyosin showed 53% homology to shrimp tropomyosin. There was also 87.7% homology to human tropomyosin isoform 5, antibodies to which are found in serum and mucosa of patients with ulcerative colitis (but not Crohn's disease). Six of the ten tilapia-allergic patients had been diagnosed with inflammatory bowel disease.

Tropomyosin (Ore m 4) is identified as the main allergen in patients with allergy to tilapia. This is the first study to report vertebrate tropomyosin as a food allergen. Further studies are needed to clarify cross-reactivity with shellfish allergens and the possible link to ulcerative colitis.

COMMENT: *Compared to shellfish and marine fish, the allergens of freshwater fish have not been as well-studied. This study evaluated 10 tilapia-allergic patients and identified the major allergen to be Ore m 4, which is a vertebrate tropomyosin. All patients had positive ELISA reactions to shrimp tropomyosin and 4 reported shrimp allergy. This appears to be the first report of a tropomyosin allergen in vertebrates. Finally and even more intriguing is the observation that Ore m 4 is nearly identical to the C-terminal peptide of human tropomyosin isoform 5, which can cause autoantibodies in ulcerative colitis. Shockingly, 6 of 10 of these Tilapia allergic patients had ulcerative colitis! Stay tuned for more on this.*
D.A.K.
Liu R, Holck AL, Yang E, et al: Tropomyosin from tilapia (Orechromis mossambicus) *as an allergen.*
Clin Exp Allergy. 2013;43:365-377. ♦♦

Long-term Nebulized Lidocaine for Chronic Cough: Safe but Unpleasant!

IN some patients with chronic cough, symptoms continue despite systematic evaluation and treatment. Some safe and effective, non-narcotic treatment for such cases of difficult-to-control cough would be of value. Nebulized lidocaine was evaluated for safety in the long-term treatment of chronic cough.

The retrospective analysis included 165 patients who had been prescribed nebulized lidocaine for chronic cough. All patients had received nurse education in the nebulized lidocaine protocol at the study center. In a follow-up questionnaire, patients were asked about the effectiveness of and adverse reactions to nebulized lidocaine. Patients were contacted by telephone for further information about reported adverse events.

Ninety-nine patients responded, for a rate of 60%. The patients' median age was 62 years; most were female and white. Cough had been present for a median of 5 years before the start of nebulized lidocaine. Forty-three percent of nebulized lidocaine users reported adverse events--most commonly unpleasant taste or irritation of the throat or mouth. Nine percent of patients reported choking on water or food, although none required any treatment (emergency department visit, hospitalization, or antibiotics) for aspiration pneumonia.

Mean cough severity score decreased from 8.4 at baseline to 5.9 on nebulized lidocaine. Eighty percent of patients had improvement within 2 weeks after starting nebulized lidocaine.

Nebulized lidocaine is a tolerable long-term treatment for adult patients with difficult-to-control chronic cough. Adverse effects are common but not serious, and treatment provides symptomatic control in about half of patients.

COMMENT: *Treatment of chronic cough is often a vexing problem for the allergist. Nebulized lidocaine has been used primarily as a short-term solution for coughing, but some practitioners have used it for chronic cough. This safety survey of patients prescribed and educated about nebulized lidocaine for chronic cough at the Mayo Clinic reported a high rate of adverse effects, but most were mild such as unpleasant taste or throat irritation. No instances of aspiration pneumonia were discovered. Given the overall high level of dissatisfaction with nebulized lidocaine, this therapy is clearly not the panacea for chronic cough. However, a 1- to 2-week trial with appropriate education may be warranted for some patients.*
D.A.K.
Lim KG, Rank MA, Hahn PY, et al: Long-term safety of nebulized lidocaine for adults with difficult-to-control chronic cough: A case series.
Chest;2013;143:1060-1065. ♦♦

Are PPIs a Risk for Development of Drug Allergy?

GASTRIC acid suppression by drugs has been shown to promote allergic reactions to acid-labile food proteins, but it's unknown whether there's any similar effect for drug hypersensitivity reactions (DHRs). Treatment with proton pump inhibitors (PPIs) was evaluated as a risk factor for DHRs in hospitalized patients.

