AllergyWatch®

"10th Anniversary Volume"

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

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Steroids for Preschoolers with Virus-Induced Wheezing? Not Anymore

WHEEZING caused by upper respiratory viral infections is very common in infants and young children. In the hospital, these patients frequently receive short courses of oral corticosteroids, but the evidence supporting this practice is unclear. This study evaluated the efficacy of a short-course oral prednisolone for preschool-aged children with virus-induced wheezing.

The randomized, placebo-controlled trial included 700 children, aged 10 to 60 months, seen at three U.K. hospitals. All had wheezing preceded by signs and symptoms of upper respiratory viral infection. Children in the intervention group received oral prednisolone: 10 mg once daily for those aged 10 to 24 months and 20 mg once daily for older children. Controls received placebo. Intention-to-treat analysis included 687 children.

Length of hospital stay, the main outcome of interest, was not significantly different between groups: median 11.0 hours for the prednisolone group and 13.9 hours for the placebo group. There was also no difference in time from presentation to signoff for discharge: 10.1 and 12.0 hours, respectively. Secondary outcomes were similar as well, including scores on the Preschool Respiratory Assessment Measure, albuterol use, 7-day symptom score, and 1-month readmission rate. There were no clinically significant adverse events.

For preschool-aged children seen at the hospital or emergency department for wheezing associated with viral infection, a 5-day course of oral prednisolone does not reduce length of hospital stay. The results agree with some recent studies but disagree with others. The authors note that the children in their study did not have the "classic atopic asthma phenotype" that responds well to oral corticosteroid therapy.

COMMENT: *Asthma guidelines support the efficacy of prednisone in atopic school-age children and adults with acute asthma attacks. However, there is debate about preschool-age children (almost one-third) with what American pediatricians call "reactive airway*➤➤

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The American College of Allergy, Asthma & Immunology expresses its appreciation to Schering-Plough for its unrestricted grant in support of the publication of *AllergyWatch*®.

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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*disease": young wheezers with viral infections, who usually outgrow the wheezing tendency by age 5 or 6. Many or most of these children are non-allergic. This new study and others by Ducharme et al (**N Engl J Med. 2009;360:339-353**) and Bacharier et al (**J Allergy Clin Immunol. 2009;122:1127-1135**) strongly suggest that neither oral nor high-dose inhaled corticosteroids are sufficiently effective to recommend their use in any except the most severely affected hospitalized children with acute wheezing. In an editorial (**N Engl J Med. 2009;360:409-410**), Dr. Andrew Bush states flatly: "[C]urrent practice must change… Prednisolone should be administered to preschoolers only when they are severely ill in the hospital. Intermittent, high-dose inhaled corticosteroids should not be used."*
R.J.M.
Panickar J, Lakhanpaul M, Lambert PC, et al: Oral prednisolone for preschool children with acute virus-induced wheezing.
N Engl J Med. 2009;360:329-338. ♦♦

Study Evaluates Algorithm for Chronic Cough in Children

ALTHOUGH chronic cough is a frequent reason for visits to physicians by children, few studies have evaluated the causes of this condition. In adults, evaluation following an algorithm yields a diagnosis in almost every case. The authors report their experience with an algorithmic approach to evaluation of chronic cough in children.

The study included 108 children with chronic cough (lasting longer than 4 weeks) seen at one Turkish hospital over a 6-month period. Evaluation followed by the algorithm suggested by the 2006 American College of Chest Physicians (ACCP) guidelines, including spirometry, chest radiographs, and other tests as indicated. The patients were 56 boys and 52 girls, mean age 8.44 years, with a mean cough duration of 4.16 months

The most frequent diagnosis was asthma and asthma-like symptoms, reached in 25.0% of children. Other common diagnoses were protracted bronchitis, 23.4% of patients; and upper airway cough syndrome, 20.3%; and gastroesophageal reflux disease, 5.0%. Bronchiectasis was diagnosed in 3 children, while 1 patient each had tuberculosis, congenital malformation, and mycoplasma infection. Two children had natural recovery.

Applying an algorithmic approach to a large group of children with chronic cough, the authors find that most cases can be classified as asthma and asthma-like symptoms, protracted bronchitis, or upper airway cough syndrome. They find the "watch, wait, and review" step of the algorithm to be especially helpful. Randomized controlled trials are needed to evaluate the use of the 2006 ACCP recommendations.

COMMENT: *Cough is a common presenting symptom for many of our pediatric referrals. This study in a pulmonary journal found nearly 25% of chronic cough in children was related to asthma and 20% to "postnasal drip syndrome" or "upper airway cough syndrome." The latter diagnosis was defined as cough responding to antihistamines or nasal steroids. Most allergists would classify that as allergic rhinitis. No sinus imaging was performed, and "chronic bronchitis," which responded to antibiotics, could have been infection of the upper airways. None of the children underwent bronchoscopy. Allergists are well suited to deal with chronic cough in children.*
S.F.W.
Asilsoy S, Bayram E, Agin H, et al: Evaluation of chronic cough in children.
Chest. 2008;134:1122-1128. ♦♦

Add-on LABA Provides Better Asthma Control than Higher-Dose ICS

WHEN asthma persists despite low-dose inhaled corticosteroids (ICS), options include adding a long-acting β_2 agonist (LABA) to ICS or increasing the ICS dose. It remains unclear which alternative provides better asthma control. This question was addressed in a post hoc analysis of data from the "Formoterol and Corticosteroid Establishing Therapy" (FACET) study.

In the FACET study, patients with moderate to severe asthma were randomly assigned to receive budesonide 200 or 800 µg/d, plus placebo or formoterol 24 µg/d. The original results showed that adding LABA reduced both mild and severe exacerbations, especially with LABA plus higher-dose ICS. The current analysis compared time spent with well-controlled versus poorly controlled asthma, based on diary cards.

Time with well-controlled asthma increased by 19% for patients assigned to low-dose budesonide plus formoterol, compared to 2% for those receiving higher-dose budesonide alone. When formoterol was added to higher-dose budesonide, time with well-controlled asthma increased by 29%. Reductions in time with poorly controlled asthma were 43% with low-dose ICS plus LABA, 22% with higher-dose ICS alone, and 50% with higher-dose ICS plus LABA. Adding formoterol to low-dose budesonide yielded a significant 16% increase in time with well-controlled asthma, compared to higher-dose budesonide alone. There was also a trend toward decreased time with poorly controlled asthma, 21%.

