AllergyWatch®

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

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Advair Diskus: Current Status of Combination Therapy for Asthma

In several clinical situations, different classes of antiasthma drugs may be combined to achieve optimal asthma control. Such combination regimens can be complex, with the potential for misuse. A new product now on the market as Advair or Seretide combines the inhaled corticosteroid fluticasone propionate with the long-acting β-adrenergic bronchodilator salmeterol in a single Diskus inhaler. The goal is to improve disease control by addressing both the inflammatory and bronchoconstrictive components of asthma. The author reviews available evidence regarding the use of combined therapy, focusing on the Advair Diskus device.

Current guidelines for asthma management emphasize a stepwise approach, starting with low-dose inhaled corticosteroids and adding other medications as needed for disease control, including long-term control medications. Inhaled corticosteroid therapy is essential, with fluticasone showing a good risk-to-benefit ratio across doses and levels of severity. Salmeterol is the only long-acting bronchodilator currently approved for use in the United States. Advair Diskus combines these two medications in a single breath-actuated device. It is available at fluticasone doses of 100, 250, and 500 μg; the salmeterol dose is held constant at 50 μg.

Recent studies have helped to alleviate concerns that long-acting bronchodilators will mask the underlying inflammation of asthma. A substantial body of evidence now supports the combined use of inhaled corticosteroids and long-acting bronchodilators. Review of the available scientific and clinical data supports the use of Advair for combined inhaled corticosteroid/long-acting bronchodilator therapy for asthma. Through the complementary actions of flutcasone and salmeterol, this combination product offers superior asthma control compared with other approaches. It addresses both the inflammation and bronchoconstriction of asthma without any new adverse effects; the ability to use a single inhaler may improve patient compliance. ➤➤

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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
- Thorax
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- Mayo Clinic Proceedings

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COMMENT: *We are fortunate these days to have many effective medications for the treatment of asthma. A mild dilemma has been, which ones to combine in moderate or persistent asthma? A new inhaler has been devised that combines salmeterol with fluticasone, and it has generated some controversy regarding the appropriateness of a combination product. In this article, Dr. Harold Nelson—a wise man of American medicine—reviews comprehensively the scientific and clinical evidence behind this new product. You will need to know this.*
R. J. M.

Nelson HS: Advair: combination treatment with fluticasone propionate/salmeterol in the treatment of asthma.
J Allergy Clin Immunol 107:397-416, 2001.

How Accurate Are Children's Peak Flow Diaries?

THE accuracy and reliability of peak flow diaries kept by pediatric asthma patients were evaluated. The study included 40 white children with stable asthma, aged 5 to 16 years. The children were given an electronic peak flow meter and asked to record twice-daily values in a diary for 4 weeks. Without the subjects' knowledge, the values were simultaneously recorded on a memory microchip. The diary data entered by the children were compared with the electronically stored data.

This children's mean reported compliance was 95.7%, but actual compliance was significantly lower: 77.1%. In the first week, the percentage of correct peak flow entries was 56%. Thereafter, this percentage dipped to less than 50%, mainly because of invented diary entries.

Even in a group of affluent, well-motivated patients, the reliability of peak flow diaries kept by asthmatic children is questionable. Up to one-half of such entries are inaccurate, the findings suggest. This study questions the reliance on peak flow diaries in pediatric asthma, both in research and clinical practice.

COMMENT: *Forty asthmatic children aged 5 to 16 years were asked to perform peak flow measurements using an electronic peak flow meter twice daily for 4 weeks. Similar to results in occupational settings, peak flow diaries were unreliable—up to 25% of entries were incorrectly recorded. The implications of these data make one wonder about the interpretation of clinical research, in which peak flow diaries are frequently used. As well, dependence on such diaries for asthma self-management seems unjustified.*
E. J. B.

Kamps AWA, Roorda RJ, Brand PLP: Peak flow diaries in childhood asthma are unreliable.
Thorax 56:180-182, 2001. ♦♦

One-Fifth of Children Outgrow Peanut Allergy

A diagnosis of peanut allergy is a significant event, as reactions to peanut are potentially serious and the risk of exposure is high. Whereas most food allergies beginning early in life resolve over time, it has traditionally been thought that children do not outgrow peanut allergy. This study examined whether children can outgrow peanut allergy, and whether there are any factors that predict its resolution.

The investigators identified 223 patients, median age 6.5 years, with a diagnosis of peanut allergy. The patients were 140 males and 83 females; median age at diagnosis of peanut allergy was 1.5 years. One hundred sixty-seven patients had had an acute reaction to peanut, 164 of whom had positive results on skin testing or RAST. The remaining 66 had peanut ➤➤

allergy diagnosis on the basis of skin test or RAST only. Based on history and a peanut IgE level of less than 20 kU of antibody per liter (kU_A/L), 129 patients were eligible for oral peanut challenge; 85 consented to the procedure. Median peanut IgE level in this group was 1.42 kU_A/L.

The results of peanut challenge were negative in 48 patients (21.5%), median age 6 years. Median peanut IgE level was 0.69 kU_A/L for challenge-negative patients, compared to 2.06 kU_A/L for those with a positive challenge. Two-thirds of children with a peanut IgE level of less than 2.0 kU_A/L had a negative challenge result. Skin tests were positive in 63% of children who passed the challenge. On analysis of the ability of the CAP system fluorescent-enzyme immunoassay to predict challenge outcome, a peanut IgE level of greater than 0.35 kU_A/L had a sensitivity of 84%, specificity of 33%, and positive and negative predictive value of 49% and 73%, respectively.

More than 20% of patients may outgrow peanut allergy, the results suggest. Peanut IgE levels are significantly lower in children who have a negative result on oral peanut challenge. The authors propose performing peanut challenge in a medical setting in patients with low peanut IgE levels to see if they can now tolerate this food. Even some patients with initially high peanut IgE levels may eventually outgrow their allergy.

COMMENT: *The experts in food allergy present this impressive study that refutes the long-standing assumption that peanut allergy is a lifelong affliction. The 48 patients (21.5% of the total) with negative challenges tended to have less severe initial allergic reactions, involving the skin only, and lower allergen sensitivities to peanut at the time of diagnosis. The authors recommend annual RAST studies for young children and consider oral challenges in those with peanut IgE levels of less than 5 kU_A/L. A negative challenge can be a major benefit for these patients, not to mention the emotional relief in their parents.*

S. M. F.

Skolnick HS, Conover-Walker MK, Koerner CB, et al: The natural history of peanut allergy.