From a cohort of 70,771 hospital admissions, the authors identified 161 confirmed cases of DHRs. These cases were matched to 318 controls in terms of drug initially suspected as the cause of hypersensitivity, time of admission, age, sex, and admission ward. The risk of DHRs associated with PPI treatment was estimated.

Eighty-one percent of the overall cohort received PPIs during their hospital stay, including 161 DHRs in 152 patients. Treatment with PPIs was significantly associated with the occurrence of DHRs: odds ratio (OR) 4.35 after controlling for confounders.

Other risk factors included personal history of drug allergy, OR 2.55; and prolonged hospital stay, OR 1.6 for longer than 19 days. The risk of DHRs occurring during PPI treatment was 3.7% per day. The hazard for immediate and accelerated DHRs was 70% greater than that of delayed reactions.

This pharmacoepidemiologic study suggests that PPI treatment is associated with a 4-fold increase in the risk of DHRs in hospitalized patients. The researchers conclude, "PPI treatment is the most preventable risk factor for DHRs."

COMMENT: *Gastric acid suppression by antacids has been suggested in prior studies to promote allergic reactions in acid-labile food proteins. This intriguing study from Spain examined whether long-lasting inhibitors of gastric acid secretion by PPIs can increase the risk of drug allergy. In the case-controlled, retrospective study, use of a PPI during hospitalization was associated with a higher odds ratio than even a personal history of drug allergy for the development of any type of drug hypersensitivity reaction! Use of PPIs was very high in both drug reaction cases (94%) and hospitalized matched controls (81%). Whether this phenomenon is causal or not remains unclear. Perhaps the bigger question is, do all of these patients really need PPI therapy? The simple answer is no.*
DAK
Ramírez E, Cabañas R, Laserna LS, et al: Proton pump inhibitors are associated with hypersensitivity reactions to drugs in hospitalized patients: a nested case-control in a retrospective cohort study.
Clin Exp Allergy. 2013;43:344-392. ♦♦

Intralymphatic Immunotherapy for Pollen Allergy: Pilot Study

SHORTER, more convenient alternatives to subcutaneous immunotherapy for allergic rhinitis treatment are needed. Injection of antigens directly into the lymph nodes, a "highly immunocompetent environment," may produce faster clinical benefits, with lower allergen doses and fewer injections. The authors evaluated the benefits of intralymphatic immunotherapy (ILIT) for patients with pollen-induced allergic rhinitis.

An open pilot study of ILIT was performed in 6 patients with pollen-induced seasonal allergic rhinitis, followed by a double-blind, placebo-controlled trial ➤➤

in 15 patients. Treatment consisted of three intralymphatic injections--using a superficial inguinal lymph node and ultrasound guidance--containing 1,000 SQ-U of birch or grass pollen (or placebo). In addition to clinical responses, evaluation included inflammatory cell counts in nasal lavage fluid and peripheral T-cell activation patterns.

The ILIT injections were well-tolerated, with no severe adverse events. Intralymphatic injection of birch or grass pollen was followed by initial increases in allergen-specific IgE levels and peripheral T-cell activation. Challenge studies documented reduction in nasal allergic symptoms along with decreased nasal inflammatory responses. Patients receiving active ILIT reported significant improvement in seasonal allergic rhinitis symptoms.

This preliminary clinical trial supports the safety and efficacy of ILIT for patients with grass or birch pollen-induced seasonal allergic rhinitis. With further study, ILIT could become a more convenient and cost-effective alternative to conventional subcutaneous allergen immunotherapy.

COMMENT: *Our patients are requesting allergy treatments that are more effective, safer, easier to use, and less time-consuming. This open pilot investigation of ILIT using either birch or grass pollen showed impressive clinical and immunologic benefit after only three inguinal injections, which the patients reported were "relatively painless." The authors suggest that ILIT is efficacious, could be more cost-effective, and is certainly less time-consuming than our usual subcutaneous immunotherapy. We'll see if our patients agree when ILIT becomes available.*
S.M.F.

Hylander T, Atiff L, Petersson-Westin U, Cardell, LO: Intralymphatic allergen-specific immunotherapy: An effective and safe alternative treatment route for pollen-induced allergic rhinitis.
J Allergy Clin Immunol. 2013;131:412-420. ♦♦

One-Half of Children Outgrow Milk Allergy by Age 5

IN most children with milk allergy, the problem resolves sometime during childhood. However, reports of the timeline for children to "outgrow" milk allergy vary widely. Prospective cohort data were analyzed to examine the natural history of milk allergy in children.