Adding a LABA to low-dose ICS therapy improves time with well-controlled asthma while reducing time with poorly controlled asthma. In contrast, increasing the dose of ICS alone does little to improve time with good asthma control, although it does reduce exacerbations and time with poor asthma control. Adding formoterol improves all aspects of disease control, without a sharp increase in budesonide dose.

COMMENT: *This post hoc analysis of data from the FACET study looking at time spent with well-controlled or poorly controlled asthma parallels results involving objective lung function. For patients with moderately severe asthma, combination therapy demonstrates improved outcomes compared to higher doses of ICS. Current guidelines reflect these data.*
S.F.W.

O'Byrne PM, Naya IP, Kallen A, et al: Increasing doses of inhaled corticosteroids compared to adding long-acting inhaled β2-agonists in achieving asthma control. **Chest**. 2008;134:1192-1199. ♦♦

With Age Comes Responsibility (For Taking Asthma Medication)

DAILY use of controller medications is essential for the management of childhood asthma. Little is known about children's responsibility for taking daily asthma medications on their own, or the relationship between this responsibility and the level of adherence to the medication regimen. Parents were surveyed regarding children's responsibility for taking daily controller medications.

A telephone survey was conducted with 351 parents of children, mean age 10.4 years, who were taking daily controller medications for asthma. The sample was predominantly white; 61.5% of the children were boys. Parents were asked to estimate, as a percentage, how much of the responsibility for use of daily controller medications was theirs and how much was their child's. They also estimated adherence. The relationship between the child's responsibility for and adherence to daily controller medications was assessed, along with associated factors.

Children's responsibility increased and parental responsibility decreased with age. The average percentage of child responsibility for daily controller medications was about 20% at age 7, 50% at age 11, 75% at age 15, and 100% at age 19. On multivariate analysis, age and sex (less responsibility for boys) were independently associated with child responsibility--together, these two factors accounted for 41% of the variance. Younger age and white race were associated with increased adherence.

Many children assume responsibility for daily controller medications at young ages. Clinicians should inquire about who is taking responsibility for daily use of asthma medications, as this may have an important impact on adherence. Children should be included in family education about asthma medications and asthma self-management.

COMMENT: *Isn't it ironic that younger teenagers have been given at least 50% of the (parentally reported) responsibility for taking their own asthma controller medication, in this study? In practice, this is the same demographic group that may have worsening control of asthma, related to medication noncompliance. While not detracting from their child's increasing independence in general, parents may need to be more involved in monitoring daily medication use, until the child is older. This also assumes they will actually be able to find the medication in their teenager's room.*
K.R.M.

Orrell-Valente JK, Jarlsberg LG, Hill LG, Cabana MD: At what age do children start taking daily asthma medicines on their own?
Pediatrics. 2008;122:e1186-e1192. ♦♦

Proposed New Regimen for Existing AD Treatment

THERE is a need for safe, effective alternatives for prolonging remission in children with atopic dermatitis (AD). Intermittent application of tacrolimus, a topical calcineurin inhibitor, to previously inflamed areas might help to prevent or reduce AD relapse. This strategy was evaluated in a randomized, double-blind trial. ➤➤

The study included 206 children and adolescents with moderate to severe AD. In the first phase, patients received 4 days of twice-daily treatment with 0.05% alclometasone ointment or 0.03% tacrolimus ointment, followed by 16 weeks of open-label treatment with twice-daily tacrolimus. In a second phase, patients whose AD stabilized were assigned to treatment with tacrolimus or vehicle, applied to normal-looking skin once daily three times per week. Treatment continued for up to 40 weeks, during which time no corticosteroid use was permitted.

Of 152 patients who completed the first phase, 107 were assigned to long-term treatment with tacrolimus or placebo. In both randomized phases, there was no significant difference in adverse events. During the acute treatment period, clinical improvement in AD was greater for children assigned to alclometasone. There were no significant differences during subsequent open-label treatment with tacrolimus.

In the second phase, outcomes were better for children receiving intermittent tacrolimus. Median time to first relapse was 116 days for the tacrolimus group versus 31 days with vehicle. Mean number of disease-free days was 174 with tacrolimus and 107 days with vehicle; disease-relapse days were 47 and 76, respectively. There was no difference in the rate of at least one relapse, but relapses tended to be fewer and less severe with tacrolimus.

For children with AD, this trial supports a regimen of initial corticosteroid treatment followed by twice-daily tacrolimus. Long-term, three-times-weekly application of tacrolimus to previously involved skin can then be used to reduce relapse. The safety profile of tacrolimus ointment is similar to that of vehicle.

COMMENT: *Tacrolimus use in children with AD has certainly waned since the FDA-mandated "black box" warning in 2006, for potential cancer risk. Given the concern, all topical calcineurin inhibitors were approved by the FDA for short-term use only. Although the results of this study are promising, in the current environment it may be difficult to convince anxious parents to apply this medication chronically to healthy-appearing (but affected) AD skin. Long-term, prospective studies regarding cancer risk with these agents are ongoing, and we all look forward to their publication. Of note, the current study was funded by the product manufacturer.*
K.R.M.

Paller AS, Eichenfeld LF, Kirsner RS, and others: Three times weekly tacrolimus ointment reduces relapse in stabilized atopic dermatitis: a new paradigm for use. **Pediatrics**. 2009;122:e1210-e1218. ♦♦

IgE to Staphylococcal Superantigens in Milder AD

PREVIOUS studies have suggest that staphylococcal superantigens may be identified in more than half of *Staphylococcus aureus* isolates from children with atopic dermatitis (AD). More than three-fourths of children with severe AD have been found to produce IgE specific to these staphylococcal superantigens. The rate of superantigen-specific IgE was assessed in children with milder AD.

The study included 34 children with mild AD and 16 with moderate AD; objective SCORAD scores were 9.9 and 19.9, respectively. The ImmunoCAP system was used to measure serum IgE to staphylococcal enterotoxins A, B, C, and D and toxic shock syndrome toxin-1. The frequency of allergic sensitization to staphylococcal superantigens was compared between the two severity groups.