J Allergy Clin Immunol 107:367-374, 2001. ♦♦

Experience Supports Safety of Oral Peanut Challenge

GIVEN the potential for life-threatening reactions, accurate diagnosis of peanut allergy is essential. There are relatively few data on the diagnostic performance of skin-prick testing for peanut allergy—oral peanut challenge remains the gold standard for diagnosis. A 4-year experience with oral peanut challenge is reviewed.

From the 1994 to 1998, the investigators performed oral peanut challenges in 140 patients with possible IgE-mediated hypersensitivity to peanut. Those with a convincing history of reaction and a skin-test reaction of 5 mm or larger were generally not challenged. Challenge testing was performed after the children had avoided antihistamines for at least 96 hours and β-agonists for at least 12 hours. The test was rescheduled if the child had any wheezing within the previous 24 hours. Peanut challenge started at a dose of 10 to 50 mg, proceeding up to 5 to 10 g, if tolerated. The children were evaluated for symptoms typical of IgE-mediated reaction in response to peanut challenge. The responses to oral challenge were compared to the skin-prick test results to estimate the diagnostic performance of the latter test.

The peanut challenges were single-blind in 112 patients and open in 28. The patients were 80 boys and 60 girls, median age 5 years. Eighteen patients had positive reactions, with clinical manifestations including urticaria, oropharyngeal irritation, rhinitis, vomiting, and abdominal pain. Ten of the 18 patients required medical treatment, consisting of antihistamines with or without epinephrine or salbutamol. There were no life-threatening reactions, however. Skin prick testing had a sensitivity of 100%, specificity of 62%, positive predictive value of 28%, and negative predictive value of 100%.

Even in children with a positive skin prick test, oral peanut challenge is usually necessary to confirm the diagnosis of peanut allergy. Oral challenge is unnecessary in children with an obvious history of anaphylactic reaction to peanut and a positive skin prick test. Although skin prick testing has low positive predictive value and specificity, its negative predictive value and sensitivity are high. Thus patients with a negative skin prick test need not undergo peanut challenge, unless they have strong evidence of immediate hypersensitivity.

COMMENT: *The authors share their experience of safely performing oral peanut challenges in 140 patients with positive skin tests to peanut. This study highlights the poor positive predictive value of skin prick testing to peanut. However, the data also suggest that nearly one-third of skin-test-positive patients who have no prior known exposure to peanut will experience clinical symptoms when eating peanuts. This poses a dilemma for the practicing clinician who may not be comfortable proceeding with oral challenges: Is it appropriate to skin-test for peanut and other foods when an adverse food reaction is not the presenting complaint? Must we advise all patients with a positive skin test to peanut to read labels, carry injectable epinephrine, and wear a Medic Alert bracelet?*

S. A. T.

Pucar F, Kagan R, Lim H, Clarke AE: Peanut challenge: a retrospective study of 140 patients.

Clin Exp Allergy 31:40-46, 2001. ♦♦

Modified Th2 Response May Explain Reduced Asthma Rates Among Children with Cats

PREVIOUS studies have established a link between asthma and immediate hypersensitivity to indoor allergens. However, it has also been suggested that having a cat in the house actually decreases asthma ➤➤

risk. This could be seen as supporting the "cleanliness" hypothesis to explain recent increases in allergic disease—ie, that increasingly clean environments have led the immune system to shift from a T-helper-1 (Th1) to a T-helper-2 cell (Th2) bias. This population-based study assessed immune responses to cat and dust mite allergens among asthmatic children.

Of 226 seventh- and eighth-graders evaluated, 47 were identified as having symptoms of asthma and bronchial hyperreactivity. A radioallergosorbent test was used to measure IgE antibodies to cat and dust mite allergen by isotype. Associations between exposure to dust mite or cat allergen at home and sensitization or antibody responses were assessed.

Children with greater exposure to dust mite allergen were more likely to be sensitized and to have IgG antibody to Der f 1. However, those with high exposure to cat allergen had a lower rate of sensitization, but a higher rate of IgG antibody to Fel d 1. On logistic regression, children in the high-exposure group were 4 times more likely to be sensitized to mite than to cat. In addition, 41% of children with 23 μg of Fel d 1 in the home had greater than 125 U of IgG antibody to Fel d 1, despite their lack of sensitization to cat. Whether or not they were allergic, the children showed a strong correlation between IgG4 isotype Fel d 1 antibodies and IgG antibody. The main risk factor for asthma was sensitization to dust mite or cat allergen.

Children exposed to cat allergen may demonstrate IgG and IgG4 antibody responses, despite a lack of sensitization or asthma. This form of tolerance represents a modification of the Th2 response, and may be the proper objective of immunotherapy. It may also explain why children with a cat at home are at lower risk of asthma.

COMMENT: *Asthma is strongly associated with hypersensitivity to indoor allergens. However, a number of studies have shown that having a cat in the home decreases the risk of asthma. These investigators measure the presence of IgG and IgE antibodies to cat and mite allergens in 226 asthmatic children. They found exposure to cat allergen could induce an IgG and IgG4 antibody response without sensitization or risk of asthma. Dust mite also appears to induce IgG but with a much higher propensity to sensitization. This study casts doubt about whether the changing prevalence of asthma and allergic disease can be explained by a shift in the balance of Th1 and Th2 responses.*
E. J. B.

Platts-Mills T, Vaughan J, Squillace S, et al: Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. **Lancet** 357:752-756, 2001.

Surgery Has Added Benefits in Nasal Polyposis

NASAL polyposis is a common condition for which both medical and surgical treatment have been recommended. There is a need for controlled trials to ascertain the benefits of surgery, over and above those of medical therapy. The results of medical treatment vs combined surgical and medical treatment were compared in patients with nasal polyposis.

The randomized trial included 32 patients with nasal polyposis and symmetric nasal airways. Initial treatment consisted of 10 days of oral prednisolone and 1 month of bilateral local nasal budesonide. The patients were then randomized to undergo endoscopic sinus surgery on one side only; postoperatively, they received local nasal budesonide. Main outcomes at 12 months' follow-up included olfaction, nasal symptoms, and an endoscopic polyp score.