Three- to fifteen- month-old children with a clinical history of milk allergy were enrolled in an observational cohort study. All had a convincing history of allergy to milk and/or egg or moderate to severe atopic dermatitis with a positive skin-prick test (SPT). On follow-up to age 5, resolution of milk allergy was defined by successful ingestion.

Of 293 children included in the study, 244 were diagnosed with milk allergy at baseline. At follow-up to a median age of 66 months, 52.6% of children had resolution of milk allergy. The median age at resolution was 63 months. Baseline predictors of resolved milk allergy were milk-specific IgE level, SPT wheal size, and atopic dermatitis severity. Resolution was not predicted by baseline milk-specific IgG_4 or milk IgE/ IgG_4 ratio, nor by various casein-stimulated T-cell expression studies.

The results suggest that just over half of infants with milk allergy will outgrow their allergy by age 5. The authors have created an online calculator to assess the probability of milk allergy resolution over time, based on important baseline predictive factors.

COMMENT: *"Will my child outgrow his (or her) allergy?" The Consortium of Food Allergy Research (CoFAR) used data from their large cohort of food-allergic patients to help answer this question. They found that 53% of milk-allergic children had resolution of their milk allergy by 66 months of age. This is somewhat longer than in previous reports, although 20% of the milk allergic children could tolerate foods with baked milk. The authors suggest that using milk-specific IgE, size of allergy skin test, and presence of atopic dermatitis can be helpful in predicting resolution of milk allergy. They have developed a web-based calculator, which can be found on the CoFAR website: https://web.emmes.com/study/cofar/MilkAllergy_chart/EmmesIGEwithGraphV05.html.*
S.M.F.

Wood RA, Sicherer SH, Vickery BP, et al: The natural history of milk allergy in an observational cohort.
J Allergy Clin Immunol. 2013;131:805-812. ♦♦

TLR-9 Inhibitor Shows Promise in Allergic Asthma

A shift toward Th2-mediated immune responses is a key event in the development of allergic asthma. Treatments targeting Toll-like receptors (TLR) have the potential to stimulate the immune system toward a Th1-mediated immune response. A new TLR-9 agonist, QbG10 ("bacteriophage Qbeta-derived virus-like particle with CpG-motif G10 inside") was evaluated for safety and efficacy in the treatment of persistent allergic asthma.

The randomized, proof-of-concept trial included 63 patients with mild to moderate persistent allergic asthma. After conversion to a standardized inhaled steroid regimen, patients received a course of seven injections with QbG10, packaged into a viruslike particle, or placebo. Subjective and objective outcomes were assessed over 12 weeks, in a study design incorporating controlled steroid withdrawal.

Even with steroid withdrawal, the QbG10 group had significant improvement in all patient-reported outcomes, including daytime and nighttime asthma symptoms, salbutamol use, and Asthma Control Questionnaire score. In contrast, asthma symptoms worsened in the placebo group. By 12 weeks, 67% of patients in the QbG10 group had well-controlled asthma--ACQ score 0.75 or less--compared to 33% in the placebo group. QbG10 was also associated with a stable FEV_1, compared to a clinically significant drop in the placebo group. Aside from injection site reactions, there were few adverse events with QbG10 treatment. ➤➤

This new form of TLR-9 agonist therapy may provide a safe and effective option for patients with persistent allergic asthma. Despite steroid reduction, patients receiving QbG10 show significant improvement in subjective and objective clinical outcomes. The authors call for confirmatory studies in larger patient samples.

COMMENT: *The recent therapeutic approach for treating allergic asthma is to adjust the Th2/Th1 imbalance, which is responsible for much of the inflammatory response in our patients. These European researchers used nanotechnology to deliver a virus-like particle that acts as a ligand for TLR-9. Activation of this TLR-9 receptor can induce T regulatory cells, which can block Th2 pathways. During the 12 weeks of seven treatment injections, those allergic asthmatic patients receiving the QbG10 were able to maintain good asthma control even with reductions of their inhaled corticosteroid dose. The authors also raise an interesting question: Should these patients be labeled "allergic" asthmatics or "atopic" asthmatics? "Atopic" might more accurately describe their inflammatory processes.*
S.M.F.
Beeh K-M, Kanniess F, Wagner F, et al: The novel TLR-9 agonist QbG10 shows clinical efficacy in persistent allergic asthma.
J Allergy Clin Immunol. 2013;131:866-874. ♦♦

Is It Possible To Prevent NSAID Urticaria/Angioedema?