Specific IgE to staphylococcal superantigens was detected in 38% of children with mild AD and 63% of those with moderate AD. On logistic regression, allergic sensitization to these antigens--especially the A and D antigens--was significantly associated with moderate AD.

High rates of sensitization to staphylococcal superantigens are found in young children with mild and especially moderate AD. The findings have important implications for disease control, with an emphasis on treatments to restore skin barrier function.

COMMENT: *We have long known that staphylococcal exotoxins act as superantigens that worsen AD. Severely affected patients have IgE-mediated inflammatory reactions to these toxins. This small study adds to our knowledge, showing IgE-mediated responses to staphylococcal exotoxins in a graded manner, in mild and moderate AD, respectively. Certainly, we are aware that appropriate antibiotic therapy improves control of AD acutely, when there is evidence of superinfection. And our ongoing topical therapy reduces staphylococcal colonization, in time.*
K.R.M.

Ong J, Patel M, Ferdman RM, et al: Association of staphylococcal superantigen-specific immunoglobulin E with mild and moderate atopic dermatitis.
Pediatrics. 2009;153:803-806. ♦♦

Eosinophilic Esophagitis and Response to PPIs

WITH evidence that significant esophageal eosinophilia has an allergic cause, treatment has shifted toward anti-allergy therapies and away from gastroesophageal reflux disease (GERD) therapies. However, questions remain about the possible pathogenetic role of GERD and the clinical use of proton pump inhibitors (PPIs), especially as initial treatment. This study sought to identify factors associated with a response to PPI therapy in children with esophageal eosinophilia.

The retrospective analysis included 326 children and adolescents with significant esophageal eosinophilia seen at the authors' pediatric gastroenterology practice between 1999 and 2006. Of these, 43 received PPI treatment, followed by repeat endoscopy. Response to PPI was defined as an eosinophil count of less than 5 per hpf on follow-up biopsy. The characteristics of chil- ➤➤

dren with and without a response to PPI therapy were compared.

The patients' mean age was 8.5 years; two-thirds were male. Forty percent of patients met the study definition of response to PPI therapy. The children who did and did not respond to PPIs had no major differences in demographic characteristics, symptoms, or endoscopic and histologic findings. Patients with a lower eosinophil count on initial biopsy tended to have a higher response rate to PPI therapy: 50% for children with a baseline count of 15 to 20 eosinophils per hpf versus 29% for those with higher eosinophil counts. The response rate was 45% for children with normal results on esophageal pH monitoring, compared to 41% for those with abnormal results.

A trial of PPI therapy produces a histologic response in 40% of this series of children with significant esophageal eosinophilia. The chances of response are apparently unrelated to the children's clinical characteristics or to the findings of esophageal pH monitoring. Prospective studies are needed to clarify the role of PPIs in treating esophageal eosinophilia.

COMMENT: *Before food allergy was identified as a possible cause of eosinophilic esophagitis, GERD was theorized to play a significant etiologic role. Based on early studies, reflux of stomach acid onto esophageal tissue was thought to directly increase eosinophil influx. Of 326 children diagnosed with eosinophilic esophagitis in this retrospective study, a total of 43 met the inclusion criteria, creating potential selection bias. Certainly, a prospective approach is necessary for further investigation. Any clues gleaned regarding management of this increasingly prevalent disorder are helpful, but GERD and PPI therapy are unlikely to be the only answer.*
K.R.M.

Dranove JE, Horn DS, Davis MA, et al: Predictors of response to proton pump inhibitor therapy among children with significant esophageal eosinophilia. **Pediatrics**. 2009;154:96-100. ♦♦

Does Treating Heartburn in Pregnancy Cause Childhood Asthma?

STUDIES in mice have suggested that treatment with acid-suppressing drugs may lead to a T helper 2-dominant pattern with a predisposition to allergy in offspring. Registry data were used to seek evidence of a similar association in humans.

Analysis of three Swedish national health registers found that 5.03% of children born between 1995 and 2004 had a diagnosis of allergic disease or a prescription for allergy medications. Just under one percent (0.96%) of children were exposed to acid-suppressing drugs during gestation. Of this group, 0.07% were receiving treatment for allergic diseases.

In utero exposure to acid-suppressing drugs was associated with an increased risk of allergic disease: odds ratio (OR) 1.43. Risk was increased for all types of acid-suppressing drugs and for treatment early versus late in gestation. The effect was also independent of maternal history of allergies. Asthma was present in 5.6% of children exposed to maternal acid-suppressing drugs, compared to 3.7% of nonexposed children: OR 1.51. Acid-suppressing drugs were not significantly related to other types of allergic disease.

This study provides the first evidence that in utero exposure to acid-suppressing drugs may increase the risk of asthma in humans. Further research, including prospective observational studies, will be needed before any recommendation to restrict the use of acid-suppressing drugs during pregnancy.

COMMENT: *This Swedish population-based study analyzed data from more than 850,000 children born in 2004.* In utero *exposure to medications that suppress gastric acid (proton pump inhibitors, H2 antagonists) was associated with an increased risk of developing asthma. Although these results are provocative, the authors point out that further studies are necessary before considering restrictions on these medications during pregnancy.*
S.A.T.

Dehlink E, Yen E, Leichtner AM, et al: First evidence of a possible association between gastric acid suppression during pregnancy and childhood asthma: a population-based register study.
Allergy. 2008;39:246-253. ♦♦

Combination Therapy Improves Outcomes in Comorbid SAR and SAA

ALTHOUGH systemic immunotherapy (SIT) is an effective treatment for seasonal allergic asthma (SAA), systemic side effects are a concern. Results in patients with seasonal allergic rhinitis (SAR) suggest that combining SIT with omalizumab might be beneficial for patients with the complex problem of SAR together with SAA. This combination approach was evaluated in a randomized controlled trial.

The study included 140 adult and adolescent patients who had comorbid SAR and SAA with sensitization to grass pollen allergens. All patients received SIT using depigmented grass pollen allergoid (Depigoid); in addition, one group received omalizumab while the other received placebo. Treatment was given during pollen season. Omalizumab or placebo was started 2 weeks before SIT; the total treatment period was 18 weeks. Daily "symptom load" was assessed as the sum of symptom severity and rescue medication use.