Treatment with local and oral steroids was associated with significant improvement in sense of smell. Medical treatment also brought significant reductions in symptom score. However, surgery conferred additional reductions in nasal obstruction and secretions. The polyp score was also significantly lower on the operated side.

For patients with nasal polyposis, medical treatment alone appears sufficient to address most symptoms. Patients whose major complaint is loss of smell are unlikely to derive further benefit from surgery. However, surgery is indicated for patients with a main complaint of nasal obstruction. Treatment for nasal polyposis should be chosen to address the patient's symptoms, not based on an examiner-determined polyp score.

COMMENT: *Patients with nasal polyps often present to allergists before surgeons. The quandary may be whether to pursue medication alone or to offer surgery as well. This Swedish group treated all patients initially with systemic and oral steroids for a brief time, then performed surgery on one side of the nose only, followed by an intranasal steroid bilaterally for one year. At the end, the operated side was less obstructed, had lower polyp scores, and had decreased secretions compared to the nonoperated side. Headaches and sense of smell were not significantly different. It would be interesting to carry this study out a few more years. For now, it appears that surgery adds real benefit.*
R. J. M.

Blomqvist EH, Lundland L, Änggård A, et al: A randomized controlled study evaluating medical treatment versus surgical treatment in addition to medical treatment of nasal polyposis.
J Allergy Clin Immunol 107:224-228, 2001. ♦♦

New Eradication Technique Lowers Home Dust Mite Allergen Levels

HOUSE dust mite allergens are a major cause of asthma symptoms, and can build up to very high levels in the home. Various methods have been explored to reduce the level of dust mite allergen in the home, with variable results. This study examined a new hot air/steam cleaning method for reducing dust mite allergen levels in the home.

The randomized, double-blind trial included 30 adult asthma patients divided into 3 groups. The homes of patients in groups 1 and 2 underwent mite erad- ➤➤

ication, including steam cleaning of carpets and upholstery. In addition, mattresses and bedding were treated with a new technique using 110° C air delivered to the inside of the mattress via a probe. This was followed by steam, and then hot air again. In addition, group 2 homes had a positive ventilation system installed above the patients' bedrooms. Homes in group 3 underwent sham treatment. The effects of the differing treatments on mite allergen levels and asthma severity were assessed.

Group 1 and 2 homes showed significant and sustained reductions in both Der p 1 and Der p 2 allergen, compared with group 3 homes. The active-treatment groups also showed a 4-fold reduction in bronchial hyperresponsiveness, compared with an increase in responsiveness in the sham treatment group. The improvements persisted through 12 months' follow-up in group 2 homes, which had bedroom ventilation units installed.

The house dust mite eradication techniques evaluated in this study significantly reduce mite allergen levels in the home after a single treatment. The result is a significant reduction in bronchial hyperresponsiveness, especially when a special bedroom ventilation system is installed. The bedding treatment used in this study is effective because it kills the mites using hot air, followed by steam that limits the antigen's ability to initiate a hypersensitivity response.

COMMENT: *This study was sponsored by the makers (Mediclean) of a novel method of injecting hot air and steam into mattresses and bedding using a probe device. The technique does appear to be efficacious at reducing dust mites and improving airway hyperreactivity in sensitive asthmatics, but it is not inexpensive—$800. One of the treatment groups also used an air-filtration system, which appeared to sustain the reduction in dust mite levels. Other investigators have not shown benefit from air cleaners for dust mite. However, the fact that the mite levels were initially reduced in this study—before the use of the air filters—may have improved their effectiveness.*
S. M. F.

Htut T, Higenbottam TW, Gill GW, et al: Eradication of house dust mite from homes of atopic asthmatic subjects: a double-blind trial.
J Allergy Clin Immunol 107:55-60, 2001. ♦♦

Meta-Analysis Supports Safety of Montelukast

GIVEN once daily by mouth, the leukotriene receptor antagonist montelukast improves disease control in adults and children with chronic asthma. Up to now, there has been no comprehensive review of available data on the safety and tolerability of this medication. A meta-analysis of pooled safety data from randomized, double-blind, placebo-controlled trials of montelukast is reported.

The analysis included data from 11 multicenter, randomized phase IIb and III trials, as well as five long-term extension studies. All included a placebo arm; some also included an active-treatment comparison with inhaled beclomethasone. Information was available on 3,386 adult patients, aged 15 to 85 years, as well as 336 children and adolescents aged 6 to 14 years. Summary statistics were used to compare the rates of adverse events among treatment groups.

For both adult and pediatric asthma patients, montelukast treatment was not associated with any increase in clinical or laboratory adverse events, compared with placebo. This included clinically relevant adverse events such as upper respiratory infections and transaminase elevations. In the adult extension studies, the rate of one or more clinical adverse events was 80% with montelukast vs 74% with beclomethasone. The rate of discontinuation because of adverse events was also similar across treatment groups. There were no cases of vasculitis or Churg-Strauss syndrome.

These pooled safety data suggest that montelukast has a good safety and tolerability profile in adult and pediatric asthma patients. With short- or long-term administration, montelukast is about as well-tolerated as placebo. This is so even at higher than recommended clinical doses, ie, 10 mg/d in adults and 5 mg/d in children age 6 or older.

COMMENT: *The results of this meta-analysis are quite reassuring since extensive safety data were monitored in more than 2,000 patients who received montelukast during clinical trials. For example, there is no evidence that a subgroup exists in whom montelukast treatment results in hepatic transaminase elevation or other significant laboratory abnormality. The safety of the drug at higher than the approved dose is also reassuring, and distinguishes montelukast from zafirlukast, the other leukotriene receptor antagonist approved in the United States. Exonerating montelukast from the proposed association of leukotriene receptor antagonists with such a rare disease as Churg-Strauss syndrome would require monitoring many more patients than were included in this meta-analysis.*
S. A. T.

Storms W, Michele TM, Knorr B, et al: Clinical safety and tolerability of montelukast, a leukotriene receptor antagonist, in controlled clinical trials in patients aged ≥ 6 years. **Clin Exp Allergy** 31:77-87, 2001. ♦♦

Montelukast Plus Cetirizine Is Effective in Allergic Rhinitis

INTRANASAL corticosteroids are the initial treatment of choice in allergic rhinitis, working through a nonselective anti-inflammatory effect. Selective histamine and leukotriene receptor antagonists are now available for specific blockade of inflammatory mediators—on their own, they are less efficacious in allergic rhinitis than intranasal corticosteroids. The current study compared the combination of a leukotriene receptor antagonist and an antihistamine vs intranasal corticosteroid in the treatment of allergic rhinitis.