NONALLERGIC urticaria and/or angioedema (U/AE) reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) are a common clinical problem. Current management options, such as drug avoidance and aspirin desensitization, have important disadvantages. This study evaluated premedication approaches to preventing U/AE reactions to NSAID administration.

The study included 65 patients with a history of NSAID-induced U/AE: 40 women and 25 men, mean age 46 years. Aspirin and ibuprofen were the most commonly involved NSAIDs. All patients underwent placebo-controlled oral challenge with the culprit drug. Those who reacted proceeded to a further challenge after premedication with antihistamines alone or antihistamines plus leukotriene antagonists.

Ninety percent of patients tolerated a normal dose of the culprit drug. Of the 6 patients with recurrent U/AE reactions, further hypersensitivity reactions were prevented in 2 by antihistamines alone and in 3 by antihistamines plus leukotriene antagonists. The remaining patient continued to react despite double premedication.

In patients with persistent recurrent U/AE reactions to NSAIDs, premedication with antihistamines alone or with leukotriene antagonists can prevent further reactions in most cases. Consistent with previous studies showing poor reproducibility of NSAID hypersensitivity reactions, a large majority of patients with a history of NSAID-induced U/AE reactions tolerate normal doses of NSAIDs.

COMMENT: *Since NSAIDs cause allergic reactions so frequently, this study looked at the use of premedication to prevent allergic reactions. The authors report that 90% of patients tolerated the NSAID dose on challenge without premedication. This supports the likely multifactorial process involved in these reactions. Of patients who reacted to the challenge, 33% tolerated the dose with antihistamine premedication. The remaining patients who failed the challenge then underwent challenge after premedication with both antihistamine and leukotriene inhibitor; three-fourths tolerated the challenge. The authors remind us that premedication appears to be a practical option for patients with urticaria/angioedema to NSAIDs. They recommend the first dose be given under medical supervision, since some patients may react.*
V.H.-T.
Nosbaum A, Braire-Bourrel M, Dubost R, et al: Prevention of nonsteroidal inflammatory drug-induced urticaria and/or angioedema.
Ann Allergy Asthma Immunol. 2013;110:263-266. ♦♦

Is It Worth Performing Skin Tests to Radiocontrast Media?

HYPERSENSITIVITY reactions to radiocontrast media (RCM) may occur through IgE- or T-cell-mediated mechanisms. Recent data suggest that skin tests could be useful for diagnosis of RCM allergy and selection of safe RCM. This study evaluated the clinical value of RCM skin testing as a prescreening tool.

A prospective study included a convenience sample of 1,084 patients scheduled for computed tomography scans using nonionic RCM. Just before their scan, these patients underwent intradermal skin testing with the RCM that was to be used. The researchers also reviewed the results of skin tests in 32 patients with previous hypersensitivity reactions to RCM who had been referred for allergy clinic evaluation.

In the prospective study, 64.1% of patients had no previous exposure to RCM. Of those with previous RCM exposure, 16.2% had had at least one mild RCM-related reaction. More than 90% of these were immediate reactions.

Skin testing with RCM produced a positive immediate hypersensitivity reaction in just 1 patient: a rate of 0.09%. In response to RCM administration, there were 51 mild immediate reactions (a rate of 4.9%), 1 moderate immediate reaction (0.09%), 8 mild nonimmediate reactions (0.76%), and 1 moderate nonimmediate reaction (0.09%).

There was 1 positive delayed hypersensitivity reaction to RCM skin testing (0.09%), in 1 patient with a nonimmediate RCM-associated reaction (11.1%). Radiocontrast media skin testing had 57.1% sensitivity for severe immediate reactions, compared to 12.9% for mild reactions and 25.0% for moderate reactions.