Combination therapy was associated with a 39% reduction in symptom load, compared to SIT alone. Most of the difference reflected lower symptom severity; there was no significant difference in rescue medication use. The combination of omalizumab and SIT was also associated with improvements in asthma control and in quality of life specific to both asthma and rhinoconjunctivitis. About three-fourths of patients and investigators rated the outcomes "excellent or good" with combination therapy, compared to less than half with SIT alone.

For patients with comorbid SAR and SAA, ➤➤

adding omalizumab to SIT yields "statistically significant and clinically relevant" improvement in outcomes. Most of the benefit results from reductions in symptom severity. The combined therapy has an excellent safety profile.

COMMENT: *In this study, 18 weeks of omalizumab treatment with subcutaneous grass pollen immunotherapy using a rush protocol reduced both asthma and rhinitis symptoms, compared to SIT alone. The grass pollen extract used was a depigmented and glutaraldehyde-modified vaccine called Depigoid. The high cost of combining these two treatments remains as a major obstacle to the widespread use of this strategy.*
S.A.T.

Kopp MV, Hamelmann E, Zielen S, et al: Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma.
Clin Exp Allergy. 2008;39:271-279. ♦♦

Omalizumab and IgE Levels Linked to Changes in Asthma Symptoms

THE anti-IgE antibody omalizumab yields clinical improvement in patients with allergic asthma by suppressing free IgE. However, the exact relationship between free IgE levels and asthma symptoms remains unclear. Data from a randomized controlled trial were used to analyze the relationship between omalizumab, free IgE, and clinical outcomes.

The analysis included data from 152 healthy volunteers and 476 patients with severe, persistent allergic asthma participating in a placebo-controlled trial of omalizumab. The investigators used a robust pharmacokinetic-pharmacodynamic model to calculate serum levels of free IgE, omalizumab, and total IgE during the 28-week treatment period and 16 weeks of follow-up. These values were plotted against data on clinical outcomes, including symptom scores and peak expiratory flow, for treatment responders.

A good fit between the study model and the observational data permitted reconstruction of the time course of omalizumab, free IgE, and total IgE. Omalizumab was associated with rapid suppression of free IgE below the target level of 50 ng/mL. However, there was a significant lag time to stabilization of clinical outcomes, which did not occur until 12 to 16 weeks. When treatment was stopped, omalizumab and free IgE levels returned to baseline, with just a short delay before asthma symptoms reappeared.

The correlation between model-derived omalizumab and free IgE levels and clinical outcomes was particularly strong among patients classified as omalizumab responders. Analysis of clinical outcomes showed a gap between the on-treatment and off-treatment curves, reflecting the time needed for pulmonary function to respond to changes in free IgE.

The analysis shows a close correlation between omalizumab and free IgE levels and clinical symptoms in severe asthma. Based on these findings, reducing the omalizumab dosage after clinical response is not recommended, as deterioration of asthma control would ensue.

COMMENT: *Using a pharmacokinetic-pharmacodynamic binding model to calculate free IgE, these researchers analyzed data from two clinical studies and found a direct correlation of asthma symptoms and free IgE in patients responsive to omalizumab therapy. These findings suggest that off-label use of omalizumab in patients with extremely high IgE values will not be beneficial, since the reduction of free IgE is important for efficacy of this therapy.*
S.M.F.

Slayvin RG, Ferioli C, Tannenbaum SJ, et al: Asthma symptom re-emergence after omalizumab withdrawal correlates well with increasing IgE and decreasing pharmacokinetic concentrations.
J Allergy Clin Immunol. 2009;123:107-113. ♦♦

Budesonide vs Montelukast for Intermittent Wheezing in Preschoolers

NEW approaches are needed to reduce morbidity among preschoolers with repeated wheezing during respiratory tract infections (RTIs). Early oral corticosteroids have been recommended, but there are questions about effectiveness and concerns about side effects. This randomized trial compared two alternatives for the management of intermittent wheezing in preschoolers: inhaled corticosteroid versus a leukotriene receptor antagonist.

The Childhood Asthma Research and Education (CARE) Network trial included 238 preschoolers with moderate to severe intermittent wheezing associated with RTIs. During each RTI identified over the 1-year study period, children received 7 days of treatment with budesonide, 1 mg twice daily, plus oral placebo; montelukast, 4 mg/d, plus inhaled placebo; or double placebo. All three groups received albuterol.

The main outcome of interest, percentage of episode-free days, did not differ significantly among the three groups--the range was 73% to 76%. There were also no differences in need for oral corticosteroids, health care utilization, quality of life, or linear group. Both active treatments reduced trouble breathing during RTIs by nearly 40%. Scores for interference with activities during RTIs were reduced by 32% with budesonide and 40% with montelukast. Children with a positive asthma predictive index (API) or previous oral corticosteroid treatment obtained greater benefit from both active treatments, with reductions in episode severity of 40% to 54% (based on trouble breathing and interference with activities).

For preschool-aged children with moderate to severe wheezing associated with RTIs, neither budesonide nor montelukast increases percentage of episode-free days or decreases the use of oral corticosteroids. However, both treatments appear to reduce episode severity among children with positive API status. These ➤➤

forms of episodic treatment may decrease respiratory morbidity during acute RTIs in children with intermittent wheezing, particularly those at high risk of subsequent asthma.

COMMENT: *Although the primary endpoints of episode-free days and decrease in corticosteroid use did not meet statistical significance, this study from the CARE multicenter research network offers an interesting insight into the management of preschoolers with recurrent wheezing. The subgroup of children with positive API did have an impressive reduction in respiratory morbidity and symptoms during acute RTIs. These data suggest that children with a positive API may benefit from intermittent treatment with either an inhaled corticosteroid or a leukotriene receptor antagonist during RTIs.*

Bacharier LB, Phillips BR, Zeiger RS, et al: Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing.
J Allergy Clin Immunol. 2008;122:1127-1135. ♦♦

Step-up Therapy for Asthma: Higher-Dose ICS vs Add-on LABA

FOR patients whose asthma is not controlled with inhaled corticosteroids (ICS), options for step-up therapy include increasing the dose of ICS or adding a long-acting β-agonist (LABA). It is unclear which alternative provides the best results in routine clinical care. The U.K. General Practice Research Database was used to compare outcomes in patients managed by these two strategies.