The study included 22 patients with seasonal allergic rhinitis. In crossover fashion, they were ➤➤

studied while receiving intranasal mometasone furoate, 10 µg once daily; and oral montelukast 10 mg plus oral cetirizine 10 mg, both given once daily. Each treatment was preceded by a 7- to 10-day placebo period.

The two treatment conditions produced similar reductions in total nasal symptoms, as well as in objective assessments of disease activity. The study found no significant differences between placebo and active treatment in the results of rhinomanometry, acoustic rhinometry, or nitric oxide. Mometasone had no detectable effect on urinary cortisol excretion or blood eosinophil count.

In patients with seasonal allergic rhinitis, the combination of oral montelukast and cetirizine appears as effective as monotherapy with intranasal mometasone furoate. Both treatments have beneficial effects on objective and subjective outcome measures. The lack of effect on nasal airways resistance or geometry underscores the importance of obtaining repeated daily measures of upper airway inflammation.

COMMENT: *Given the recent emphasis on allergic rhinitis and asthma as systemic diseases, systemic therapy targeting both histamine and leukotriene receptors is an attractive strategy. However, the efficacy of nasal corticosteroids is well known to be superior to antihistamines in controlling nasal symptoms associated with allergic rhinitis. This study suggests that combining a potent antihistamine with a leukotriene receptor antagonist does not compromise the benefit that would have been afforded by a nasal corticosteroid. The cost-effectiveness of such a strategy would be improved in those patients who also have asthma.*
S. A. T.

Wilson AM, Orr LC, Sims EJ, Lipworth BJ: Effects of monotherapy with intra-nasal corticosteroid or combined oral histamine and leukotriene receptor antagonists in seasonal allergic rhinitis.
Clin Exp Allergy 31:61-68, 2001. ♦♦

"Tuna Burgers" Lead to Histamine Poisoning

IN 1998-99, a sharp increase in the number of cases of histamine poisoning was reported to North Carolina health officials. Histamine poisoning may result from bacterial conversion of histidine to histamine in stored fish—a process prevented by adequate cold storage of fish. These authors trace several outbreaks of histamine poisoning to ingestion of processed fish.

Cases of histamine poisoning were defined by the presence of two or more of the following: a rash, facial flushing, vomiting, diarrhea, dyspnea, tightness in the throat, or metallic/peppery taste in the mouth. A total of 22 cases occurring during an 8-month period in 1998-99 were identified, 20 of them occurring in 5 outbreaks. In contrast, no more than 4 cases per year were reported from 1994 through 1997. The cases were traced to specific shipments of fish, which were investigated through interviews with seafood distributors and review of restaurant and seafood supply orders. Samples of the fish were tested for histamine, with a level of greater than 50 ppm constituting evidence of decomposition.

The cases were traced to processed tuna, mainly consumed in the form of tuna burgers at restaurants. During processing, several freezing and thawing cycles occurred. High levels of histamine were measured in processed samples, with the highest levels recorded in ground tuna burgers.

The outbreaks of histamine poisoning in North Carolina are linked to consumption of tuna burgers. Underreporting is likely, as this syndrome—the only form of fish poisoning caused by bacterial contamination—is underappreciated in the medical community. The authors call for efforts to improve recognition and surveillance of fish-related seafood poisoning. The FDA recently updated its regulations for seafood processing.

COMMENT: *Fish-induced anaphylaxis is mimicked by ingestion of fish contaminated with histamine created by bacterial conversion of histidine in the muscle. The complicated food-processing system in the United States introduces opportunities during which the temperature of fish may increase to levels that permit bacterial activity. In addition, food processing with grinders, used to make ground fish for burgers, temporarily increases the temperature of the meat and facilitates histamine formation. Allergists should be wary that outbreaks of fish allergy may be secondary to histamine poisoning from contaminated fish.*
D. K. L.

Becker K, Southwick K, Reardon J, Berg R, MacCormack JN: Histamine poisoning associated with eating tuna burgers. **JAMA** 285:1327-1330.

Wine Intolerance Can't Be Linked to Histamine Content

THIS study evaluated the role of histamine content in causing intolerance to wine. Sixteen patients with wine intolerance underwent two double-blind challenges with wines: one with a low histamine content, 0.4 mg/L; and one with a high histamine content, 13.8 mg/L. Radioimmunoassays were used to measure histamine and methylhistamine in blood samples taken at baseline and at 10 to 45 minutes after wine challenge. Urine levels of methylhistamine and methylimidazolacetic acid were measured 5 hours before and 5 hours after challenge.

There was no difference in the symptomatic reaction between the two wines, and the low-histamine wine actually produced a higher increase in plasma histamine. Neither were there any differences in methylhistamine or methylimidazolacetic acid levels.

Wine intolerance appears to be unrelated to the histamine content of the wine consumed. Other histamine-releasing substances found in wine may play a role. One candidate for further examination is acetaldehyde.

COMMENT: *Adverse reactions to wines are thought to be possibly related to their pre-existing hista-* ➤➤

mine content. These authors investigated 16 patients with chronic urticaria, but not asthma, who reported an adverse reaction to wines. They were not sulfite sensitive. They were challenged with wines having low and high histamine content. The resultant symptoms were comparable—the subjects' plasma histamine content was actually higher after the histamine-poor wine. Unidentified histamine-releasing substances seem to be involved. Back to the drawing board.
R. J. M.
Kanny G, Gerbaux V, Olszewski A, et al: No correlation between wine intolerance and histamine content of wine. **J Allergy Clin Immunol** 107:375-378, 2001. ♦♦

C1-Inhibitor Concentrate Is Effective for Laryngeal Edema in HAE

THE autosomal dominant disease hereditary angioedema (HAE) results from an inherited deficiency of C1-esterase inhibitor. Affecting 1/10,000 to 1/50,000 persons, HAE causes recurrent, transient episodes of cutaneous swelling and intestinal and laryngeal edema, which resolve spontaneously after 2 to 5 days. Death may result from asphyxiation if laryngeal edema develops. Previous studies have evaluated the use of C1-inhibitor concentrate for prophylactic therapy or for treatment of acute abdominal pain and skin swelling. The use of C1-inhibitor concentrate in treating airway compromise in patients with HAE was studied.