The study shows little or no clinical value of RCM skin testing to identify patients at risk of hypersensitivity reactions. Skin testing may have "modest utility" in evaluating patients with previous severe adverse reactions to RCM. ➤➤

COMMENT: *This prospective study looked at the utility of skin testing to RCM. Of patients with negative skin tests, 5% had an immediate hypersensitivity reaction after RCM administration, with 0.8% having non-immediate reactions. In patients with a history of reaction to RCM, the negative predictive value was only 80.3%. Of greatest concern, none of the patients with immediate hypersensitivity reactions to RCM had a positive screening skin test to the RCM agent responsible for the reaction. The authors do not recommend using skin prick testing to predict reactions to RCM; further studies are needed to confirm their results.*
V.H.-T.
Kim S-H, Jo E-J, Kim M-Y, et al: Clinical value of radiocontrast media skin tests as a prescreening and diagnostic tool in hypersensitivity reactions.
Ann Allergy Asthma Immunol. 2013;110: 258-262. ♦♦

Is Microarray Component Testing Related to Self-Reported Food Allergies?

MICROARRAY techniques for component-resolved diagnosis are a potentially valuable new tool for assessment of food allergy. Automated microarray systems now on the market could offer important advantages over whole-allergen specific IgE techniques. This "real world" study evaluated associations between automated microarray results and patient reports of food allergy and food-triggered atopic dermatitis (AD).

The study included 73 children with food allergies, including food-triggered AD, from 23 families, drawn from a Jewish community. Unaffected family members served as controls. Microarray components for milk, egg, and peanut were related to patient reports of food allergy and food-triggered AD.

The greater the number of detectable microarray components to a particular food, the greater the odds of self-reported food allergy or food-reported AD. Components individually related to self-reported peanut allergy included Ara h 1, Ara h 2, and Ara h 6, while Bos d 4 was individually related to self-reported milk allergy. Patients with more detected components to egg had increased odds of food-triggered AD.

On automated microarray component testing, a high diversity of detectable peanut, egg, and milk allergen components is significantly associated with reported patient reactions to these foods. With proper scoring tools, microarray component testing could be a valuable tool for prediction of food allergies.

COMMENT: *Microarray food testing provides a unique method for testing purified or recombinant protein components for each food extract. The authors demonstrate that a high diversity of food allergen components--such as Ara h1,2,6 for peanut, Bos d 4 for milk, and a number of egg component proteins--are associated with patient-reported histories of food allergy and food-related AS. The practicing allergist should be aware that microarray component tests under development for individual food extracts may give a "fingerprint" of the relevant food proteins that exacerbate atopic dermatitis or food allergy in individual patients.*
C.C.R.
Fung I, Kim JS, Spergel JM: Relating microarray component testing and reported food allergy and food-triggered atopic dermatitis: a real-world analysis.
Ann Allergy Asthma Immunol. 2013;110:171-177. ♦♦

Is It Time for Wider Use of Component Testing for Diagnosis of Peanut Allergy?

SKIN-prick testing and specific IgE measurement are limited in their ability to predict positive or negative responses to oral peanut challenge. Few studies have examined the role of component-resolved diagnostics (CRD) in clinical management of suspected peanut allergy. This study correlated the results of CRD with the outcomes of oral peanut challenge.

The retrospective analysis included 175 positive and 30 negative oral peanut challenges performed at one center between 2003 and 2009. All challenges were performed for clinical indications in patients with a history of reactions to peanut, ranging from mild to very severe. The challenge results were correlated with the CRD results for Ara h 1-3, h 8, and h 9.

The CRD result most strongly correlated with clinical responses to peanut challenge was Ara h 2. At a cutoff of greater than 1.63 kU/L, Ara h 2 was 70% sensitive and 100% specific for positive peanut challenge. The Ara h 2 level was also related to the severity of symptoms in response to peanut challenge, but with large intraindividual variation.

The Ara h 2 IgE level on CRD is a more accurate predictor of the response to oral peanut challenge, compared to specific IgE to peanut. In the study population, this information could have reduced the number of patients undergoing oral peanut challenge by more than half. The authors discuss the limitations of CRD for diagnosis of peanut allergy, including the need for decision points specific to the patient population and setting.