Two groups of asthma patients receiving their first "step-up" for ICS monotherapy were identified: 49,630 patients receiving an increase in ICS dosage and 17,418 receiving an add-on LABA. Outcomes over the subsequent 12 months were analyzed, with logistic regression to adjust for a wide range of baseline differences between groups. Treatment success was defined as no hospital admission, no oral corticosteroid treatment, and average short-acting β-agonist (SABA) use of less than one dose per day.

The treatment success rate was lower among patients receiving an increased dose of ICS: adjusted odds ratio (OR) 0.75. The higher-dose ICS group was also more likely to require a rescue SABA prescription, OR 1.67. In contrast, patients in the high-dose ICS group were less likely to require any oral corticosteroid treatment, OR 0.75. For three or more courses of oral corticosteroid, the OR was 0.50. Higher-dose ICS was also associated with a reduced rate of hospitalization for respiratory causes, OR 0.69.

For patients whose asthma is not controlled with ICS, add-on LABA therapy leads to improved symptom control and reduced need for rescue bronchodilators. However, higher-dose ICS may reduce the risk of severe exacerbations and respiratory hospitalization. Pending further research, the authors suggest that increased anti-inflammatory medication may be more appropriate for patients considered at risk of exacerbations, while add-on LABA may be preferred for those with a persistent need for bronchodilators.

COMMENT: *Current asthma treatment guidelines recommend either higher-dose ICS or addition of LABA in patients not controlled with lower-dose ICS alone. This retrospective observational study suggests that an adequate dose of ICS is critical to control airway inflammation, even in those patients who seem to be doing well with combination LABA and lower-dose ICS. S.M.F.*

Thomas M, von Ziegenweidt J, Lee AJ, Price D: High-dose inhaled corticosteroids (ICS) versus add-on long-acting β-agonists in asthma: an observational study.
J Allergy Clin Immunol. 2009;123:116-121 ♦♦

Anaphylaxis Incidence Is Rising

IN the absence of a standard definition, reported incidence rates of anaphylaxis vary widely: from 3.2 to 20 cases per 100,000 person-years. Increased rates of food allergies and asthma may have lead to increases in anaphylaxis as well. Population-based data were used to monitor changes in the incidence and causes of anaphylaxis in one U.S. community over a 10-year period.

The investigators analyzed data from the Rochester (Minn.) Epidemiology Project for 1990 through 2000. Cases of anaphylaxis were confirmed by review of medical records, defined by signs and symptoms of mast cell and basophil mediator release plus involvement of the gastrointestinal, respiratory, or cardiovascular system.

Over the 10-year period studied, there were 211 cases of anaphylaxis. The patients' mean age was 29.3 years; 55.9% were women. With adjustment for age and sex, the incidence of anaphylaxis was 49.8 per 100,000 person years. The incidence was highest in children aged 0 to 19: incidence rate 70 per 100,000 person-years.

About two-thirds of cases of anaphylaxis were caused by food ingestion. Insect stings were the next most common cause, 18.5%; followed by medications, 13.7%. One case was caused by radiologic contrast agent. In the remaining cases, the cause was unknown or "other"--the latter category included cats, latex, cleaning agents, environmental allergens, and exercise. The incidence of anaphylaxis increased from 46.9 per 100,000 person-years in 1990 to 58.9 per 100,000 person-years in 2000.

This population-based study finds a higher incidence rate of anaphylaxis than reported in previous studies. The incidence of anaphylaxis appears to have increased substantially from 1990 to 2000. Food and insect allergies continue to be the most important causes.

COMMENT: *This impressive report documents the dramatic increase in the incidence of anaphylaxis, compared to the same population 10 to 15 years earlier. As suggested in the accompanying editorial (**J Allergy Clin Immunol**. 2008;122:1166-1168), this increase is not due to an artifact of coding. Rather, we truly have an epidemic of anaphylaxis and allergic diseases. S.M.F.*

➤➤

Decker WW, Campbell RL, Manivannan V, et al: The etiology and incidence of anaphylaxis in Rochester, Minnesota: A report from the Rochester Epidemiology Project.
J Allergy Clin Immunol. 2008;122:1161-1165. ♦♦

No Best Definition of Asthma Control

IN recent years, efforts have been made to develop a composite measure of asthma control for use in clinical trials and developing management approaches. The National Asthma Education and Prevention Program (NAEPP) provides guidance on categorizing asthma control, but is flexible in terms of measuring the impairment components of control. Three different definitions of asthma control were compared in a large patient cohort.

The analysis included data on 3,061 patients, aged 12 years or older, from a larger observational study of difficult-to-treat or severe asthma. The three definitions, all informed by NAEPP, included information from differing assessments--eg, a quality-of-life questionnaire, measures of self-perceived asthma control, and lung function measurements. Associations with clinically and economically relevant outcomes were compared between the different definitions.

The percentage of patients rated well-controlled at baseline was 9.1% with one definition, 17.1% with another, and 33.5% with a third. The latter definition was the only one that did not include pulmonary function data. Weighted kappa statistics used to compare the three definitions of baseline control ranged from 0.36 to 0.67. On regression analysis, all three definitions were significantly related to future disease control and health economic outcomes. However, there were significant differences across definitions, including the percentages of patients at different levels of disease control.

The findings highlight the difficulty of selecting and interpreting measures of asthma control. The authors call for more research into the factors included in definitions of asthma control, with the goal of developing standardized definitions of control for specific purposes.

COMMENT: *Asthma control is the goal, but what is control? Experienced clinicians may feel that asthma control is like love: you will know it when you have it. But the reality is that the definition varies with the eye of the evaluator.*
D.K.L.
Campbell JD, Blough DK, Sullivan SD: Comparison of guideline-based control definitions and associations with outcomes in severe or difficult-to-treat asthma.
Ann Allergy Asthma Immunol. 2008;101:474-481. ♦♦

Dialyzed Venom Makes Skin Testing More Accurate

IN patients undergoing intradermal skin testing with yellow jacket venom, nonspecific test responses can occur at venom concentrations greater than 1.0 µg/mL. This limits the diagnostic range of venom skin testing and makes testing less accurate in some allergic patients. Negative venom skin tests occur in up to one-third of patients with a history of reactions to stings. The results of testing with dialyzed venom extracts were evaluated in patients with apparent allergy but negative skin tests.