The study included 95 patients with HAE followed for up to 20 years by a department of dermatology. Of these, 42 had a history of sudden airway obstruction. Eighteen patients received C1-inhibitor concentrate, prepared from pooled plasma, as treatment for laryngeal edema. All 95 patients had been given a vial of C1-inhibitor concentrate, 500 U, and told to store it at home in the refrigerator. If they had an episode of laryngeal edema, they were to take the vial for injection by their general practitioner or at the nearest hospital. If laryngeal edema had not cleared within 1 hour, they were to receive another injection of C1-inhibitor concentrate in the hospital. Efficacy was assessed by comparing the duration of laryngeal edema between treated and untreated episodes within patients, as well as between patients who did and did not receive C1-inhibitor concentrate.

Of the 42 HAE patients experiencing attacks of laryngeal edema, 24 never received C1-inhibitor concentrate, whether because their condition was undiagnosed or the concentrate was not yet available. The 18 patients who did receive C1-inhibitor concentrate experienced a total of 345 attacks of laryngeal edema, 193 of which were treated with C1-inhibitor concentrate. In all of the latter cases, C1-inhibitor treatment was effective. Onset of relief started within 4 hours after injection in all cases, and within 30 to 60 minutes in most. The mean duration of laryngeal edema was 101 hours in untreated episodes, compared with 15 hours in treated episodes. There were no adverse reactions to C1-inhibitor concentrate.

This study supports the use of C1-inhibitor concentrate for rapid resolution of episodes of laryngeal edema in patients with HAE. Most attacks begin to respond within 1 hour or less, and treatment greatly reduces the total duration of attacks.

COMMENT: *This study involves a large number of patients, most of whom had type I HAE. It establishes the safety and effectiveness of C1 inhibitor concentrate in providing quick relief from potentially life-threatening laryngeal edema. It also describes an interesting strategy whereby patients keep their supply of concentrate in the refrigerator at home and take it to a nearby practitioner or health care facility when infusions are needed for attacks. It is hoped that this product will someday be available in the United States.*
J. R. B.
Bork K, Barnstedt S-E: Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema.
Arch Intern Med 161:714-718, 2001. ♦♦

Endotoxin Linked to Wheezing Risk in Infants

THIS study examined the contribution of exposure to endotoxin from house dust in the development of wheezing in infants with a family history of asthma. The subjects were a birth cohort of 499 infants with one or more allergic/asthmatic parents. Within 3 months after birth, home visits were performed to measure levels of endotoxin in dust from the baby's bed, bedroom floor, family room, and kitchen floor. The infants were followed up for onset of wheezing and for repeated wheezing during the first year of life.

The geometric mean maximum home endotoxin level in all study homes was 100 EU/mg. An endotoxin level of 100 EU/mg or greater in the family room was associated with a significantly increased risk of any wheezing, relative risk (RR) 1.29 (95% confidence interval [CI] 1.03 to 1.62). On multivariate analysis, this relationship was unaffected by other factors, including cockroach allergen, lower respiratory illness, smoking during pregnancy, lower birth weight, maternal asthma, dog, or race/ethnicity. The relative risk (RR) was 1.33, 95% CI 1.00 to 1.76. When all other variables were accounted for, an elevated endotoxin level in family room dust was significantly associated with an increased risk of repeated wheezing: RR 1.56, 95% CI 1.03 to 2.38.

Levels of endotoxin in the home appear to affect the risk of wheezing in infants with a familial predisposition to asthma or allergy. The association is particularly strong for repeated wheezing. An accompanying editorial suggests that endotoxin may be linked to a biologically unique form of asthma and should be considered an important environmental risk factor for the disease.

COMMENT: *These results suggest that problems with house dust exposure are caused by more than the content of mite, animal dander, and insect allergens. In particular, endotoxin—the ubiquitous cell wall* ➤➤

component of gram-negative bacteria—may be important. This substance is known to produce airway inflammation by nonallergic mechanisms. In this study endotoxin exposure was strongly associated with wheezing and repeated wheezing in the first year of life in children from atopic families. The question of whether endotoxin plays a role in stimulating Th1 or Th2 cell response is unanswered, and we do not know if early endotoxin exposure influences the long-term development of sustained asthma.
J. R. B.
Park J-H, Gold DR, Spiegelman DL, et al: House dust endotoxin and wheeze in the first year of life.
Am J Respir Crit Care Med 163:322-328, 2001. ♦♦

Bronchodilator Effects of Cumulative-Dose Salbutamol Assessed

With the phaseout of chlorofluorocarbon-containing inhalers, aerosols using alternative propellants and new dry-powder devices have been assessed. Studies of the dose-response curve for an inhaled β_2-agonist using single-dose, separate-day designs show a distinct plateau at dose levels within the usual single-dose range. However, giving the same medication in a cumulative dose over the course of a day produces a continuous increase in effect, perhaps related to increasingly peripheral deposition of the drug. The bronchodilator effects of salbutamol in a high vs low cumulative dose regimen were assessed in a randomized, placebo-controlled, crossover study.

The study included 24 adult asthma patients, mean age 32 years, who were highly responsive to salbutamol. On four study days, in random order, they received salbutamol via Turbuhaler in a 400 μg cumulative dose, an 800 μg cumulative dose, and a 400 μg single dose, and placebo. The doses were given in 30-minute intervals. The bronchodilator effects of the various dosing regimens were compared.

The bronchodilator response to single doses of 50, 100, and 400 μg of salbutamol were similar to each other and greater than placebo. There was little difference in the bronchodilator response to the two cumulative dose regimens. The change in FEV_1 from baseline, measured at equal times after the last active inhalation, was significantly greater with the 400 μg cumulative dose than the 400 μg single dose.

The results underscore the need for caution in comparing different β_2-agonists or inhalation devices using cumulative- or single-dose designs. For a short-acting agent such as salbutamol, a lower than normally recommended dose may be effective. Giving repeated low doses over a 1-hour period may provide a better bronchodilator response than a single, higher dose.