COMMENT: *The lack of specificity of peanut skin testing and in vitro specific IgE testing, along with concerns about the expense and safety of oral challenges, has led to continued strict avoidance of peanut in many patients who are not peanut allergic. This study analyzed the correlation between food challenge outcomes and component testing. An Ara h 2 level greater than 1.63 kU/L had 100% specificity. If this cutoff is validated in prospective studies, it would reduce the need for oral food challenges. Of course, third-party payer reimbursement for component testing is another story.*
S.A.T.
Eller E, Bindslev-Jensen C, et al: Clinical value of component-resolved diagnostics in peanut-allergic patients.
Allergy. 2013;68:190-194. ♦♦

Depo-Provera for HAE: A New Treatment Paradigm?

ESTROGENS contained in oral contraceptives can induce or worsen attacks of hereditary angioedema (HAE) in women. The use of progestin-only alternatives could not only provide good contraception, but also have beneficial effects on HAE. The effects of progestin contraceptives on the clinical manifestations of HAE were analyzed.

The retrospective study included 55 women, mean age 32.1 years, with nonallergic angioedema receiving progestin contraceptives. The diagnosis was type I HAE in 25.4% of women, type II HAE in 3.6%, type III HAE in 34%, and idiopathic angioedema in 36%. Type of contraceptive was a low-dose progestin-only pill (POP) in 17 women, antigonadotropic progestins (AGP) in 24, and both types successively in 14.

The women were followed up for a mean of 32.4 months. Overall, 81.8% of patients had partial or total improvement in angioedema symptoms while taking progestin contraceptives. For patients taking an AGP agent, the improvement rate was 89.5%, compared to 61.3% for those taking a POP. There were no serious adverse events.

In women with HAE or idiopathic angioedema, progestin contraceptives may favorably affect the course of angioedema. Use of AGP agents is particularly beneficial, leading to improved outcomes in close to 90% of patients.

COMMENT: *With the recent explosion of industry-sponsored HAE educational programs and clinical studies, sometimes treatment options other than expensive new drugs are either overlooked or criticized as unsafe. This retrospective study found a decreased frequency of attacks in female HAE patients treated with higher-dose progestins. Although prospective studies are needed, this may be a good option for women with frequent attacks who do not want, or do not have access to, C1 esterase inhibitor replacement. The authors provide a table that lists appropriate HAE dosing of various progestin contraceptives. An accompanying editorial endorses this treatment strategy and speculates regarding the mechanism(s) involved.*
S.A.T.
Saule C, Boccon-Gibod, Fain O, et al: Benefits of progestin contraception in non-allergic angioedema.
Clin Exp Allergy. 2013;43:475-482. ♦♦

Do Patients with Angioedema Who Present to the ER Receive Proper Treatment?

THERE are many possible causes of nonallergic angioedema--a potentially life-threatening condition that is commonly seen in the emergency department. The distinction between allergic and nonallergic angioedema can be difficult to make, but it is important because of the availability of C1 esterase concentrate and other newer treatments for angioedema. This study analyzed the characteristics of patients seen in the ER for acute angioedema and allergic reactions.

Using 2001-09 data from the National Hospital Ambulatory Medical Care Survey, the researchers analyzed the characteristics of visits to U.S. emergency departments for angioedema and allergic reactions. A weighted sampling design was used to estimate the annual number of such visits, the characteristics of affected patients, the care provided, and patient outcomes.

Out of 1.05 billion emergency department visits, there were 979,432 for angioedema, compared to 8.8 million for allergic reactions. Thus each year, there were an estimated 108,816 visits for angioedema and 979,400 for allergic reactions.

Compared to patients with allergic reactions, those with angioedema spent more time in the hospital, 3.1 versus 2.2 hours; and were more likely to be hospitalized, 11.0% versus 2.2%. Steroids and antihistamines were the most frequent treatments in both groups, but patients with angioedema were more likely to receive intravenous fluids. On sensitivity analysis, the results were about the same after exclusion of patients with urticaria in the allergic reaction group.

Each year, patients with angioedema account for more than 100,000 visits to U.S. emergency departments. The study highlights some important similarities and differences between patients presenting with angioedema versus allergic reactions. The findings "present opportunities for novel angioedema therapy use" in the ER setting.