Yellow jacket venom was dialyzed to remove low-molecular-weight amines and irritants, which may lead to false-positive skin tests at higher concentrations. The dialyzed venom, and undialyzed venom from the same lot, was diluted to skin test concentrations of 0.1 to 10.0 µg/mL. The two venoms were then used to perform intradermal skin testing in 24 patients with a positive history but negative results of skin testing, 17 of whom had venom-specific IgE. Testing was also performed in 20 patients with a positive history and positive skin tests and in 10 nonallergic controls.

In 79% of patients with a positive history but negative results on testing with undialyzed venom, positive results were obtained using dialyzed venom at concentrations of 10 µg/mL or less. On regression analysis, dialyzed venom was associated with a half-log shift to the left, compared to undialyzed venom. Of 4 patients who had negative results on testing with undialyzed venom but systemic reactions to challenge stings, 3 had positive results on testing with dialyzed venom.

The use of dialyzed yellow jacket venom improves the accuracy of intradermal skin testing for yellow jacket allergy. With dialyzed venom, skin tests are positive in most patients with a positive clinical history but negative results on testing with undialyzed venom.

COMMENT: *A convincing history of insect sting anaphylaxis with a negative skin test is a clinical conundrum and difficult to explain. An inhibitor of skin test response within the venom is an interesting explanation. Perhaps commercial testing reagents should be dialyzed to enhance sensitivity without losing specificity. This is unlikely to happen, but at least there is a possible explanation for a negative skin test with a convincing history.*
D.K.L.
Golden DBK, Kelly D, Hamilton RG, et al: Dialyzed venom skin tests for identifying yellow jacket-allergic patients not detected using standard venom.
Ann Allergy Asthma Immunol. 2009;102:47-50. ♦♦

Daclizumab Shows Benefits in Persistent Asthma

THE airway inflammatory changes associated with asthma include increased numbers of activated CD25+ T cells, as well as increased levels of interleukin-2 (IL-2) and its soluble receptors (sIL-2Rs). Daclizumab is a new humanized IgG1 monocolonal antibody➤➤

that binds to the α subunit of the high-affinity IL-2R, thus inhibiting binding and biologic activity of IL-2. A trial of daclizumab for patients with moderate to severe persistent asthma is reported.

The multicenter study included patients who had moderate to severe persistent asthma despite medium to high doses of inhaled corticosteroids. Patients were switched to equivalent-dose triamcinolone acetate acetonide (TAA), then randomized in a 3:1 ratio to daclizumab or placebo. Daclizumab was given in an intravenous loading dose of 2 mg/kg, then 1 mg/kg every 2 weeks. Daclizumab (or placebo) was added to stable-dose TAA for the first 12 weeks. From week 12 to 20, the TAA dosage was tapered while patients continued their assigned treatment. Follow-up continued for 16 weeks after the end of study treatment.

The final analysis included 115 patients: 88 in the daclizumab group and 27 in the placebo group. During the first treatment phase, FEV_1 improved by 4.4% in the daclizumab group, compared to 1.5% with placebo. Daclizumab was also associated with decreases in daytime asthma symptoms and short-acting inhaled β_2-agonist use. Patients in the daclizumab group had a longer time to exacerbation. They also had a higher rate of serious adverse events, including one acute allergic reaction.

The anti-CD25 antibody daclizumab produces small but significant benefits for patients with moderate to severe persistent asthma. Treatment effects include improved lung function, better symptom control, and decreased blood eosinophils. Further study is needed to evaluate daclizumab as add-on therapy for patients with inadequate disease control despite inhaled corticosteroids.

COMMENT: *The use of anti-CD25 antibody to the α chain of IL-2R in patients with moderate asthma brought an improvement in lung function and downregulation of eosinophils in the peripheral blood. The treatment options for patients with this degree of impairment from asthma are extremely limited. Although this is a small study, it looks promising. More experience must be gained with this drug before any recommendations can be made regarding its role in therapy.*
B.E.C.

Busse WW, Israel E, Nelson HS, et al: Daclimuzab improves asthma control in patients with moderate to severe persistent asthma: a randomized, controlled trial.
Am J Respir Crit Care Med. 2008;178:1002-1008. ♦♦

Itraconazole Helps in Severe Asthma with Fungal Sensitization

SOME patients have a severe asthma phenotype associated with sensitization to fungi. The investigators assessed the response to oral itraconazole in this group of patients with "severe asthma with fungal sensitization (SAFS)"

The authors identified 58 patients meeting their criteria for SAFS at four U.K. centers. All patients had severe asthma plus sensitization to at least one of seven fungi, confirmed by skin prick testing or specific IgE measurement. They also had serum total IgE of less than 1,000 IU/mL and negative results for *Aspergillus* precipitin. Forty-one percent of patients had been hospitalized in the past year; mean Asthma Quality of Life Questionnaire (AQLQ) score at baseline was 4.13.

Patients were randomly assigned to receive 32 weeks of treatment with oral itraconazole, 200 mg twice daily, or placebo. Follow-up continued for 16 weeks after treatment.

After 32 weeks, the AQLQ score had improved by a mean of 0.85 point in the itraconazole group, compared to little or no change in the placebo group. Antifungal treatment was also associated with significant improvement in rhinitis score. Patients receiving itraconazole had a 20.8 L/min improvement in morning peak flow. Serum total IgE decreased by 51 IU/mL in the antifungal group, compared to a 30 IU/mL increase in the placebo group. Of 7 adverse events requiring treatment discontinuation, 5 occurred in the itraconazole group. There were no severe adverse events.

For patients with severe asthma associated with fungal sensitization, oral itraconazole has clinical benefits. Antifungal therapy yields significant improvements in quality of life in about 60% of patients meeting criteria for SAFS, compared to placebo. The relationship between fungal exposure and asthma is "important but poorly understood," the authors believe.

COMMENT: *This study adds to our knowledge regarding the treatment of a small group of patients with severe, refractory asthma. The results build on Platts-Mills' observations regarding the treatment of nail fungus (**J Allergy Clin Immunol**. 1999;104:541-546). Might this be similar to the mechanism seen in chronic hyperplastic sinusitis, when an irrigational antifungal drug is used as an anti-inflammatory, rather than for its anti-infective properties?*
B.E.C.