COMMENT: *The take-home message here for practicing physicians may be that higher doses of β-agonists administered via hand-held inhalers must be administered gradually over time to achieve optimal effect. Another point is that doses of albuterol lower than those normally recommended might be employed for patients who need a fast-acting bronchodilator, but who object to side effects such as tremulousness.*
J. R. B.
Fishwick D, Bradshaw L, MacDonald C, et al: Cumulative and single-dose design to assess the bronchodilator effects of β_2-agonists in individuals with asthma.
Am J Respir Crit Care Med 163:474-477, 2001. ♦♦

Croup With Wheezing Linked to Persistent Wheezing and Reduced Airway Function

There is some evidence from retrospective studies to suggest that children with severe or recurrent viral croup are more likely to develop asthma. Long-term outcomes of a large number of young children with croup were analyzed, including assessment of croup with or without wheezing.

The study included 884 children from a 1980-84 birth cohort enrolled in the Tucson Children's Respiratory Study. Croup and other lower respiratory illnesses (LRIs) during the first 3 years of life were assessed by a physician, who noted whether or not croup was accompanied by wheezing. The children were followed up to 13 years of age, including pulmonary function tests, markers of atopy, and episodes of wheezing.

Croup with wheezing was diagnosed in 10% of children and croup without wheezing in 5%. Other LRIs were diagnosed in 36% of patients, while 48% had no LRIs. Measured during the first year of life, pulmonary function measures were significantly lower in children who had croup with wheezing and those with other LRIs, compared to those with no LRIs. The same groups also showed decreased airway function at ages 6 and 11, while those with "pure" croup had normal airway function at all ages. Croup with wheezing and other LRIs were also associated with lower mean values for indices derived from expiratory flow-volume loops, measured before as well as after lower respiratory symptoms developed. These children were also more likely to develop persistent wheezing.

The development of croup with wheezing early in life is associated with reduced airway function and with persistent wheezing, unlike croup without wheezing. Whether croup is associated with subsequent risk of lower airway obstruction may depend on initial lower airway involvement, and on abnormalities of lung function present even before the development of croup. Regardless of whether it is accompanied by wheezing, croup does not appear to be associated with allergies.

COMMENT: *The longitudinal study that has been ongoing in Tucson since the early 1980s has provided us with a great deal of insight into factors that lead to development of asthma. In this study, the investigators studied the outcomes of children who presented with croup with or without wheezing. While the presence of croup alone did not predict subsequent wheezing, if it was associated with wheezing initially, the child was more likely to have subsequent asthma. This again suggests that children who wheeze when they get their infections are predisposed to develop asthma* ➤➤

because of innate host factors. We hope that someday we will figure out what those factors are.
J. M. P.
Castro-Rodriguez JA, Holberg CJ, Morgan WJ, et al: Relation of two different subtypes of croup before age three to wheezing, atopy, and pulmonary function during childhood: a prospective study.
Pediatrics 170:512-518, 2001. ♦♦

Formoterol vs Terbutaline for As-Needed Treatment of Asthma

TWICE-DAILY treatment with long-acting β_2-agonists is beneficial for asthma patients who have persistent symptoms with inhaled corticosteroids. This study compared two inhaled β-agonists for use as maintenance therapy for patients with inadequate asthma control on inhaled corticosteroids: formoterol and terbutaline.

The randomized, double-blind trial included patients from 35 centers in four European countries. There were 205 women and 157 men, mean age 47 years. All had an FEV_1 of at least 50% predicted—mean FEV_1 was 74%—while taking a mean inhaled corticosteroid dose of 870 μg/d. All randomized patients required inhaled β-agonist therapy 3 to 8 times daily. They were randomized to receive as-needed treatment with formoterol 4.5 μg or terbutaline 0.5 mg via Turbuhaler. Safety and efficacy variables were analyzed by intention to treat.

The two groups were comparable in their baseline characteristics. Time to first severe asthma exacerbation significantly longer in the formoterol group. Patients taking formoterol also had a 5% greater increase in FEV_1, a mean 11 L/min greater increase in morning peak expiratory flow, and a mean 8 L/min greater increase in evening peak expiratory flow. Twenty-six patients dropped out of the study because they required more than 12 inhalations per day and/or experienced adverse events. Neither medication was associated with safety issues.

These results support the use of formoterol over terbutaline in asthma patients who have inadequate disease control with inhaled corticosteroids. The findings support further studies showing the efficacy of formoterol. Formoterol's longer duration of action does not appear to raise any safety issues.

COMMENT: *Four prior short studies have compared formoterol with salbutamol taken as needed in addition to twice-daily maintenance treatment, and all showed greater improvement in asthma control with formoterol. In this study, patients taking formoterol had a longer period of control before the first severe exacerbation of asthma. As well, lung function improved to a greater extent with fewer doses of rescue medication in the formoterol group. No safety issues were identified.*
E. J. B.
Tattersfield AE, Löfdahl C-G, Postma DS, et al: Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial.
Lancet 357:257-261, 2001. ♦♦

Systemic Activity of Fluticasone vs Budesonide in Normal vs Asthmatic Subjects

STUDIES of systemic absorption of inhaled corticosteroids are generally of short duration and use proxy indicators. Studies comparing systemic absorption of fluticasone propionate and budesonide have yielded conflicting results, whether because of differences in the study samples or the systemic markers used. Three different markers were used to compare the systemic effects of fluticasone propionate and budesonide in asthmatic and healthy subjects.

In the randomized trial, 46 healthy subjects received inhaled fluticasone 1,500 μg/d via Accuhaler, budesonide 1,600 μg/d via Turbuhaler, or placebo. In addition, 31 patients with moderate asthma received either fluticasone or budesonide in the same doses. Various systemic markers were assessed after 7 days. In the asthma patients, asthma control and systemic effects were also assessed after 21 days.

At baseline, the healthy controls had higher levels of total cortisol metabolites (TCM) in urine than the asthmatic patients. After 7 days' treatment, urinary TCM levels were significantly lower in healthy subjects than in asthmatic subjects in the fluticasone group. In contrast, among subjects taking budesonide, urinary TCM levels remained higher in the healthy group. Compared with morning serum cortisol or osteocalcin level, urinary TCM was a more sensitive marker of the effects of inhaled corticosteroids.

Seven days of treatment with inhaled fluticasone propionate, 1,500 μg/d, has a more marked effect on the hypothalamic-pituitary-adrenal axis in healthy subjects than in asthmatic patients. No such effect is noted with inhaled budesonide, 1,600 μg/d. Some of the inconsistent results of previous studies may reflect this difference between healthy and asthmatic subjects, as well as differences in the sensitivity of the markers used.