COMMENT: *This study demonstrates that more than 100,000 visits to U.S. emergency departments each year are due to angioedema. The cross-sectional analysis of ER visits found that patients with angioedema were commonly diagnosed with allergic reactions. Patients with angioedema were older than patients who presented to the ER with allergic reactions. Patients with angioedema were treated with steroids and intravenous fluids more frequently than patients with allergic reactions, and were more likely to be admitted to the hospital. The authors challenge us to consider treatments specifically for angioedema in the emergency department.*
V.H.-T.
Kelly M, Donnelly JP, McAnnally J-R, Wang, HE: National estimates of emergency department visits for angioedema and allergic reactions in the United States.
Allergy Asthma Proc. 2013;34:150-154. ♦♦

CLINICAL TIDBITS

Possible Stress-Related Asthma Genotype in African Americans

STRESS is an important psychosocial factor potentially affecting the course of asthma. Cluster analysis of a group of African-American asthma patients identified a specific genotype with a history of asthma exacerbations linked to emotions and stress.

Supervised cluster analysis including 475 African Americans with asthma, drawn from a previous ➤➤

clinical trial, identified four clusters with differing annualized exacerbation rates. The cluster with the highest exacerbation rate, 1.18 events per year, was more than 80% female with a mean body mass index of 34. Patients in this cluster reported a history of stress and emotions as the cause of previous exacerbation. They also had decreased lung function and increased rescue medication use.

The results of cluster analysis were compared with analysis of genes previously linked to asthma exacerbations in 332 patients. The findings suggested that the rs4950928 single-nucleotide polymorphism of *CHI3L1*, the gene encoding YKL40, was significantly associated with the cluster reported stress-associated exacerbations.

The results suggest a specific genotype is associated with frequent exacerbations and stress as a cause of exacerbations in African American asthma patients. The study adds to the evidence that YKL-40 may be a biomarker of asthma severity or steroid insensitivity.

COMMENT: *Genetic cluster analysis revealed that a single gene polymorphism located on the promoter region of* CHI3L1*--the chitinase 3 like 1 gene encoding YKL-40--is highly correlated with a history of asthma exacerbations with stress and emotions in African Americans. The genetic imprint in asthma is being elucidated, and in the future may help to predict asthma severity and exacerbation risk.*
C.C.R.
Ortega H, Prazma C, Suruki RY, et al: Association of CHI3L1 in African-Americans with prior history of asthma exacerbations and stress.
J Asthma 2013;50:7-13. ♦♦

Tralokinumab for Moderate to Severe Asthma: Randomized Trial

INTERLEUKIN-13 (IL-13) is thought to play a key role in the development and maintenance of asthma. The investigational IL-13 inhibitor tralokinumab was evaluated for treatment of uncontrolled, moderate to severe asthma.

The phase II trial included 194 patients with moderate to severe asthma that was uncontrolled despite standard therapies. They were randomly assigned to treatment with tralokinumab, 150, 300, or 600 mg sc every 2 weeks, or placebo.

At 13-week assessment, tralokinumab did not significantly improve the Asthma Control Questionnaire (ACG-6) score, the primary endpoint. However, FEV_1 increased by 0.21 L in the combined tralokinumab group versus 0.06 L in the placebo group, with evidence of a dose-response effect. Use of β_2-agonists decreased by 0.68 puffs per day, compared to 0.10 with placebo. The improvement in FEV_1 was still apparent 12 weeks after the last dose of tralokinumab. There were no serious adverse events related to tralokinumab.

Anti-IL-13 therapy with tralokinumab may improve lung function in patients with poorly controlled, moderate to severe asthma. Larger studies with longer-term follow-up are needed to define the clinical role of tralokinumab.

COMMENT: *This phase II study of anti-IL-13 therapy with tralokinumab supports the previous trial of lebrikizumab* (**N Engl J Med**. 2011;365:1088-1098). *Tralokinumab led to significant improvement in* FEV_1 *and decreased beta agonist use, although the primary ACQ-6 endpoint was not met. Periostin was not used as a marker of response. These data are supportive but clearly show that more work is needed to define the role of anti-IL-13 in asthma care. Also see the accompanying editorial by Corren.*
B.E.C.
Piper E, Brightling C, Niven R, et al: A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma.
Eur Respir J. 2013:41;330-338. ♦♦

Identify and Address Bullying of Food-Allergic Children

CHILDREN with food allergies are socially vulnerable, and may be at increased risk of bullying and harassment. The prevalence and impact of bullying in food-allergic children were analyzed.