Denning DW, O'Driscoll BR, Powell G, et al: Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitization: the Fungal Asthma Sensitization Trial (FAST) study.
Am J Respir Crit Care Med. 2008:179:11-18. ♦♦

Eosinophils Express Tissue Factor in Chronic Urticaria

SEVERAL characteristics of chronic urticaria (CU) suggest an autoimmune origin. However, other findings include activation of blood coagulation by tissue factor (TF), along with TF expression in involved skin specimens. Eosinophils, which are the main source of TF in blood, are also found in CU lesions. This study sought evidence of TF expression by eosinophils in patients with CU.

Specimens of skin involved by wheals were obtained from 20 CU patients. Two groups of comparison specimens were also studied: perilesonal normal skin ➤➤

from patients with various skin tumors and from patients with various skin disorders associated with non-eosinophilic infiltrates, including leukocytoclastic vasculitis, lichen planus and mastocytosis.

On immunohistochemical studies using an anti-TF antibody, expression of TF was identified in all samples from CU patients, but none of the control specimens. In experiments using double-staining for TF and eosinophilic cationic protein, the TF-positive cells were clearly identified as eosinophils.

The results identify eosinophils as the source of TF in skin lesions in patients with CU. The study aids in understanding the pathophysiologic role of eosinophils in CU, and may lead to new treatment approaches.

COMMENT: *Chronic urticaria is frequently considered autoimmune in origin. This condition is associated with circulating histamine-releasing autoantibodies directed against the subunit of the high-affinity IgE receptor or against IgE, as well as activation of blood coagulation via TF. This study shows that TF is expressed in skin biopsies from patients with CU, and that eosinophils are the main source of TF in CU lesional skin. The findings underline the role of eosinophils in the pathophysiology of CU, which might pave the way for new therapeutic strategies*
M.F.
Cugno M, Marzano AV, Tedeschi A, et al: Expression of tissue factor by eosinophils in patients with chronic urticaria.
Int Arch Allergy Immunol. 2009;148:170-174. ♦♦

Women with Allergic Rhinitis Have Higher Leptin Levels

THERE is evidence of an association between obesity and respiratory allergic diseases, including asthma. Leptin reportedly plays a key role in controlling proliferation of regulatory T lymphocytes. Serum leptin levels were compared in subjects with and without respiratory allergies.

The study included 41 patients with moderate to severe persistent allergic rhinitis associated with pollen allergy and 34 healthy controls. Blood measurements and allergy tests were performed outside of pollen season. Serum leptin levels were higher in women, but not men, with allergic rhinitis. In both allergic and nonallergic women, serum leptin was significantly associated with age. In the allergic group, leptin level was correlated with body mass index. Serum leptin was also associated with symptom severity in women and peripheral blood eosinophils in men. In both sexes, leptin level was related to the allergen threshold dose on nasal challenge testing.

Women with pollen allergy and allergic rhinitis may have elevated serum leptin levels, compared to nonallergic controls. The findings may lend new insights into the association between allergies and body weight.

COMMENT: *Several studies have indicated a possible relationship between an increased body mass index and respiratory allergic diseases, and have suggested that obesity is a risk factor for the development of asthma. In this study, female patients with moderate-severe persistent allergic rhinitis due to pollen allergy showed significantly higher serum leptin levels than normal females. This, along with the other associations noted, provides support for the hypothesis that leptin exerts proinflammatory effects.*
M.F.
Ciprandi G, Filaci G, Negrini S et al: Serum leptin levels in patients with pollen-induced allergic rhinitis.
Int Arch Allergy Immunol. 2009;148:211-218. ♦♦

CLINICAL TIDBITS

Reactions to HPV Vaccine Are Rare

THE quadrivalent human papillomavirus (HPV) vaccine is now recommended for girls and young women. Two pediatric allergy centers report their experience of 35 schoolgirls, aged 12 to 19 years, with suspected hypersensitivity reactions to HPV vaccine.

The cases were referred from Australian schools where more than 380,000 doses of HPV vaccine had been administered. Allergic evaluation of 25 patients found that 92% reacted to the first dose. Urticaria or angioedemia occurred in 52% of patients, including 2 with anaphylaxis. Median time to reaction was 90 minutes after vaccination.

Skin-prick tests were negative in 19 of 19 girls, while 1 patient had a positive response to intradermal skin testing. Subsequent vaccine challenge was tolerated in 17 of 18 girls; the remaining patient had a limited urticarial response. Just 3 of 25 girls were thought to have probable hypersensitivity reactions.

The rate of hypersensitivity reactions to HPV vaccine appears low. Most girls with suspected reactions are able to tolerate subsequent vaccine doses.

COMMENT: *Quadrivalent HPV immunization is universally recommended for young girls. This study found that hypersensitivity reactions are rare (35/380,000 doses). Only one reaction was anaphylactic and was associated with a positive skin test. Schoolgirls who elected to receive subsequent immunizations did not have any significant reactions. Negative skin tests should encourage physicians to administer HPV immunizations.*
S.F.W.
COMMENT: Kang LW, Crawford N, Tang MLK, et al: Hypersensitivity reactions to human papillomavirus vaccine in Australian schoolgirls: retrospective cohort study.
BMJ. 2008;337:a2642. ♦♦

Long-term Benefits of SLIT for Allergic Asthma

A growing body of evidence supports the use of sublingual immunotherapy (SLIT) for patients with allergic asthma. This study compares the 5-year results of SLIT vs inhaled budesonide in patients with mild persistent asthma associated with grass pollen allergy.

Fifty-one patients were randomly assigned to receive inhaled budesonide (800 µg/d) given during pollen season or grass pollen SLIT given year-round. Forty-six patients completed the 5-year study. Both treatments reduced bronchial symptom scores and bronchodilator use, but SLIT produced greater improvement. Nasal symptom score and nasal steroid intake decreased only in the SLIT group. Improvements in nasal eosinophils and bronchial hyperresponsiveness were also observed only with SLIT.

The results support the long-term effectiveness of SLIT for patients with asthma related to grass pollen allergy. Compared to inhaled budesonide, SLIT has additional benefits in terms of nasal symptoms and bronchial hyperresponsiveness.