COMMENT: *These investigators compared the effects of fluticasone propionate and budesonide in healthy and asthmatic subjects and measured the impact of treatment on three systemic markers. Fluticasone propionate at 1,500 μg/d had a greater effect on the hypothalamic-pituitary-adrenal axis in healthy subjects than in patients with asthma, which was not seen with budesonide at 1,600 μg/d. These observations may help explain many discrepancies in the literature. Extrapolation of findings from healthy subjects may be misleading in the clinical setting.* (*See* AllergyWatch, *Nov/Dec 2000, p. 11.*)
E. J. B.
Harrison TW, Wisniewski A, Honour J, Tattersfield AE: Comparison of the systemic effects of fluticasone propionate and budesonide given by dry powder inhaler in healthy and asthmatic subjects.
Thorax 56:186-191, 2001. ♦♦

Allergic and Nonallergic Perennial Rhinitis: Biopsy Findings Compared

THE mucosal inflammation in perennial rhinitis may result from allergic or nonallergic mecha- ➤➤

nisms. The cellular and structural characteristics of the nasal mucous membrane were compared between patients with allergic vs nonallergic perennial rhinitis, and with normal controls.

The biopsy study included 27 patients with perennial allergic rhinitis, 12 patients with perennial nonallergic rhinitis showing eosinophils in the nasal smear, and 6 nonrhinitic controls. Perennial rhinitis was associated with accumulation in the mucosa of activated, degranulated mast cells and eosinophils. Both perennial rhinitis groups showed a higher tissue eosinophil/neutrophil ratio and greater loss of epithelial integrity than the control group. The amount of epithelial damage was greatest in biopsies taken from patients with allergic rhinitis during pollen season. Eosinophil and mast cell numbers were higher in the nonallergic group, and eosinophil number was correlated with loss of epithelial integrity.

Biopsy specimens from patients with perennial rhinitis show accumulation of eosinophils and mast cells with loss of epithelial integrity. Mast cell numbers are higher in patients with nonallergic vs allergic rhinitis. Eosinophils, but not mast cells, appear to play a role in the epithelial damage in perennial rhinitis.

COMMENT: *Perennial rhinitis is much like asthma, in that the pathophysiology can involve allergy, or not. These Finnish investigators examined biopsies from both allergic and nonallergic patients with perennial rhinitis. Accumulation of eosinophils and degranulated mast cells, and epithelial disruption, characterized both groups to the same degree. However, biopsies in relevant seasons were worse. Perennial nonallergic rhinitis is still an* atopic *disease.*
R. J. M.

Amin K, Rinne J, Haahtela T, et al: Inflammatory cell and epithelial characteristics of perennial allergic and nonallergic rhinitis with a symptom history of 1 to 3 years' duration.
J Allergy Clin Immunol 107:249-257, 2001. ♦♦

Mometasone via Dry-Powder Inhaler Is Effective for Moderate Persistent Asthma

MOMETASONE furoate is a new, synthetic, highly potent inhaled glucocorticoid. Given as a nasal spray, mometasone has almost no systemic bioavailability and no hypothalamic-pituitary-adrenal axis suppression. This placebo-controlled study compared the effects of mometasone given via dry-powder inhaler with beclomethasone dipropionate given via metered-dose inhaler in patients with moderate persistent asthma.

The study included 227 adolescent or adult patients with moderate persistent asthma previously maintained on inhaled glucocorticoids. They were randomly assigned to mometasone, 100 or 200 μg twice daily; beclomethasone, 168 μg twice daily; or placebo. Treatment continued for 12 weeks; safety and efficacy variables were assessed in double-blind fashion.

All patients taking mometasone or beclomethasone had improvement in FEV_1, compared with the placebo group. The response to the higher dose of mometasone was almost twice as great as that to the lower dose of mometasone or to beclomethasone, although the difference was not significant. The higher dose of mometasone also yielded greater improvement in peak expiratory flow rate, symptoms, nocturnal awakenings, and albuterol use.

In this study, both tested doses of mometasone furoate via dry-powder inhaler were efficacious and well-tolerated in patients with moderate persistent asthma. Efficacy variables favor a mometasone dosage of 200 μg twice daily. This dosage achieves greater improvements in pulmonary function and asthma symptoms than mometasone 100 μg twice daily or beclomethasone 168 μg twice daily.

COMMENT: *With the anticipated release of mometasone, this study should be of great interest. High-dose mometasone appears to be more efficacious than currently recommended doses of beclomethasone, regardless of the outcome parameter measured. Interestingly, low-dose mometasone was very similar to beclomethasone in clinically significant outcomes. Mometasone will provide us with another high-potency, low-systemic-bioavailability inhaled steroid that is safe and effective.*
A. M.

Nathan RA, Nayak AS, Graft DF, et al: Mometasone furoate: efficacy and safety in moderate asthma compared with beclomethasone dipropionate.
Ann Allergy Asthma Immunol 86:203-210, 2001. ♦♦

Many Elderly Asthma Patients Don't Receive Inhaled Corticosteroids

RECENT years have seen sharp rises in asthma-related mortality for the elderly population. Appropriate use of inhaled steroid therapy might address this problem, but little is known about the rate of such treatment among elderly asthma patients or the risk factors for suboptimal therapy. Population-based data were used to assess the use of inhaled steroid therapy by elderly asthma patients and factors associated with nonuse.

Canadian hospital discharge and drug data bases were used to identify all Ontario residents aged 65 or older who survived an acute asthma exacerbation between 1992 and 1997. There were 6,554 such patients: 68% of them women, and the average age was 74 years. Comorbidity was high, including an 8% rate of congestive heart failure. Forty percent of patients received no inhaled steroid therapy within 90 days after hospital discharge. Lack of inhaled steroid therapy was more likely for patients over age 80 and for patients with multiple comorbidity. Patients receiving care from a respirologist/allergist were 50% more likely to receive inhaled steroids than those treated by a family physician/general practitioner.

Inhaled steroid therapy appears to be underused by elderly survivors of acute asthma exacerbations. Older patients and those with greater comorbidity are less likely to receive this proven therapy, as are ➤➤

patients treated by nonspecialists. The study included no information on adverse reactions to inhaled steroids.