During allergy clinic visits, 251 children with food allergies and their parents (usually mothers) were independently surveyed regarding bullying. Bullying and harassment of the child for any reason was reported by 45.4% of children and 36.3% of parents. Bullying specifically related to food allergies was reported by 31.5% of children and 24.7% of parents. Bullying was mainly perpetrated by classmates, and often included being threatened with foods.

Bullied children reported decreased quality of life and increased distress, independent of allergy severity. Only about half of parents were aware of the bullying; when they were, the impact on the child was lessened.

The findings highlight a high rate of bullying in children with food allergies. The authors call for proactive efforts to identify and address bullying in this population of patients.

COMMENT: *Bullying can occur in up to 3 out of 10 children with food allergies, as demonstrated in this survey of 251 families attending an allergy clinic. The bullying frequently included threats with foods and was done primarily by classmates. It was associated with impaired quality of life and was independent of reported severity of food allergies. Parental awareness of bullying was reported in about half of the cases, and was associated with better social and emotional functioning in the child. The authors highlight the importance of proactively identifying and addressing bullying in this vulnerable population.*
C.D.
Shemesh E, Annunziato RA, Ambrose MA, et al: Child and parental reports of bullying in a consecutive sample of children with food allergy.
Pediatrics. 2013;131:e10-e17 ♦♦

REVIEWS OF NOTE

COMMENT: *Complementing our special focus section on asthma and allergy risk factors, this is an excellent review of the evidence of prenatal and postnatal dietary interventions that may prevent allergic disease.*
S.A.T.
Jemmalm MC, Duchén K: Timing of allergy-preventive and immunomodulatory dietary interventions--are prenatal, perinatal or postnatal strategies optimal?
Clin Exp Allergy. 2012;43:273-278. ♦♦

COMMENT: *Patients with cardiovascular disease and aspirin sensitivity often pose a treatment dilemma. This review discusses a practical approach to the treatment of these patients. The authors remind us to investigate the possibility of tolerance to another nonsteroidal anti-inflammatory drug. In the face of an unstable arterial lesion, the intravascular intervention can occur first, followed later, if clinically indicated, by challenge or desensitization to aspirin. They also recommend screening patients with asthma for aspirin-exacerbated respiratory disease. For these patients, pretreatment with leukotriene receptor antagonist, systemic steroid, antihistamine, and inhaled steroid/long-acting β-agonist before a 40.5 mg dose is recommended. Even in patients who react to the first or second dose, later doses are often tolerated. For patients with urticaria or rash, challenge is recommended with premedication, and treatment given if reaction occurs.*
V.H.-T.
White AA, Stevenson DD, Woessner KM, Simon RA: Approach to patients with aspirin hypersensitivity and acute cardiovascular emergencies.
Allergy Asthma Proc. 2013;34:138-142. ♦♦

COMMENT: *This is an excellent review of the sequelae of rhinovirus infections relating to airway injury and bronchial hyperreactivity.*
B.E.C.
Kieninger E, Fuchs O, Latzin P, et al: Rhinovirus infections in infancy and early childhood.
Eur Respir J. 2013;41:443-452. ♦♦

COMMENT: *This is an excellent executive summary of the new Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. It's a must-read for all practicing respiratory physicians.*
B.E.C.
Vestbo J, Hurd SS, Agustí AG, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary.
Am J Respir Crit Care Med. 2013;187:347-365. ♦♦

COMMENT: *This revision of the acute otitis media (AOM) guideline from the American Academy of Pediatrics and American Academy of Family Physicians provides recommendations to primary care clinicians for the management of children from 6 months through 12 years of age with uncomplicated AOM. New aspects include recommendations that clinicians should not diagnose AOM in children who do not have middle ear effusion and discussion of management issues pertaining to recurrent AOM.*
C.D.
Lieberthal AS, Carroll AE, Chonmaitree T, et al: The diagnosis and management of acute otitis media.
Pediatrics. 2012;131:e964-e999. ♦♦