COMMENT: *This group of authors has long-term experience with SLIT, a treatment modality about which many questions remain. Grass allergen is one of the most effective SLIT allergens for sublingual therapy, but the North American trial with grass-pollen SLIT has not been positive. Nevertheless, the literature grows with respect to SLIT and its potential benefits for both rhinitis and asthma. The dose of sublingual allergen used in these trials is two to five times the monthly maintenance of injection immunotherapy, given three times a week. Keep the dose effect in mind as you review the literature.*
D.K.L.
Marogna M, Spadolini I, Massolo A, et al: Long-term comparison of sublingual immunotherapy vs inhaled budesonide in patients with mild persistent asthma due to grass pollen.
Ann Allergy Asthma Immunol. 2009;102:69-75. ♦♦

Can We Switch to ARBs after Angioedema with ACEIs?

ANGIOEDEMA is a well-recognized complication of treatment with angiotensin-converting enzyme inhibitors (ACEIs). There have been reports of subsequent episodes of angioedema in patients after switching to angiotensin-receptor blockers (ARBs).

A review and meta-analysis were performed to assess the evidence on the risk of angioedema related to ARBs in patients with previous angioedema related to ACEIs. Three articles providing data on 71 patients were identified; all studies included at least 1 month of follow-up after switching to an ARB. The rate of subsequent angioedema was 9.4% for possible cases and 3.5% for confirmed cases. None of the patients died.

Based on limited data, the risk of ARB-related angioedema in a patient with previous ACEI-related angioedema (including possible angioedema) is between 2% and 17% (based on 95% confidence interval). This information will be useful for patient counseling.

COMMENT: *The ACEIs and ARBs offer unique advantages for the treatment of select cardiovascular and renovascular diseases. The question of using an ARB following angioedema with an ACEI often arises. This article will enable you to quote the medical literature, although meager, showing that the risk is as great as great as 10%. Maybe these individuals would be at increased risk of angioedema with other therapies as well. It would be ideal to have a control group, with a history of ACEI angioedema, who were receiving other classes of antihypertensives.*
D.K.L.
Haymore BR, Yoon J, Mikita CP, et al: Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis.
Ann Allergy Asthma Immunol. 2008;101:495-499. ♦♦

Editor's note: In this issue we present a special editorial by Peter B. Boggs, M.D., of LSU School of Medicine, Shreveport, La.

FeNO: An Evolving Paradigm Change

AS someone who has used the fraction of exhaled nitric oxide (FeNO) as a routine part of the assessment of patients with asthma for 7 years and thousands of patient encounters, it is disappointing to see this test being demeaned by literature whose focus is too narrow and correlations of dubious value. The key pathophysiologic process in asthma is airway inflammation. Exhaled NO has been shown to be a valid proxy for eosinophilic inflammation, the most common inflammatory asthma phenotype. The traditional tools by which clinicians assess asthma--the history, physical exam, pulmonary function tests, and quality of life instruments--are not valid proxies for airway inflammation. They do not correlate well with one another and do not correlate with FeNO measurements. The latter explains the lack of correlation of FeNo with traditional markers in recent studies.

Exhaled NO can be helpful to clinicians in a range of circumstances of practical clinical value: making the diagnosis and differential diagnosis of asthma and chronic cough; assessing the change in inflammation associated with the use of inhaled corticosteroids (ICS); comparing ICS medications, their delivery systems, and their impact on airway inflammation; dosing ICS agents; stepping-up and stepping-down doses; evaluating adherence/nonadherence to ICS medications; alerting you to a change in exposure to inflammatory triggers; assessing whether an episode is driven by inflammatory or bronchospastic triggers; and anticipating loss of asthma control. Needed are studies that address the actual clinical usefulness of FeNO.
P.B.B. ♦♦

REVIEWS OF NOTE

COMMENT: *In our practices, we see considerable numbers of patients with seborrheic dermatitis, some of whom think it's eczema or contact allergy. Other times it's an incidental finding. This review discusses the differential diagnosis and treatment, emphasizing the role of anti-fungal medicines. It is a valuable guide to managing a chronic, relapsing condition that is poorly understood.*
R.J.M.
Naldi L, Rebora A: Seborrheic dermatitis.
N Engl J Med. 2009:360:387-396. ♦♦

COMMENT: *In the 1990s, the average death toll from influenza was 51,000 per year. There were up to a half-million hospitalizations and an annual economic cost of nearly $90 billion. Many epidemiologists predict a coming pandemic that may dwarf those numbers. The influenza vaccines are 70% to 90% protective when there's a good match with the prevalent virus; nasal attenuated virus vaccine is slightly more effective in children than the injected inactivated vaccine. Drug treatment of existing disease has been complicated recently by resistance. If this review doesn't motivate doctors and the public to aim for universal vaccination, nothing will.*
R.J.M.
Glezen WP: Prevention and treatment of seasonal influenza.
N Engl J Med. 2008:359:2579-2585. ♦♦

COMMENT: *The bottom line is that specific immunotherapy consistently improves symptoms and reduces medication use in subjects with rhinitis and asthma. The relative efficacy of the subcutaneous and sublingual routes remains a point for discussion. Allergists should unite around the* appropriate *use of immunotherapy.*
D.K.L.
Compalati E, Penagos M, Tarantini F, et al: Specific immunotherapy for respiratory allergy: state of the art according to current meta-analyses.
Ann Allergy Asthma Immunol. 2009;102:22-28. ♦♦

COMMENT: *This paper provides a succinct summary of the data supporting a role of leukotrienes in modifying bronchial smooth muscle hyperplasia. The variety of growth factors and cytokines implicated helps to explain why single-drug treatment to date has not made a significant impact on bronchial remodeling in asthma.*
D.K.L.
Bossé Y, Stankova J, Rola-Pleszczynski M: Cysteinyl-leukotrienes in asthmatic airway smooth muscle cell hyperplasia.
Ann Allergy Asthma Immunol. 2009;102:16-21. ♦♦

COMMENT: *This elegant analysis groups available data from placebo-controlled studies done to date, assessing inhaled corticosteroid efficacy and safety in children. Findings are viewed through the lens of the Expert Panel Report 3 guidelines.*
K.R.M.
Rachelefsky G: Inhaled corticosteroids and asthma control in children: assessing impairment and risk. ♦♦

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