COMMENT: *This Canadian population-based study reminds us that moderate-severe asthma is not a disease of just children and young adults. We must guard against being distracted away from optimal asthma care by comorbid conditions in elderly patients, especially when the basics of asthma care (such as metered-dose inhaler technique) may require extra attention in this rapidly expanding population.*
S. A. T.
Sin DD, Tu JV: Underuse of inhaled steroid therapy in elderly patients with asthma.
Chest 119:720-725, 2001. ♦♦

Near-Fatal Asthma in Washington, D.C.: 35 Cases

FIVE thousand Americans die from asthma each year, yet many or most of these deaths may be preventable. This study analyzed the experience with near-fatal asthma in Washington D.C. during 1993. Biweekly telephone calls were made to each ICU in Washington to identify cases of near-fatal asthma All subjects required intubation for respiratory failure—patients who later died in the hospital were included. An attempt was then made to interview the patients or a proxy. Thirty-five cases of fatal asthma and 33 of near-fatal asthma were identified.

Thirty-one patients or proxies were interviewed. The average age was 29 years; 45% of patients were under age 18. Sixty-one percent of the patients were female and 84% were African-American. The average duration of known asthma diagnosis was 14 years. Fifty-two percent of patients had been hospitalized at least once previously, and two-thirds had been intubated. Most patients reported contact with tobacco smoke, including 27% with a personal smoking history. Fifty-five percent had taken no special steps to modify their home environment because of their asthma. Most of the patients were insured and received usual care from a private physician or ambulatory clinic. Eighty percent of patients had a short-acting β_2-agonist; 7% used Primatene Mist. Twenty-nine were receiving no anti-inflammatory medication. Although more than three-fourths of patients had had trouble breathing in the day before the near-fatal event, less than two-thirds sought health care.

Near-fatal asthma is a common event in Washington, D.C. Some of the risk factors for near-fatal asthma may differ from those for fatal asthma, such as the young age studied in this report. About one-third of cases of near-fatal asthma in this study may have been preventable.

COMMENT: *This uncontrolled study found that near-fatal asthma was frequent in the Washington, D.C., community. As in other studies of fatal or near-fatal asthma, some 30% of 35 patients were not on anti-inflammatory medications. As well, though three-quarters of the subjects experienced respiratory distress 24 hours before their incident, only 64% contacted a health care provider. The most interesting feature of this study was the suggestion that some of the factors associated with near-fatal events may be different from those associated with fatal asthma.*
A. M.
Moore BB, Wagner R, Weiss KB: A community-based study of near-fatal asthma.
Ann Allergy Asthma Immunol 86:190-195, 2001. ♦♦

Questionnaire Helps Evaluate Effectiveness of Immunotherapy

IT can be difficult to measure the success of treatments for allergic rhinitis, such as immunotherapy. These authors evaluated the use of the rhinitis outcomes questionnaire (ROQ) to evaluate the results of immunotherapy in the private-practice setting. The ROQ is a recently validated, 26-item, Likert-type questionnaire, designed to be completed in 5 minutes. A random sample of 175 patients with allergic rhinitis were asked to complete the ROQ twice in one sitting. First they rated their symptoms before immunotherapy, followed by an evaluation of their current symptoms.

Eighty-one percent of patients believed that immunotherapy worked for them, while 19% were uncertain. Scores improved by an average of 52% after immunotherapy. The patients reported reductions of 67% in antibiotic use, 68% in emergency department visits, 75% in missed work/school days, and 79% in hospital admissions.

The ROQ is a promising tool for assessing the effectiveness of immunotherapy in allergy practice. The questionnaire is quick, inexpensive, and user-friendly. The authors plan a 3-year prospective study using an updated version of the ROQ.

COMMENT: *A relatively simple, reliable instrument to confirm the clinical improvement associated with allergen vaccine immunotherapy would be a welcome tool for the practicing allergist/immunologist. This study was completed using patients in busy practice settings, demonstrating the clinical utility of the questionnaire. The major deficiency is that the comparison was made based on recall data rather than a prospective assessment. This is a start, but additional data are needed.*
D. K. L.
Santilli J, Nathan R, Glassheim J, Rockwell W: Patients receiving immunotherapy report it is effective as assessed by the rhinitis outcomes questionnaire (ROQ) in a private practice setting.
Ann Allergy Asthma Immunol 86:219-221, 2001. ♦♦

REVIEWS OF NOTE

Frenz DA: Interpreting atmospheric pollen counts for use in clinical allergy: allergic symptomatology. Ann Allergy Asthma Immunol 86:150-158, 2001.

COMMENT: *This review addresses some of the issues relating pollen counts and allergy symptoms. The article discusses comparing individual or local exposure to airborne allergen in contrast to community or rooftop data, nonlinear dose-response relationships between symptoms and pollen counts, and the assessment of pollen counts in relation to allergenicity. The available data are reviewed and areas of need are identified.*
D. K. L.

Mersfelder TL: Phenylpropanolamine and stroke: the study, the FDA ruling, the implications. **Cleveland Clinic J Med** 68:208-223, 2001.

COMMENT: *This article includes an outstanding list of phenylpropanolamine-containing over-the-counter and prescription drugs, as well as a review of the literature on the possible association with hemorrhagic stroke. This paper should be immediately available to clinicians treating patients with rhinosinusitis.*
A. M.

Paller AS: Use of nonsteroid topical immunomodulators for the treatment of atopic dermatitis in the pediatric population. **J Pediatr** 138:163-168, 2001.

COMMENT: *Atopic dermatitis affects about 20% of the population. Topical corticosteroids are the most widely used therapeutic agents, and have the potential for side effects. This article reviews several novel nonsteroidal immunomodulators—ie, tacrolimus and the ascomycin derivative SDZ—as showing promise in FDA trials in children. These agents offer several advantages over standard corticosteroid therapy. They are effective on the face and intertriginous areas without concern over atrophy and/or telangiectasia. They do not induce glaucoma or cataract formation.*
J. B.-M.

Montanaro A, Tilles ST: Update in allergy and immunology. Ann Intern Med 134:291-297, 2001.

COMMENT: *This update represents an excellent review of the published literature between 1998 and 1999, focusing on topics especially important to the practicing internist.*
E. J. B.

Gonzales R, Bartlett JG, Besser RE, et al: Principles of appropriate antibiotic use for treatment of acute respiratory tract infections in adults: background, specific aims, and methods. Ann Intern Med 134:479-486, 2001.

COMMENT: *This article leads off an outstanding collection of American College of Physicians position papers covering antibiotic use for nonspecific upper respiratory infection, acute pharyngitis, sinusitis, and bronchitis.*
A. M.

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